No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
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TAB 119

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.,

Plaintiffs,

v. Case No. 4:22-cv-00325-RH-MAF

JASON WEIDA, et al.,

Defendants.
_____/

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF SOPHIE SCOTT, PH.D., AND SUPPORTING MEMORANDUM OF LAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403 and 702, Plaintiffs respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert Professor Sophie Scott ***in its entirety***. Professor Scott is not a qualified expert on gender dysphoria or its treatment, and her opinions and testimony are neither relevant nor reliable under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. Her opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

WHEREFORE, Plaintiffs respectfully request an order excluding Professor Scott's report, expert opinions and testimony in their entirety.

MEMORANDUM OF LAW

Professor Scott is not qualified to offer the opinions stated in her report. She opines that puberty delaying medication administered to teenagers "*may have*" unknown, negative effects on brain development. Report, ¶ 15 (**Exhibit A**). She also believes without any scientific support that it is "very possible" that teenagers cannot "fully grasp the implications of puberty blocking treatment." *Id.* ¶ 16. But Professor Scott is not qualified to give these opinions because she has never treated patients with gender dysphoria (at any age) given that she is not a medical provider of any kind, nor has she administered or studied the effects of puberty delaying treatment in any clinical or academic setting. She has never written on these subjects either—except on Twitter.

Aside from her lack of qualifications, Professor Scott's opinions are inadmissible because they are entirely speculative and lack any reliable or testable foundation or methodology. There is no existing data to support her ultimate conclusions, which means her opinions are based on impermissible "leaps of faith." The data that does exist directly contradicts her conclusions, but, strikingly, she never mentions this data in her report. Her opinions moreover are based solely on her unqualified review of other studies, and they are far outside the scientific mainstream. The Court should therefore exercise its gatekeeping function under Rule 702 and exclude Professor Scott's testimony. *See Rink v Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005).

A. Legal Standard

Rule 702 of the Federal Rules of Evidence governs the admissibility of expert testimony. Pursuant to *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993), and Rule 702, district courts must perform a "gatekeeping" role "to ensure that speculative, unreliable expert testimony does not reach the jury under the mantle of reliability[.]" *Rink*, 400 F.3d at 1291; *Kilpatrick v. Berg, Inc.*, 613 F.3d 1329, 1335 (11th Cir. 2010) ("The trial court must make certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").

To do so, the Court must engage in a rigorous inquiry to determine whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in Daubert; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

E.g., *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) (en banc), *cert. denied*, 544 U.S. 1063 (2005). The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence. *Rink*, 400 F.3d at 1292.

B. Professor Scott is Not Qualified To Offer An Expert Opinion on Any Issue in the Case.

A witness may be qualified as an expert by virtue of her "knowledge, skill,

experience, training, or education." Fed. R. Evid. 702. However, "[e]xpertise in one field does not qualify a witness to testify about others." *Lebron v. Secretary of Florida Dept. of Children and Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use because he had never conducted research on the subject, and instead relied on studies to form his opinion).

A scientist, however well credentialed, cannot be "the mouthpiece of a scientist in a different specialty." *Id*. at 1369 (quoting *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002)); *TB Food USA, LLC v. American Mariculture, Inc*., 2021 WL 4962969, at *4 (M.D. Fla. October 26, 2021) ("[A]n expert must have at least some minimum training, education, experience, knowledge, or skill pertaining to the particular subject matter of his proposed testimony.") (cleaned up). "Merely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel v. Folwell*, 2022 WL 3226731, at *9, 13 (M.D.N.C. August 10, 2022) (excluding Dr. Lappert's expert opinion about puberty delaying medication because he is a surgeon, not an endocrinologist, and he never treated a patient with hormone therapies). If an expert witness does not intend to testify about matters growing directly out of "research [s]he had conducted independent of the litigation," the expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702).

Professor Scott is the Director of University College London's Institute of Cognitive Neuroscience. Report ¶ 6.[1] Her main area of research is "speech, laughter and sound." Tr. 48:25 – 49:4 ("Q. All of these publications are about speech, laughter and sound. Isn't that right? A. There are a few other things. But yeah, that's the majority. That is my main area of research.") (**Exhibit B**). She is proffered as an expert based on her "training and experience as a neuroscientist," her reading and assessment of "the relevant neuroscientific literature on brain development, and the potential effects of [puberty delaying medication] on the developing brain." Report, ¶ 4. However, she has no experience with the provision of puberty delaying medication, gender-affirming medical care or medical treatment of gender dysphoria. She has never published any papers or studies on gender dysphoria, gender-affirming care or puberty delaying medication. Nor has she published any reviews of such studies in her entire career. Tr. 49:5-12 ("Q. Are any of [your publications] about gender-affirming care? A. No. Q. Are any of these publications specific to gender dysphoria? A. No. Q. Any about puberty blockers? No.").

Professor Scott is not a medical doctor, a psychiatrist or a clinical psychologist; she has no medical training. Tr. 34:25 – 35:4; Tr. 35:13-14. She does

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[1] According to Professor Scott, cognitive neuroscience is "a scientific field that examines the relationships between human behaviour to the human brain, and how these can be affected by age, disease and individual differences." Report, ¶ 6; Tr. 37:6-10 ("A neuroscientist is somebody who studies brains…[H]e's studying it in a purely basic science position. They're not treating people. They're not prescribing things.").

not treat patients. Tr. 44:22-23. She has never studied gender dysphoria in a clinical setting, nor has she ever administered puberty delaying medication or studied their effects, let alone in humans. Tr. 31:18-24 (Q. So you've never conducted any clinical studies yourself related to gender dysphoria? A. No. Q. What about the effects of gender-affirming care? A. Nope."). Nor has anyone at Professor Scott's place of employment, the Institute for Cognitive Neuroscience ever studied gender dysphoria or the effects of gender-affirming medical care either, meaning Professor Scott has not overseen any such study. Tr. 31:6-8 ("Q. Has anyone at the Institute ever conducted any clinical studies related to gender dysphoria? A. No, not that I'm aware of."; Tr. 31:25-32:2 (Q. Has the Institute ever studied the effects of puberty blockers? A. No.").

Without *any* qualifications, training or experience related to gender dysphoria or puberty delaying medication, Professor Scott is not qualified to give an expert opinion on these subjects. *See Kadel*, 2022 WL 3226731, at *13.[2] Nor is she

[2] *See also, e.g.*, *Fernandez v United States*, 2020 WL 3105925, at *5 (N.D. Fla. June 4, 2020) (excluding an expert because the Plaintiff offered "no information indicating that he has any experience or specialized knowledge regarding medicine generally or any of the branches of medical science which might be relevant to causation); *Doctors Licensure Group, Inc. v. Continental Casualty Company*, 2011 WL 13182969, at *4 (N.D. Fla. September 26, 2011) (excluding a proffered expert on accounting because he was "not an accountant" and had "virtually no experience in accounting"); *Webb v. Carnival Corporation*, 321 F.R.D. 420, 429 (S.D. Fla. 2017) ("Because Mr. Jaques has no experience in toxicology, responsible alcohol vending policies, nor medicine, and has never served onboard the California Dream, he is unqualified to opine on the Decedent's level of intoxication[.]").

qualified to opine on studies related to gender dysphoria or puberty delaying medication conducted by others. *See Dura Automotive*, 285 F.3d at 614 ("[A] scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

This is so particularly here where Professor Scott's opinions and so-called review of literature did not "grow[] naturally and directly out of research [s]he had conducted independent of the litigation." *Lebron*, 772 F.3d at 1369 (cleaned up); *see also* Fed. R. Evid. 702, Advisory Comm. Notes (2000 Amendments). Here, Professor Scott reviewed the literature and developed her opinions in connection with litigation in the UK, namely, *Bell v. Tavistock*, and now seeks to transpose those opinions here without still having done any independent work in the area. Tr. 52:7-18 ("Q. Why did you think that you had an opinion to give in this case? A. *Because I provided an opinion before for the Keira Bell case.* And I discussed that a lot with Paul Conrathe at the time for all the reasons you said. I'm not a clinician. *I haven't worked in this area.* … And I did some reading into the literature, … ."); Tr. 53:6-9 ("Q. So you formed your opinion about puberty blockers in adolescents while you were working on the Bell case? A. Yeah.").

In *Kadel*, a case similar to this one about insurance coverage for gender-affirming medical care, the court excluded a proposed expert (Dr. Lappert) because "[h]e is not a psychiatrist, psychologist, or mental health professional, nor has he

ever diagnosed a patient with gender dysphoria,"[3] and "[h]e is not an endocrinologist, nor has he ever treated a patient with hormone therapies." *Kadel*, 2022 WL 3226731, at *13. Here, Professor Scott, who unlike the excluded expert in *Kadel*, has no medical degree and has never provided medical or mental health care, is likewise "not qualified to render opinions about the diagnosis of gender dysphoria, its possible causes, … the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for mental health professionals or endocrinologists, or any opinion on the non-surgical treatments obtained by Plaintiffs." *Id.* Her opinions should be excluded *in toto*.

C. Professor Scott's Opinions are Unreliable.

An expert's reliability concerns whether the reasoning or methodology underlying the testimony is scientifically valid and whether that reasoning or methodology properly can be applied to the facts in issue. *Kilpatrick*, 613 F.3d at 1335. When evaluating whether an expert's methodology is reliable, the Court considers, among other things:

> (1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4) whether the technique is generally accepted in the scientific community.

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[3] While Dr. Scott has an undergraduate degree where she minored in psychology, she is not certified as psychologist, and admits she's "not clinically qualified." Tr. 35:8-17. In her words, she is "a basic scientist." *Id.*

Frazier, 387 F.3d at 1262. The court must undertake an independent analysis of each step in the logic leading to the expert's conclusions, and if any step in the logic is deemed unreliable, the expert's entire opinion must be excluded. *Hendrix v Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009) (citing *McClain v. Metabolife Int'l., Inc.*, 401 F.3d 1233, 1245 (11th Cir. 2005)). Likewise, if the expert's opinions are vague or based on "leaps of faith unsupported by good science," then those opinions should be excluded as well. *Id*. at 579; *McDowell v. Brown*, 392 F.3d 1283, 1299, 1301 (11th Cir. 2004) (characterizing the experts' opinions as "too vague" and "more of a guess than a scientific theory."); *Rosen v. Ciba-Geigy Corp*., 78 F.3d 316, 319 (7th Cir. 1996) ([T]he courtroom is not the place for scientific guesswork, even of the inspired sort.").

1. Professor Scott's Opinions Lack Reliability Because They Are Based on Flawed Reasoning or Methodology.

Professor Scott's Report does not provide any basis for her "concern" about puberty delaying medication or her speculations about a teenager's ability to grasp its implications. The reason for this is simple: Professor Scott does not know what the effects of puberty delaying medication are on the brain, and she does not know whether teenagers can fully grasp its implications. She does not know what these implications are herself, and accordingly, all her opinions are hypothetical and unmoored from facts or data.

a. Puberty Delaying Medication

Her report is full of statements about the alleged lack of studies pertinent to the effects of puberty delaying medication. Report, ¶ 7 ("My concern is that we do not yet have enough evidence about the best ways to identify the individuals for whom [puberty delaying medication] are appropriate."); Report, ¶ 15 ("All the papers I can find suggest that we need much more data on the long-term brain effects of [puberty delaying medication] when administered around puberty, [and] the effects this can have on behaviour[.]"). Without any evidence (and with no experience or training in the subject), Professor Scott can only guess the effects of these treatments. Report, ¶ 15 ("As puberty is associated with very marked changes in the structure of the brain…the use of puberty blockers *may* have serious consequences for the development of the human brain.") (emphasis added); Report, ¶ 16 ("We need more research to be able to determine the *potential* for puberty blockers to be effective in alleviating some aspects of gender dysphoria[.]") (emphasis added). Guessing is not permitted under Rule 702. *McDowell*, 392 F.3d at 1301 (noting that while an expert may "draw conclusions from existing data," drawing "conclusions where there was no existing data" amounted to a "mere guess" that "fails the tests for expert opinion"); *Magical Farms, Inc. v. Land O'Lakes, Inc.*, 2007 WL 4727225, at *2 (N.D. Ohio March 8, 2007) ("Dr. Ames' report is replete with statements like, 'suggest the possibility,' 'may have,' and 'I would be concerned,' all of which fail to rise to the level of a reasonable degree of certainty required by courts.").

To substantiate her untrained guesswork, Professor Scott briefly discusses—in a single paragraph—just five articles related to puberty delaying medication. *See* Report, ¶ 15. Only one of the articles is an original study pertaining to humans, namely, children with precocious puberty (Mul et al., 2001). *See* Report, ¶ 15; Scott Bibliography. Two other articles are not studies themselves, but rather a single commentary piece (Hayes, 2017) and a review of literature (Wojniusz et al., 2016), both pertaining to the treatment of precocious puberty. *See* Report, ¶ 15; Scott Bibliography. Finally, the other two studies pertain to sheep not people. *See* Report, ¶ 15; Scott Bibliography.[4] None of the studies pertain the use of puberty delaying medications for gender dysphoria in adolescents.

Notwithstanding the above, Professor Scott's discussion is nothing more than a recitation of findings from the above papers. She does not say anything about the methodologies behind those studies, whether they have been peer reviewed, or whether or how they are applicable to the context of using puberty delaying medications as treatment of gender dysphoria in adolescents. In fact, she disclaims them away after discussing them, saying "we cannot say if the results are due to direct effects of [puberty delaying medication] on the brain, heart and behaviour, or if they are secondary to this[.]" Report, ¶ 15. Without any qualifications or training in

[4] *But see Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is "simply too great an analytical gap between the data and the opinion offered").

these areas, her use of these articles to support her opinions about puberty delaying medication is completely unreliable and the type of hypothetical guesswork prohibited by Rule 702. *Lebron*, 772 F.3d at 1368 ("Expertise in one field does not qualify a witness to testify about others."); *Dura Automotive*, 285 F.3d at 614 ("A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

Most disturbingly, however, and demonstrative of her extremely flawed methodology, is the fact that she does not discuss any of the original studies that exist pertaining to the use of puberty delaying medications on transgender adolescents. There are at least three original, peer-reviewed studies that have looked specifically into the effects of puberty delaying medications on brain structure and function in transgender adolescents. *See* Corrected Edmiston Rebuttal Report, at ¶¶ 26, 29 (**Exhibit C**) (discussing Heesewijk et al., 2022; Soleman et al., 2016; Staphorsius et al., 2015). Indeed, none of these have found any significant effects of treatment on the brain. *Id.* Plaintiffs do not refer to these studies to argue the merits, but rather to starkly illustrate the flawed nature of Professor Scott's methodology. How can Professor Scott opine of the effects of puberty delaying medications on transgender adolescents' brains when she does not discuss any of the original, peer-reviewed studies looking at that question? The answer is she cannot.

Simply put, Professor Scott's concern over puberty delaying medication as a

treatment for gender dysphoria stems from her own lack of knowledge.[5] Not only does she not cite, let alone discuss, the most relevant studies in this area, but throughout her testimony, she repeatedly used the words "we don't know," when referring to the effects of puberty delaying medication. Tr. 24:11-14 ("[W]hat evidence we do have suggests that there are effects on the brain of delaying puberty. And we don't know what that might mean further down the line. We just don't know."); Tr. 68:20-21 ("Q. But you can't say here that these puberty blockers have any harmful effects on the brain? A. But we know that they change the brain and we don't know that that's not harmful."). Her concern is completely unreliable however because it ignores what we do know about puberty delaying medication. In other

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[5] It could be argued that Professor Scott's opinions really stem not out of just concern or lack of knowledge, but rather from personal feelings and biases about transgender people. Professor Scott is an active Twitter user. She often uses this platform to comment on a wide variety of topics outside her field of expertise, including transgender issues and treatments for gender dysphoria. In one tweet about a children's book for transgender youth and their families—that she did not read—she called the book a "cheap shot" and "reductive" because it "says that girls who like bugs and wear super hero capes and who don't like pink dresses are in fact boys." [**Exhibit E**]; Tr. 163:6-10; Tr. 164:12-16 ("Q. The book is about addressing that issue with your family. You didn't read the book? A. Well, that was – I've just quoted off the bits I saw. This is – you've asked me why I said it and that's why I said it."). Her rash comments about a children's book she did not read suggest a bias against the trans community.

In another tweet, Professor Scott showed disdain for a scholarship application that allowed applicants to "self-identify" as female. She wrote "Of God" in response to a tweet about the scholarship application. **[Exhibit F]** While her explanation speaks for itself, in summary, she believes that the trans community should be sectioned off from the cis community in what she calls "positive discrimination." Tr. 166:11 – 167:10.

words, her opinion ignores the research we have done on these treatments, none of which shows any significant effects on the brain. *See* Corrected Edmiston Rebuttal Report, ¶¶ 26, 29-30. In sum, Professor Scott's overall discussion about these studies is completely unreliable and should be excluded *in toto*.

b. Decision-making

Her concerns about a teenager's ability to grasp the implications of treatment is equally unreliable because the steps in her "analysis" are disconnected. In paragraphs 8-13 of the Report, Professor Scott explains how the brain develops over childhood and adolescence. Then, at paragraph 14, she says this pattern of brain development "*suggests*" that teenagers are prone to risky decision-making more than adults. From there she somehow concludes it is "very possible" that teenagers are unable to "fully grasp the implications of puberty blocking treatment." Report, ¶ 16.

There are several problems with this "analysis." First, her conclusion about teenagers being prone to risky behavior because of brain development is a guess, just like her concerns over puberty delaying medication. She cannot say with any certainty (or authority) that the pattern of brain development during adolescence leads to more risky behavior in teenagers. The same is true for her ultimate opinion about a teenager's ability to grasp the implications of these treatments. She does not cite a single study that supports this opinion. *McDowell*, 392 F.3d at 1301 (drawing "conclusions where there was no existing data" amounted to a "mere guess" that "fails the tests for expert opinion").

Second, there is a disconnect between the two steps in her analysis. Professor Scott never explains how a tendency toward risky behavior effects a teenager's ability to understand the implications of that behavior. In other words, she never explains how her conclusion about risky behavior leads to her concern over whether teenagers can grasp the implications of puberty delaying treatment. She There is thus a large "analytical gap" in her methodology that renders her ultimate conclusion unreliable. *See Joiner*, 522 U.S. at 146.

For her opinions to be reliable, Professor Scott must have "knowledge," which requires "more than subjective belief or unsupported assumptions." *Daubert*, 509 U.S. at 590. Professor Scott does not have the requisite knowledge for either of her opinions. To assume that her opinions are correct (despite a lack of evidence and experience) would be to rely on her *ipse dixit* based on conjecture to judge the reliability of her conclusion. *See Bowers v Norfolk Southern Corp.*, 537 F.Supp.2d 1343, 1355 (M.D. Ga. 2007) (" The Court cannot rely on [the expert's] *ipse dixit* to judge the reliability of his conclusion[.]").

2. Professor Scott's Opinions are Vague and Imprecise.

Despite her "concerns" over the "potential effects" of puberty delaying medication, *see* Report, ¶¶ 4, 7, Professor Scott does not believe these treatments should be denied to all teenagers with gender dysphoria. She begins her report by saying it is "entirely possible that the use of puberty blockers is appropriate in some exceptional cases of gender dysphoria in prepubescent and adolescent individuals."

Report, ¶ 7. She repeated that sentiment in her deposition. Tr. 13:10-13 ("I think it's entirely possible that there are people, young people who this is an entirely appropriate course of treatment potentially."). When asked about whether she approves of complete bans pertaining to gender-affirming care, like the Challenged Exclusion in this case, Professor Scott could not give a straight answer. On the one hand, she acknowledged that all-inclusive bans on coverage are a bad idea. Tr. 13:22-23 ("I don't think it's a good idea to ban treatment in a blanket way."; Tr. 14:21-23 ("I think it should be something that's worked out in terms of a scientific and medical approach."). On the other hand, she understood she was offering an opinion in support of one such blanket ban. Tr. 12:21 – 13:8. When asked whether she would vote for or against the Challenged Exclusion in this case, she said she would "abstain like a coward." Tr. 16:17.

Opinions like these are too vague and imprecise to be sufficiently reliable. Professor Scott cannot identify when, or under what circumstances, puberty delaying medication may be appropriate for teenagers. She thus cannot say when the unknown risks of these treatments outweigh their benefits. Where she draws the line is completely unknown, making her opinion vague and imprecise. *See Ward v Carnival Corporation*, 2018 WL 11383459, at *6 (S.D. Fla. July 31, 2018) (excluding expert testimony because it was "unclear precisely what [the expert] was claiming.").

Her opinion about a teenager's decision-making ability is equally imprecise. Professor Scott is not certain whether all teenagers are prone to risky behavior, which

is the sole basis for her opinion. Tr. 141:9-19 (Q. Is [riskiness] common for all adolescents?" A. Well, I mean adolescence is very variable like all humans."). Her opinion is also based on research related to decision-making in a "hot context," Report, ¶ 14, which ignores the body of research and peer-reviewed literature on the contextual nature of decision-making in adolescence. Corrected Edmiston Rebuttal Report at ¶ 18 (discussing eleven (11) peer-reviewed papers on the contextual nature of adolescent decision-making). She also omits all literature on decision-making in the medical context and particularly decision-making about treatment of gender dysphoria occurring over several years. These cavernous omissions render her opinion about decision-making in the "hot" context both imprecise and misleading by leaving out the proper context.

3. Professor Scott's Opinions are Far Outside the Mainstream

General acceptance in the relevant scientific community is an important element to the reliability inquiry. See *Allison v. McGahn Medical*, 184 F.3d 1300, 1313 (11th Cir. 1999). Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Professor Scott's opinions about the propriety of puberty delaying treatment is far outside the mainstream of medical and scientific opinion. In fact, her views have been explicitly rejected by every relevant scientific and medical community. Professor Scott says she is "slightly

worried" about using puberty delaying medication to treat even precocious puberty, the indication for which it was originally developed and for which it is approved by the FDA. Tr. 78:7-8; *see id*. 78:14-18 (expressing concerns about using puberty delaying treatment for any purpose because it is not "necessarily . . . safe" and "the data is not 100 percent clear that it doesn't have an effect" on cognitive function); Tr. 156:19-21 ("[M]y primary concern is about puberty blockers and giving them in adolescents and the risk associated with that."). Professor Scott claims she "doesn't know" whether her "concerns with puberty blockers for precocious puberty [are] shared by the medical community." Tr. 78:19-22. In fact, they are not shared, and indeed, run counter to the opinions of mainstream scientists and clinicians. See Corrected Edmiston Report, ¶ 38; Shumer Rebuttal Report ¶¶ 7, 54, 64 (**Exhibit D**); Dekker P.I. Hrg. Tr., at 29:16- 36:18 [ECF 62] (noting that the majority of major medical associations support gender-affirming care for adolescents and adults); *see also, e.g.*, *Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The consensus recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care [include puberty delaying treatment]."") (emphasis added), *aff'd*, 47 F.4th at 671. Because Professor Scott's opinions about puberty delaying treatment are "not generally accepted by the scientific community, and [are] unsupported by other studies" her testimony is unreliable. *Allison*, 184 F.3d at 1319.

D. Professor Scott's Opinions Will Not Assist the Trier of Fact.

Expert testimony is helpful to the trier of fact if it explains subjects that are beyond the understanding of the average lay person. *Frazier*, 387 F.3d at 1262. The testimony must offer more than what lawyers can argue in closing arguments. *Id*. Expert testimony is not helpful if it fails to "fit" with the facts of the case. *McDowell*, 392 F.3d at 1299. This happens when a large analytical leap must be made between the facts and the opinion. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is considered "too great an analytical gap").

Professor Scott's expert testimony will not assist the trier of fact for several reasons. *First*, her opinion about the ability of teenagers to fully grasp their decision to undergo treatment does not "fit" the facts of the case. She references these decisions as if they were made by the adolescent patient alone, that is, without any advice or assistance from medical professionals or other adults. Report, ¶ 16 ("All the evidence we have suggests that the complex, emotionally charged decisions required to engage with this treatment are not yet acquired as a skill at this age, both in terms of brain maturation and in terms of behaviour."). But the reality is that all decisions about whether to administer gender-affirming care are made by a group of individuals including the patient's family and healthcare providers. And, for individuals under 18, these decisions are ultimately made by the patient's parent or legal guardian. Professor Scott acknowledged this point in her deposition. Tr. 146:5-

10 (Q. But we're not talking about teenagers deciding about gender-affirming care themselves in this case, right? A. No. I understand that this would be something where the consent is not with the teenager."). Accordingly, her opinion on teenager decision-making is irrelevant to the facts of the case. *See Kadel*, 2022 WL 3226731, at *14 (excluding Dr. Lappert's opinion on informed consent in the context of gender dysphoria because the patient's father gave consent).

Second, this same opinion is well within the understanding of the average lay person, and it is certainly something counsel can argue in closing. Professor Scott concedes this point in her report when she describes the following as a "lay understanding of what neuroscience is now confirming." She says: "teenage brains on the whole are structurally and functionally different from adult brains, and this affects both their engaging with risky behaviour, and their understanding of the implications of risky behaviour." Report, ¶ 8. She confirmed the same in her deposition. Tr. 143:7-11 ("Q. Do you need to be an expert in neuroscience to understand that teenagers on the whole engage in risky behavior? A. No. Like I said in my report, it's something that all cultures recognize."). Since there already exists a "lay understanding" of her opinion about teenage behavior that "all cultures recognize," her opinion will not assist the trier of fact in this case. It is well-established that untestable "common sense" does not satisfy Rule 702's requirements. *See Fedor v. Freightliner, Inc.*, 193 F.Supp.2d 820, 832 (E.D. Pa. 2002) ("Generalized common sense does not rise to the level of expert opinion solely

because it is offered by someone with an academic pedigree.").

Third, her opinion about the unknown effects of puberty delaying medication is also within the understanding of the average person. The Court does not need an expert to explain the things we do not know. These can easily be explained in closing argument. *See Frazier*, 387 F.3d at 1262 ("Proffered expert testimony generally will not help the trier of fact when it offers nothing more than what lawyers for the parties can argue in closing arguments.").

Fourth, as noted above, her opinion about puberty delaying medication is based in part on animal studies without any connection to the treatment of gender dysphoria in humans. Report, ¶ 15; Tr. 71:11-15. Professor Scott does not even attempt to link these animal studies to humans, and as a result, such studies do not offer any support for her conclusions about the human brain. Therefore, they do not assist the trier of fact. *Joiner*, 522 U.S. at 146; *Kilpatrick*, 613 F.3d at 1338.

CONCLUSION

WHEREFORE, based on the foregoing, Plaintiffs respectfully request that the Court grant the instant Motion and exclude Professor Scott's expert report, opinions and testimony in their entirety under *Daubert* and the Federal Rules of Evidence.

* * *

Respectfully submitted this 7th day of April, 2023.

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CERTIFICATE OF WORD COUNT

According to Microsoft Word, the word-processing system used to prepare this Motion and Memorandum, there is a combined total of 5,455 words in the Motion and the Memorandum of Law.

/s/ Gary J. Shaw
Gary J. Shaw

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for the Plaintiffs conferred with counsel for the Defendants on April 5, 2023. Counsel for Defendants indicated that same day that Defendants oppose the relief sought.

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by email on April 7, 2023, on all counsel of record:

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TAB 127

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO PARTIALLY EXCLUDE EXPERT TESTIMONY OF DR. PATRICK W. LAPPERT AND INCORPORATED MEMORANDUM OF LAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and Rule 702, Plaintiffs move to partially exclude certain testimony of Defendants' expert Dr. Patrick W. Lappert, M.D., on the grounds that he fails to meet the qualification, reliability, and helpfulness requirements imposed by Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993). Specifically, Dr. Lappert's testimony should be limited to his area of expertise: the field of plastic surgery. To the extent that any of Dr. Lappert's purported opinions beyond plastic surgery hold any probative value (they do not), it is far outweighed by unfair prejudice and confusion of the issues and therefore the testimony should

be excluded pursuant to Fed. R. Evid 403. In support of this motion, Plaintiffs state as follows:

FACTUAL BACKGROUND

On February 17, 2023, Defendants served their expert witness disclosures for Dr. Lappert and thereafter provided his rebuttal opinions.[1] His rebuttal opinions were primarily directed to the reports of Dr. Loren S. Schechter, M.D., and Dr. Johanna Olson-Kennedy, M.D., M.S. Lappert Rebuttal ¶ 1.

In his reports, Dr. Lappert opines on numerous subjects that fall well outside the scope of his experience in plastic surgery, including the nature, causes, and diagnosis of gender dysphoria, non-surgical treatments for gender dysphoria, the quality of the evidence supporting medical treatments for gender dysphoria, and the development of clinical practice guidelines by professional medical associations of which he is not even a member. *See generally*, Lappert Rep.; Lappert Rebuttal.

However, as a retired plastic surgeon, Dr. Lappert is not qualified to offer expert testimony on these matters. Indeed, in a prior case in the Middle District of North Carolina involving a challenge to a categorical exclusion of gender-affirming health services from coverage through a state-sponsored health plan, the District Court precluded the vast majority of Dr. Lappert's proffered opinions based on his

[1] *See* Declaration of William Miller ("Miller Dec.") ¶¶ 4-5; Ex. A, Expert Declaration of Patrick W. Lappert, M.D. ("Lappert Rep."); Ex. B, Rebuttal Expert Report of Patrick W. Lappert, M.D. ("Lappert Rebuttal").

lack qualifications and the unreliability of his testimony, limiting his testimony solely to those opinions related to the field of plastic surgery. *Kadel v. Folwell*, Case No. 1:19CV272, 2022 WL 3226731, *13-14 (M.D.N.C. Aug. 10, 2022).[2] Notably, the Court also found that the available evidence "call[ed] Lappert's bias and reliability ***into serious question***." *Id*. at *12 (emphasis added).

Similarly, in *Brandt v. Rutledge*, the court curtailed Dr. Lappert's testimony even further, limiting Dr. Lappert to offering opinions solely "to his practice," "to what he has personally done in his practice," and "his actual interaction with patients and what the outcomes were." Miller Dec. ¶ 6; Ex. C, Excerpts of *Brandt v. Rutledge* Trial Transcript ("*Brandt* Tr."), at 1058:25, 1059:11-15. Indeed, the court sustained objections that sought to elicit Dr. Lappert's testimony about what the clinical practice guidelines pertaining to gender-affirming medical treatment entail and any specific risks for transgender individuals because Dr. Lappert "is not an expert in gender-affirming care" and such testimony "is outside the scope of the doctor's practice." *Brandt* Tr. 1058:4-10, 1067:10-14.

This Court should do the same. Dr. Lappert lacks the necessary qualifications to so testify regarding any subject matter beyond the field of plastic surgery,

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[2] Specifically, the court in *Kadel* held that Dr. Lappert was "limited to testifying to (1) the risks associated with the surgeries at issue in this case; (2) his anecdotal experience treating patients seeking to "de-transition"; and (3) the WPATH recommended role of the surgeon in treating gender dysphoria as compared to the role of the surgeon in other surgical contexts." 2022 WL 3226731, at *15.

including as to the nature, causes, or diagnosis of gender dysphoria, non-surgical treatments for gender dysphoria, the quality of evidence supporting medical treatments for gender dysphoria, and the development of clinical practice guidelines for the treatment of gender dysphoria, and any such testimony is otherwise unreliable, unhelpful, or its probative value is outweighed by potential prejudice.

LEGAL STANDARD

Federal Rule of Evidence 702 places "a special gatekeeping obligation" on the trial court to ensure that an expert's testimony is "relevant to the task at hand" and "rests on a reliable foundation." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993). As articulated by the Eleventh Circuit, "[t]he importance of Daubert's gatekeeping requirement cannot be overstated." *United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004).

In determining admissibility under Rule 702, courts must engage in a "rigorous" inquiry to determine whether (1) the expert is qualified to testify regarding the matters they intend to address; (2) the methodology employed by the expert to reach their conclusions is sufficiently reliable, as determined by the inquiry mandated under *Daubert*; and (3) the testimony assists the trier of fact to understand the evidence or determine a fact at issue. *Id.*, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). These considerations of "qualification," "reliability," and "helpfulness"

are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). Crucially, the party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260.

ARGUMENT

I. Dr. Lappert Is Not Qualified to Offer a Significant Portion of His Purported Opinions

"A witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342. But "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject and instead relied on studies to form his opinion). "A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Id.* (quoting *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002)). Indeed, even "a supremely qualified expert cannot waltz into the courtroom and render opinions unless those opinions are based upon some recognized scientific method and are reliable and relevant." *Clark v. Takata Corp.*, 192 F.3d 750, 759 n.5 (7th Cir. 1999).

If a designated expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," the expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)). Simply put, "an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Martinez v. Sakurai Graphic Sys. Corp.*, 2007 WL 2570362, at *2 (N.D. Ill. Aug. 30, 2007).

Indeed, the qualification inquiry is subject-specific because "[g]eneralized knowledge of a particular subject will not necessarily enable an expert to testify as to a specific subset of the general field of the expert's knowledge." *Id.*, at *2. "For example, no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F. Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994). Here, Dr. Lappert's opinions topics relating to plastic surgery fail to meet the most basic standard for admissibility and must be excluded.

A. Dr. Lappert is Not Qualified to Offer Opinions on Topics Other Than Plastic Surgery

Dr. Lappert offers a clutter of opinions far afield from his experience as a plastic surgeon, including regarding the fields of endocrinology, psychology,

psychiatry, and treatment guidelines issued within those specialties. But Dr. Lappert lacks the necessary qualifications, or any other basis, to offer an expert opinion in these areas.[3] To be clear, Dr. Lappert has previously testified he "do[es] not claim to be an expert in the treatment of gender dysphoria." *Brandt* Tr. 1042:13-15.

Recognizing Dr. Lappert's lack of expertise on precisely the same subjects on which he purports to opine in this case, the court in *Kadel* precluded Dr. Lappert from providing expert testimony on matters outside the realm of plastic surgery and his anecdotal experiences as a surgeon. *See* 2022 WL 3226731 at *12-15. Similarly, at trial, the Court in *Brandt* limited his testimony solely "to his practice," "to what he has personally done in his practice," and "his actual interaction with patients and what the outcomes were." *Brandt* Tr. 1058:25, 1059:11-15. The Court should adopt the same approach here.

For example, Dr. Lappert proselytizes on the efficacy of hormone therapy as a treatment for gender dysphoria, and on the reliability of peer-reviewed medical

[3] Although Plaintiffs do not move to exclude Dr. Lappert's opinions, however fringe, within his own field, it must be noted that he has conceded that he has "never performed any kind of gender-affirming surgery in transgender patients." Miller Dec. ¶ 7; Ex. D, Excerpts of Sept. 30, 2021 Deposition Transcript ("Lappert Tr."), at 168; *id.* at 151 ("I have never treated a patient with gender dysphoria surgically."). He has also emphatically stated that he would never perform such surgeries, because in his personal view he does not "see them as beneficial" and thinks they are "incorrect treatments." *Id.* at 150. Indeed, Dr. Lappert believes that "in all instances" gender-affirming genital surgery is "an irreversible mutilation[.]" Lappert Rep. ¶ 42.

publications, and in particular clinical practice guidelines issued by the Endocrine Society (the nationally recognized professional society for endocrinologists), cited as support for the use of such treatments. *See* Lappert Rep. ¶¶ 33, 38-42. Dr. Lappert further purports to opine on the nature of, and differences between, gender and sex. *Id.* ¶¶ 31-32. But Dr. Lappert has previously conceded that he is "not an endocrinologist" and has "no specialized training or expertise in endocrinology." Lappert Tr., at 153, 204; *see also Brandt* Tr. 1040:22-25 ("Q And you're not an endocrinologist? A I am not. Q You're not an expert in endocrinology? A I am not.").

Dr. Lappert likewise admitted that he has "never prescribed cross-sex hormones for treatment of gender dysphoria," and that he has "no firsthand experience with advising [his] patients about potential risks and benefits" of such treatment. Lappert Tr., at 214. He has acknowledged that he does not "hold [himself] out as an expert in endocrinology," and indicated in a prior case that he did not plan to offer "any expert opinions in endocrinology . . . because that's outside [his] scope of expertise." Lappert Tr., at 204. Accordingly, as previously held in *Kadel*, all of Dr. Lappert's purported opinions relating to endocrinology should be excluded. *Kadel*, 2022 WL 3226731 at *13.

Dr. Lappert likewise is not qualified to opine regarding the development or efficacy of the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition ("DSM-V"), the diagnosis of gender dysphoria, or the treatment of gender dysphoria

by a mental health provider. *See, e.g.*, Lapper Rep. ¶¶ 46, 74-76, 93-94. The reasoning in *Kadel* applies equally here. Dr. Lappert "is not a psychiatrist, psychologist, or mental health professional, nor has he ever diagnosed a patient with gender dysphoria," but he nonetheless provides opinions in these areas. *Kadel*, 2022 WL 3226731 at *13. Dr. Lappert himself has acknowledged that he "do[es] not hold [himself] out as an expert in diagnosing mental health conditions[,]" and that he also does "not have special[ized] training or expertise in treating mental health conditions." Lappert Tr., at 75; *see also Brandt* Tr. 1041:6-8 ("Q You don't claim to be an expert in the diagnosis of gender dysphoria? A Expertise, no. … ."). He further admitted that he has never been involved in the development of the DSM-V, and does not know "what kind of scientific literature review was done" during that development or what went on during "different meetings or conferences" to "discuss that development[;]" thus, Dr. Lappert "do[es] ***not have expert firsthand knowledge*** of how the DSM-V was developed." Lappert Tr., at 190-93 (emphasis added).

In sum, Dr. Lappert's ability to read and regurgitate information pertaining to the treatment of gender dysphoria does not qualify him as an expert. Because Dr. Lappert's purported opinions about matters within the fields of psychology, psychiatry, and endocrinology are outside of his training and expertise, such opinions should be precluded, as they were in *Kadel* and *Brandt*. *See Kadel*, 2022 WL 3226731 at *12-15; *see also, e.g.*, *Lebron*, 772 F.3d at 1368-69.

B. Dr. Lappert is Not Qualified to Opine on the Quality of the Studies Supporting Gender-Affirming Care

Aware that his views on gender dysphoria and gender-affirming care are contradicted by the position of every major medical society and professional organization in the country, Dr. Lappert goes to great lengths to attempt to undermine the validity and basis of a select few of the multitude of medical studies that support the safety and efficacy of gender-affirming care by pointing out what he perceives as methodological flaws. *See, e.g.*, Lappert Rep ¶¶ 38-41, 58-67, 85-87; Lappert Rebuttal ¶¶ 8, 11-12, 16-22. He repeatedly contends that the existing studies do not constitute "quality evidence," and as a result, gender-affirming care is experimental or unsupported by reliable science. *See* Lappert Rep. ¶¶ 24-25, 57, 59, 106; Lappert Rebuttal ¶ 25. But once again, such opinions are far afield from Dr. Lappert's professional experience.

As the court in *Kadel* noted, Dr. Lappert is "not a statistician or epidemiologist, and there is no evidence . . . that he has any experience, specialized training, or knowledge about crafting a research study, analyzing data, or conducting a clinical trial." *Kadel*, 2022 WL 3226731 at *13. Given his lack of personal experience with the study of gender-affirming care, the court in *Brandt* similarly limited his testimony to "to what he has personally done in his practice, not what the evidence shows." *Brandt* Tr. 1059:9-13. Indeed, Dr. Lappert's prior publications (seven in total) include case reports and opinion essays, and he has not published in

a peer-reviewed journal in over ***twenty-five years***. *See* Lappert Rep., at 69 (curriculum vitae). His curriculum vitae notes a brief academic career, but that role appears limited to overseeing clinical practitioners and did not involve conducting research or clinical trials of any kind. *See id*., at 68; *see also Kadel*, 2022 WL 3226731 at *13.

In sum, as the court in *Kadel* noted, "[j]ust as an epidemiologist or statistician would not be qualified to perform surgery, a surgeon with little to no research experience is not qualified to opine of the veracity of statistical studies." *Kadel*, 2022 WL 3226731 at *13. Accordingly, Dr. Lappert's proffered opinions regarding the validity or veracity of studies pertaining to gender-affirming care or gender dysphoria should be excluded.

II. Dr. Lappert's Opinions on Topics Other than Plastic Surgery are Also Either Unreliable, Unhelpful, or Both

As a rule, an expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The reliability requirement in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage, the court must undertake an independent analysis of each step in the logic leading to

the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

To satisfy the helpfulness requirement, the proffered testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Daubert*, 509 U.S. at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* Where the court determines that proffered expert testimony does not "fit" the facts of the case, it is properly excluded. *See id.*, at 1301.

Here, Plaintiffs' case turns primarily on two issues, among others, (1) whether the Agency employed a process that was reasonable and (2) whether gender-affirming medical care is experimental or investigational. Many of Dr. Lappert's opinions are both unreliable and unhelpful to the issues before this Court, as detailed below.

A. Dr. Lappert's Opinions are Rejected by the Vast Majority of the Scientific and Medical Community and Lack Credible Support

General acceptance in the relevant scientific community is an important element to the reliability inquiry. *Allison v. McGhan Medical Corp*., 184 F.3d 1300, 1313 (11th Cir. 1999). Moreover, the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Lappert's opinions about the effectiveness and propriety of gender-affirming care, which he is not qualified to present, are far outside the mainstream of medical and scientific opinion and have been explicitly rejected by every relevant scientific and medical community. While undoubtedly Dr. Lappert "has strong beliefs," the fact that his opinions are "not generally accepted by the scientific community, and [are] unsupported by other studies" means that "his testimony is based more on personal opinion than on scientific knowledge," making it unreliable. *Allison*, 184 F.3d at 1319.

Dr. Lappert cites virtually no evidentiary support for his critiques of medical studies substantiating the need for gender-affirming care. *See generally*, Lappert Rep.; Lappert Rebuttal. And to the contrary, the evidence shows that Dr. Lappert's opinions regarding the supposedly "experimental" nature of gender-affirming care are on the scientific fringe. *See, e.g.*, Lappert Rep. ¶¶ 23, 97-98; Lappert Rebuttal ¶¶ 21-22, 25 n. 3. For example, in a recent case addressing a challenge to Arkansas' state-law ban on gender-affirming treatment for minors, Dr. Lappert offered

substantially similar opinions in support of the ban, contending that "[g]ender affirming' treatments are experimental[.]" *See Brandt v. Rutledge*, 551 F.Supp.3d 882 (E.D. Ark. 2021); Lappert Tr., at 33-35; Miller Dec. ¶ 8; Ex. E, Declaration of Dr. Lappert in *Brandt v. Rutledge*.

Nevertheless, the *Brandt* court preliminarily enjoined the ban, recognizing that "the consensus recommendation of medical organizations is that the only effective treatment for . . . gender dysphoria is to provide gender-affirming care," citing briefs from organizations like the American Medical Association, American Academy of Pediatrics, and many more. *Brandt*, 551 F.Supp.3d at 890 n.3. *Brandt* also found that "gender-affirming treatment is supported by medical evidence that has been subject to rigorous study," and that "every major expert medical association recognizes that gender-affirming care for transgender minors may be medically appropriate and necessary to improve the physical and mental health of transgender people." *Id.*, at 891; *see also Fain v. Crouch*, Case No. 3:20-0740, 2022 WL 3051015, *10 ("[m]any of the major medical organizations have opposed the blanket denial of this medically necessary [gender-affirming] care.").

Dr. Lappert himself has previously acknowledged that "every major expert medical association disagrees with [him] because they've all taken [the] position that this treatment is in fact medically necessary." Lappert Tr., at 40. Dr. Lappert's own

former association, the American Society of Plastic Surgeons[4] ("ASPS") (whose categorizations of evidence for prognostic and therapeutic studies Dr. Lappert repeatedly relies upon in critiquing the studies and evidence in support of gender-affirming care) issued a statement in February 2021 stating that it "firmly believes that plastic surgery services can help gender dysphoria patients align their bodies with whom they know themselves to be," and promising to "continue its efforts to advocate across state legislatures for full access to medically necessary transition care." Miller Dec. ¶ 9; Ex. F, Feb. 25, 2021 ASPS Statement. So as Dr. Lappert has admitted, the ASPS also "does not agree with [his] opinions that gender affirming surgery is experimental." Lappert Tr., at 112-13. In short, the overwhelming consensus confirms that, far from being generally accepted, Dr. Lappert's opinions regarding gender-affirming care are unsupported and unreliable.

B. Dr. Lappert's Critiques of the WPATH Standards of Care, the Endocrine Society Guidelines, and Other Organizations' Positions Are Unreliable

Given that his views are unsupported by any reliable scientific evidence, and indeed run contrary to the position of every major medical society and professional organization, Dr. Lappert attempts to discredit the clinical guidelines and standards of care espoused by these respected organizations, including the World Professional

[4] Dr. Lappert's report misidentifies his own former professional organization as the "American Society of Plastic Surgery." *E.g.*, Lappert Rep. ¶ 24.

Association for Transgender Health ("WPATH") and the Endocrine Society. For example, Dr. Lappert asserts that "the WPATH standard of medical necessity is not supported in reliable scientific evidence" and he purports to "examine how such guidelines are developed." Lappert Rep. ¶¶ 36, 51; *see also, e.g.,* Lappert Rebuttal ¶ 8 (contending that the "evidence cited in support of the WPATH Standard reveals a lack of evidence even to support a weak recommendation in a treatment guideline.").

But Dr. Lappert has previously conceded that he was "not involved with the development" of WPATH guidelines, he did not "know what kind of scientific literature [review] the WPATH conducted as part of drafting" the guidelines, or what other forms of "peer review," "outside experts," or "public comments" the WPATH may have relied on in developing their guidelines. Lappert Tr., at 184-87. To the point, Dr. Lappert admitted that he is "***not an expert***" in the development of either versions 7 or 8 of the WPATH standards of care. *Id.*, at 188-89. The court in *Kadel* agreed, precluding Dr. Lappert's views on the WPATH standards as "unscientific opinion and speculation." *Kadel*, 2022 WL 3226731 at *14. So did the court in *Brandt*, which sustained an objection to an attempt to elicit testimony from Dr. Lappert as to what the WPATH guidelines mean. *Brandt* Tr. 1058:4-10.

Dr. Lappert similarly opines that the "scientific evidence used to support the Endocrine Society's special treatment guidelines for gender dysphoric/gender

incongruent persons appears to be of low to very low quality[.]" Lappert Rep. ¶ 38. Yet Dr. Lappert has admitted that he does not know when these guidelines "were initially published" or "last revised;" he was "not involved with the[ir] development;" he does not know "what kind of scientific literature review" went into that development; thus, he agreed he is "not an expert in how the Endocrine Society developed the original 2009 guidelines" or "the 2017 updates." Lappert Tr., at 195-200.

At bottom, Dr. Lappert has no expertise or understanding of the development of the WPATH or Endocrine Society guidelines, and therefore his criticism of the evidence in support of these standards is unreliable. *See Kadel*, 2022 WL 3226731 at *14. Consequently, he should not be permitted to mislead a factfinder with his baseless *ipse dixit* critiques. *See Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997).

C. Dr. Lappert's Opinions Regarding Informed Consent, "Desistance," and Changes in Demographics are Unreliable, Unhelpful, and Irrelevant.

Dr. Lappert dedicates a portion of his report to his opinions on whether patients diagnosed with gender dysphoria can provide "meaningful consent" to gender-affirming treatment, and he makes a number of claims regarding statistics pertaining to the supposed "resolution" of the condition of "transgenderism" absent gender-affirming care, and changes in the rates of diagnosis and makeup of the population of individuals diagnosed with gender dysphoria. *E.g.*, Lappert Rep. ¶¶

69-70, 73. But these purported opinions are unreliable, unhelpful, and irrelevant to the issues before the Court.

First, Dr. Lappert has failed to support his opinions regarding "informed consent" with any credible evidence or data. *See generally*, Lappert Rep. Accordingly, his conclusions regarding informed or meaningful consent are speculative and unreliable and should be excluded. *See Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988) ("relevant testimony from a qualified expert is admissible only if the expert knows of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation."); *see also Hendrix*, 255 F.R.D. at 578; *Kadel*, 2022 WL 3226731, at *14 (concluding that Dr. Lappert's opinions regarding informed consent to gender-affirming care were "irrelevant" and "not admissible.").

Second, Dr. Lappert's opinions that gender dysphoria may resolve on its through his mischaracterizing description of "watchful waiting" (e.g., Lappert Rep. ¶¶ 93, 94, 98) are based on a severely flawed reading of the literature, which renders his opinions unreliable, and regardless, such opinions are also irrelevant. Specifically, Dr. Lappert cites a single article by Zucker et al. in support of this proposition. But that study pertains to (1) *preadolescent/prepubertal* youth not *adolescents after the onset of puberty* and (2) who were diagnosed with *gender identity disorder* under the DSM-III or the DSM-IV not *gender dysphoria* under the

DSM-V. It is therefore inapplicable and irrelevant in this context, where the changes from the DSM-IV diagnosis of gender identity disorder to the DSM-V diagnosis of gender dysphoria in 2013 made "the diagnosis more restrictive and conservative" to reduce "false positives." *See* Miller Dec. ¶ 10; Ex. G, Memo Outlining Evidence for Change for Gender Identity Disorder, at 904-05.

Dr. Lappert's assertions are also flawed because they misrepresent Dr. Zucker's work. Indeed, Dr. Zucker authored the chapter in "Gender Dysphoria and Gender Incongruence" in the medical textbook *Lewis's Child and Adolescent Psychiatry, Fifth Edition*, published in 2018. *See* Miller Dec. ¶ 11, Ex. H, Excerpt of *Lewis's Child and Adolescent Psychiatry, Fifth Edition*. That chapter states that: (1) "it appears that the vast majority of transgender adolescents persist in their transgender identity," *id.* at 638; and (2) "Once children have reached puberty, transgender identity persists in the vast majority of cases, and medical intervention is often considered[.]" *Id.* at 640. Given that this case pertains to gender-affirming medical treatments which are not provided until after the *onset of puberty*, Dr. Lappert's opinions, premised on his flawed reading and understanding of the "desistance" literature, are irrelevant and unreliable.

Third, Dr. Lappert's opinions regarding a change of demographics are wholly unreliable and irrelevant. Lappert Rep. ¶ 73. He cites no scientific or peer-reviewed literature. To the contrary, he cites solely to a non-medical, non-scientific book by

an anti-transgender activist.[5] But Rule 703 requires that "[t]he facts or data … upon which an expert bases an opinion or inference" must be "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject," Fed. R. Evid. 703, and the book upon which Dr. Lappert relies is *not* the type of material reasonably relied upon by experts in any field of medicine. Moreover, Dr. Lappert's opinion is irrelevant. Gender dysphoria is a real and recognized condition that requires treatment – whether the demographics have changed has no bearing on that or the questions before the Court.

D. Dr. Lappert's Commentary on Gender-Affirming Care Provided in Other Countries is Unreliable and Unhelpful

Dr. Lappert also offers opinion regarding the treatment of gender dysphoria and the provision of gender-affirming care in certain European countries, including the United Kingdom, Sweden, Finland, France, and Italy, and cites developments in those countries as evidence in support of his opinions proffered in this case. *See* Lappert Rep. ¶¶ 104-05; Lappert Rebuttal ¶ 24. But, according to the curriculum vitae he supplied, Dr. Lappert is not licensed to practice in any of those countries. *See* Lappert Rep., at 67-69. His report and rebuttal report likewise offer no

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[5] Abigail Shrier is not a doctor but an anti-transgender activist and opinion columnist. She has described transgender rights as a "war on women" and has advocated against what she considers to be a "transgender craze." GLAAD, GLAAD Accountability Project: Abigail Shrier, https://www.glaad.org/gap/abigail-shrier (accessed Apr. 6, 2023).

indication that Dr. Lappert has personal knowledge regarding the policies regarding gender-affirming care issued in those countries or how those policies were developed. *See generally*, Lappert Rep.; Lappert Rebuttal. Dr. Lappert also either wholly fails to cite any facts or data in support of his opinions regarding developments in these countries, or the data he cites is insufficient to support those opinions. *See* Lappert Rep. ¶¶ 104-05; Lappert Rebuttal ¶¶ 24-25. Consequently, the Court should exclude Dr. Lappert's testimony regarding such opinions. *See Jones*, 861 F.2d at 662.

III. Dr. Lappert's Opinions are Based on His Personal Beliefs and Not Science

Reliability is a flexible inquiry, under which "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 281 (4th Cir. 2021); *see also Jones*, 861 F.2d at 662 ("relevant testimony from a qualified expert is admissible only if the expert knows of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation."). Here, there is abundant evidence that Dr. Lappert's opinions are so tainted by his strong personal views against gender-affirming care as to render those opinions unreliable. Although Plaintiffs of course do not seek to impugn any moral or religious views that Dr. Lappert may hold, those views plainly inform the opinions he proffers in this case (and indeed appear to be the primary motivation for those opinions), and

therefore the Court must consider those views in assessing the reliability of Dr. Lappert's conclusions.

Dr. Lappert has previously testified that he has "strong personal opinions on whether doctors should be providing gender-affirming treatment to minors." Lappert Tr., at 78. That is an understatement. He has previously lobbied state legislatures in, at a minimum, Utah, Arkansas, Alabama, Texas to pass laws or regulations that would ban doctors from providing gender-affirming medical care to adolescents. *See id.*, at 57, 61-62; *id.* at 54-55 (agreeing he has "actively lobbied to get these kinds of bans passed"). In Alabama he spoke in favor of a ban on gender-affirming care for adolescents, and "publish[ed] an op-ed" that urged the legislature to protect what he called "gender-confused children." *Id.*, at 76, 63-64. He argued to the Utah legislature that "you can't change a person's sex," and that "all that is happening is that the patient is undergoing an intentional mutilation in order to create a counterfeit appearance of the other sex." *Id.*, at 57-60.

Dr. Lappert also affirmed in deposition testimony that he "absolutely" considers "gender reassignment surgery to be an intentional mutilation." *Id.*, at 60. He further testified that he would like to see doctors who perform these gender-affirming surgeries to be "criminally prosecute[d] – confirming that he thinks "that's a good idea." *Id.*, at 52. Dr. Lappert went so far as to confirm in his report in this

case that "in all instances" gender-affirming genital surgery is "an irreversible mutilation[.]" Lappert Rep. ¶ 42.

Dr. Lappert has also worked hand in hand with the Alliance Defending Freedom ("ADF"), an organization he agrees has "moral objections" to gender-affirming healthcare. Lappert Tr., at 81. Among other things, he attended an ADF conference that discussed the "poverty of [experts] who are willing to testify" about these anti-gender-affirming treatments. *Id.*, at 90-91. Attendees at that conference "were asked whether they would be willing as participate as expert witnesses[;]" not coincidentally, Dr. Lappert became an expert witness for the first time after attending that conference. *Id.*, at 91; *see also Brandt* Tr. 1080:5-1081:11. In this sense, Dr. Lappert is the definition of a manufactured "expert witness" who "developed his opinions expressly for purposes of testifying" in an area that he did not otherwise specialize in. *Lebron*, 772 F.3d at 1369.

Dr. Lappert's public interviews and presentations reinforce his vehement opposition to any form of gender-affirming care. These include, for example, his views that the religious conception of "the human person" "defines the 'end' of medical and surgical care." Lappert Tr., at 459. They also include his opinions that "changing a person's sex is a lie and also a moral violation for a physician," and that gender-affirming surgery is "diabolical in every sense of the word." *Id.*, at 464-65; *see also* Miller Dec. ¶ 12; Ex. I, Article titled *Plastic surgeon: Sex-change operation*

'utterly unacceptable' and a form of 'child abuse' ("LifeSite Article"), at 1, 7; Lappert Tr., at 465 (agreeing that he "hold[s] those views"). And finally, these also include his inflammatory views that parents who "discuss[] gender identity issues with children" are "sexualizing them" (Lappert Tr., at 462), and that these conversations are "grooming a generation" for abuse. *Id.* at 461; Miller Dec. ¶ 13; Ex. J, Presentation by Dr. Lappert titled "Transgender Surgery & Christian Anthropology," at 24; *see also* LifeSite Article, at 1, 2 (reporting that "regarding children, Lappert said, sexualizing them at a young age with these ideas is grooming them for later abuse.").

As the court in *Kadel* found, these positions call "Lappert's bias and credibility into serious question." *Kadel*, 2022 WL 3226731, at *12.

IV. Dr. Lappert's Opinions Lack Probative Value and are Therefore Neither Helpful to the Fact-Finder Nor Admissible Under Fed. R. Evid. 403

Finally, the Court should exclude the opinions and testimony of Dr. Lappert outside the field of plastic surgery because introduction of those opinions will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. As articulated above, Dr. Lappert's non-surgical opinions are irrelevant to the issues in this case, and are otherwise speculative, unhelpful, and unreliable. His testimony outside of his discipline would also result in prejudice, as it would sow confusion about the propriety of gender-confirming care based on speculation and irrelevant, misleading, and biased opinions. Accordingly, to the extent not

excluded for the reasons detailed above, Dr. Lappert's opinions outside of plastic surgery should be precluded under Rule 403.

CONCLUSION

For the foregoing reasons, the Court should exclude any opinion proffered by Dr. Lappert outside the field of plastic surgery and limit his testimony to the provision of surgical care generally.

Dated: April 7, 2023

Respectfully Submitted,

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CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Motion and Incorporated Memorandum of Law contains 5,753 words.

/s/ William C. Miller
Attorney for Plaintiffs

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for Plaintiffs and counsel for Defendants conferred regarding the instant motion during a Zoom conference on April 6, 2023. Defendants indicated they do not consent to the relief requested herein.

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April, 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ William C. Miller
Attorney for Plaintiffs

TAB 133

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE
EXPERT TESTIMONY OF MICHAEL LAIDLAW

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702, Plaintiffs respectfully move this court to exclude the expert testimony of Defendants' proposed expert, Dr. Michael Laidlaw. As explained more fully below, Dr. Laidlaw is not a qualified expert and his opinions and testimony are neither reliable nor helpful to the trier of fact pursuant to the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible pursuant to Fed. R. Evid. 403. As grounds, Plaintiffs state:

1. Defendants propose Dr. Laidlaw, an adult endocrinologist, as their expert and submitted a report with their Rule 26 Disclosures. (Exhibit 1, Laidlaw Expert Report.)

2. According to Dr. Laidlaw's expert report, he was retained in this case to provide "expert opinion on the efficacy and safety of sex reassignment treatment." (Ex. 1, ¶ 5).

3. Yet Dr. Laidlaw's expert reports also contain opinions about the causes, diagnosis, and treatment of gender dysphoria, including the use of puberty-delaying medication, hormone treatment, and surgery, the propriety of the physician-recommended treatment received by the Plaintiffs, as well as their physical and mental health. (Ex. 1, Exhibit 2, Laidlaw Rebuttal Report, Exhibit 3, Laidlaw Declaration in support of Defendants' Opposition to Preliminary Injunction).

4. Dr. Laidlaw also submitted a declaration in support of Defendants' Response in Opposition to Plaintiffs' Motion for Preliminary Injunction. (Ex. 3).

5. Defendants have not met their burden of establishing that Dr. Laidlaw is qualified to proffer an opinion on the assessment of gender dysphoria generally, or regarding his alleged concerns related to the assessment of Plaintiffs in particular, nor have they established that Dr. Laidlaw is qualified to testify about the appropriateness of surgery to treat gender dysphoria generally, or the

appropriateness of any surgeries received by Plaintiffs in the past or any surgical procedures they might undergo in the future. Dr. Laidlaw is not a mental health professional or a surgeon, has never provided treatment for gender dysphoria, he has never conducted any original research on the issue nor published any peer-reviewed literature on these matters, has never diagnosed a patient with gender dysphoria, and has only treated one patient with gender dysphoria nearly two decades ago.

6. Defendants similarly have not met their burden of showing that Dr. Laidlaw's opinions are reliable. The opinions offered in his reports and testimony on the effectiveness of gender-affirming care, the harms it may pose, "desistence," informed consent, and WPATH fall outside of his qualifications, are based on speculation and ipse dixit, and lack any reliable scientific methodology.

7. Nor have Defendants met their burden of showing that Dr. Laidlaw's opinions are relevant. Dr. Laidlaw offers opinions and testimony regarding the number of people diagnosed with gender dysphoria, human sexual development, the difference between gender identity and biological sex (including whether biological sex can be changed), social transition, and the policies of other counties. None of this testimony has a connection to the existing data or issues in this case and are therefore not helpful to the trier of fact.

8. The probative value of Dr. Laidlaw's testimony is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence.

WHEREFORE, Plaintiffs Request that the Court enter an Order excluding Dr. Laidlaw's opinions in this case, except as they relate to the risks associated with puberty suppressing medication and hormone therapy, including those contained in his expert declaration (Ex. 1), and rebuttal declaration (Ex. 2), and prohibit Defendants from relying on testimony for any purpose other than describing the risks associated with puberty suppressing medication and hormone therapy for any purpose during trial.

MEMORANDUM OF LAW

The vast majority of Dr. Laidlaw's opinions and testimony lack any indicia of admissibility required under *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and the Federal Rules of Evidence. This testimony should be excluded because Dr. Laidlaw is not qualified to serve as an expert witness on matters beyond the scope of his expertise as an adult endocrinologist, and his opinions and testimony are not reliable, helpful to the trier of fact, or probative of the issues in this case.

I. LEGAL STANDARD

Federal Rule of Evidence 702 governs the admissibility of expert testimony. *Daubert* requires district courts, pursuant to Rule 702, to perform a critical "gatekeeping" function concerning the admissibility of expert scientific evidence, ensuring that the testimony or evidence is both relevant and reliable. *Daubert*, 509 U.S. at 597; *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of Daubert's gatekeeping requirement cannot be overstated.").

In determining the admissibility of expert testimony under Rule 702, courts engage in a "rigorous" three-part inquiry and must consider whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). The party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592. (emphasis added). "Rule 702 applies whether the trier of fact is a judge or a jury." *UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 832 (3d Cir. 2020); *see also Kadel v. Folwell*, 2022 WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (granting motions to exclude in the context of summary judgment).

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403.

Here, Defendants have failed to demonstrate that the majority of Dr. Laidlaw's proffered testimony is relevant and meets the requirements of Rule 702 as interpreted by *Daubert*, or the requirements of Rule 403. It should be excluded.

II. DR. LAIDLAW'S OPINIONS THAT GO BEYOND HIS QUALIFICATIONS AS AN ADULT ENDOCRINOLOGIST SHOULD BE EXCLUDED.

It is axiomatic that "[a] witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342; Fed. R. Evid. 702. However, credentials are not dispositive when determining qualification, particularly where an expert offers testimony in areas outside of their knowledge, skill, experience, training, or education. "Expertise in one field does not qualify a witness to testify about others." *Lebron v. Secretary of Florida Dept. of Children and Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). If a potential expert witness does not "propose to testify about matters

growing naturally and directly out of research he had conducted independent of the litigation," that testimony should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

Dr. Laidlaw offers numerous opinions related to areas of medicine far afield from his experience and training as an endocrinologist. He is unqualified to offer these opinions, since "no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F.Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994). Here, Dr. Laidlaw, an adult endocrinologist,[1] is not qualified to render most of the opinions he proffers. Dr. Laidlaw: (1) has never conducted any original, peer-reviewed research about gender identity, transgender people, or gender dysphoria, Exhibit 4, PI Hearing Transcript, at 10:15- 11:13; Exhibit 5, Deposition of Dr. Laidlaw in *C.P. v. Blue Cross*, at 29:23-30:6; (2) has not published any scientific, peer-reviewed literature on gender dysphoria or transgender people, Ex. 5 at 42:10-42:22;[2] (3) has never diagnosed a patient with gender dysphoria, Ex. 4 at 11:19-

[1] Dr. Laidlaw testified that fewer than 5% of his patients are under 18. Ex. 4 at 8:14-16.

[2] Dr. Laidlaw's only publications relating to gender dysphoria in a peer-reviewed journal are letters to the editor not based on any original research or scientific

11:21; Ex. 5 at 45:21-46:3; (4) has only treated one patient with gender dysphoria (nearly two decades ago, prior to the existence of the DSM-5's gender dysphoria diagnosis), Ex. 4 at 11:22-12:16; Ex. 5 at 43:11-43:17; (5) is not a psychiatrist, a psychologist, nor mental health care provider of any kind, Ex. 4 at 7:20-8:2; Ex 5 at 184:8-11; and (6) is not a surgeon and has never provided gender-affirming surgery, Ex. 4 at 8:9-10, 87:8-14; Ex. 5 at 184:12-13.

One. Dr. Laidlaw is not a mental health care provider, and is therefore unqualified to opine on the "[a]ssessment of the patient with gender dysphoria." (Ex. 1 ¶¶ 228-29; Ex 2 ¶¶ 15-16), or the appropriate treatment for people with suicidal ideation (Ex. 1 ¶¶ 176-78; Ex. 2 ¶¶ 78-85). For the same reasons, he is unqualified to testify as to the Plaintiffs' mental health. (Ex. 1 ¶¶ 141, 231-33, 238-42, 249-50, 253-55, 267-70, 272, 274-75, 279-84, 291-93, 294-99, 305).

The district court's decision in *Kadel v. Folwell* is most illustrative here. Like Dr. Laidlaw, Dr. Hruz, the endocrinologist at issue in *Kadel,* "offer[ed] a wide range of conclusions that fall into five main categories: mental healthcare, medical and surgical care, informed consent, criticism of medical associations, and political criticisms." *Kadel,* 2022 WL 3226731, at *8. The *Kadel* court excluded

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study, and which he cannot confirm are subjected to peer-review. Ex. 4 at 9:21-11:18; Ex. 5 at 31:14-39:23.

most of his proffered testimony and limited the testimony "to a discussion of the risks associated with prescribing hormone treatments to adolescents and adults," the only possible area of expertise for Dr. Hruz, as well as his colleague, Dr. Laidlaw. *Id.*, at *10.

Kadel found that, given his lack of experience in those areas, Dr. Hruz was "not qualified to offer expert opinions on the diagnosis of gender dysphoria, the DSM, gender dysphoria's potential causes, the likelihood that a patient will 'desist,' or the efficacy of mental health treatments." *Id.*, at *9. The *Kadel* Court emphasized that Dr. Hruz was "not a psychiatrist, psychologist, or mental healthcare professional," and "ha[d] never diagnosed a patient with gender dysphoria, treated gender dysphoria, treated a transgender patient, conducted any original research about gender dysphoria diagnosis or its causes, or published any scientific, peer-reviewed literature on gender dysphoria." *Id.*

Two. Like Dr. Hruz, Dr. Laidlaw "is not a surgeon and has no experience with surgery for gender dysphoria and, therefore, is not qualified to testify to the risks associated with surgery or the standard of care used by surgeons for obtaining informed consent for surgery." *Kadel*, 2022 *WL 3226731*, at *9; *see* Ex. 4 at 8:9-

10, 87:8-87:9; Ex. 5 at 47:16- 47:17.[3] Dr. Laidlaw bases his opinions solely on his review of literature (Ex. 4 at 15:24-16:2). Simply reading about these issues does not qualify Dr. Laidlaw as an expert, however. *See* Ex. 4 at 18:20-18:25; Fed. R. Ev. 702. "Merely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel*, 2022 WL 3226731, at *9; *see also Lebron*, 772 F.3d at 1369; *Dura Auto. Sys. Of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty.").

* * *

In sum, Dr. Laidlaw is not qualified to serve as an expert on the diagnosis of or mental health or surgical treatment paradigms for gender dysphoria. He is "not qualified by background, training, or expertise to opine" about these issues. *Lebron*, 772 F.3d at 1369. At most, Dr. Laidlaw can testify as "to the risks associated with puberty blocking medication and hormone therapy," but much of

[3] Notwithstanding that he is not a surgeon of any kind and has no clinical or research experience with surgeries used to treat gender dysphoria, Dr. Laidlaw opines broadly about surgery (Ex. 1. ¶¶ 160-75; Ex. 2 ¶¶ 60-68, Ex. 3 at 23-25), as well as more specifically about two Plaintiffs' chest surgeries (Ex. 1 ¶¶ 257-59, 270, 295-300), and the potential for one Plaintiff to successfully undergo surgery in the future (Ex. 1 ¶ 290). Not only is Dr. Laidlaw unqualified to offer these opinions, but such testimony is wholly unreliable given Dr. Laidlaw's lack of expertise, skill, and experience with surgery.

his testimony on these subjects is not reliable, as described below. *See Kade*l, 2022 WL 3226731, at *10.

III. THE MAJORITY OF DR. LAIDLAW'S EXPERT OPINION IS WHOLLY UNRELIABLE.

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

In making this determination the court can consider a variety of factors, including whether the purported expert's theory has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink v. Cheminova, Inc.*, 400 F.3d

1286, 1291-92 (11th Cir. 2005).[4] To be reliable, the expert's testimony must always be based on "good grounds," *Daubert,* 509 U.S. at 590, and must represent more than scientifically unsupported "leaps of faith." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002). As such, courts must assess "whether the evidence is genuinely scientific, as distinct from being unscientific speculation offered by a genuine scientist." *Chapman v. Procter & Gamble Distributing, LLC*, 766 F.3d 1296, 1306 (11th Cir. 2014). "In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." *Rink*, 400 F.3d at 1293, n.7.

Here, Dr. Laidlaw offers several opinions that fail to meet any indicia of reliability. His proffered opinions are not consistent with generally accepted scientific consensus, but are based entirely on rank speculation, unfounded assumptions, and bias. These opinions should be excluded.

[4] Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *Hendrix*, 255 F.R.D. at 578-79.

A. Dr. Laidlaw's opinions about the effectiveness of gender-affirming medical care are not generally accepted and are unreliable.

General acceptance in the relevant scientific community is an important element to the reliability inquiry. *See Allison*, 184 F.3d at 1313. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Laidlaw's opinions about the effectiveness and propriety of gender-affirming medical care are far outside the mainstream of medical and scientific opinion and have been explicitly rejected by every relevant scientific and medical community. Nor do his opinions stem from any accepted scientific methodology, rather, they are frequently contradicted by existing scientific literature.

Dr. Laidlaw falsely testifies that the "'professional consensus' [supporting gender-affirming medical care] exists only within the confines of" WPATH (Ex. 1 ¶ 185; *see also* Ex. 2 ¶ 28, Ex. 3 at 27, 29-30). Dr. Laidlaw offers no evidence to support this contention, and instead attempts to legitimize his opinions by nitpicking at and mischaracterizing a few of the studies that fall within the broad consensus of clinicians, scientists, and researchers in finding that the three services at issue in this case are effective in treating gender dysphoria. Specifically:

- Dr. Laidlaw cites Dhejne (2011) for the proposition that the study showed that gender-affirming care was not effective (Ex. 1 ¶ 202 & Ex. 3 at 31). This characterization flatly contradicts the study's own conclusion that "surgery and hormonal therapy alleviates gender dysphoria" (Exhibit 6, Dhejne et al. (2011), at e16885).
- Dr. Laidlaw emphasizes the fact that Branstrom & Pachankis (2020) issued corrections after Dr. Laidlaw and others wrote letters to the editor of the journal in which it was published (Ex. 1 ¶¶ 203-09 & Ex. 3 at 31-33). Dr. Laidlaw suggests that the article was completely retracted or repudiated, which is not true. Rather, a corrected version was published which changed the conclusion from "the longitudinal association between gender-affirming surgery and lower use of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them" to "the longitudinal association between gender-affirming surgery and reduced likelihood of mental health treatment lends support to the decision to provide gender-affirming surgeries to transgender individuals who seek them." (Exhibit 7, Bränström & Pachankis (2020), at 734, 727).

- Dr. Laidlaw also maligns studies based on the 2015 US Transgender Survey because it was not a randomized control study but used convenience sampling (Ex. 1 ¶¶ 210-11; Ex. 2 at ¶ 71; Ex. 3 at 33). While there are inherent limitations to convenience sampling, it is an important methodology to capture information about large cohorts. Importantly, Dr. Laidlaw does not point to any studies that contradict the findings of the 2015 USTS. And in fact, many of its findings were recently confirmed by a Kaiser Family Foundation / Washington Post survey that used a random sampling methodology, conducted in 2022 (Exhibit 8, Parks et al. (2023), at 8).
- Dr. Laidlaw similarly denigrates various studies on mastectomy for minors (Ex. 1 ¶¶ 212-19 & Ex. 3 at 33-35). He makes various complaints about the methodology used by these studies, but again, does not show that these methodological flaws render the studies completely unreliable, and he fails to point to any studies that reach contrary conclusions. No study is perfect, but the collection of imperfect studies finding similar results creates scientific consensus. Dr. Laidlaw's opinions fall outside of that consensus.

- Dr. Laidlaw also spends considerable time discussing a 2016 Center for Medicare & Medicaid Services (CMS) review of gender-affirming surgery coverage in Medicare (Ex. 1 ¶¶ 220-21, Ex. 2 at 35-36). But again, Dr. Laidlaw overstates his case. The decision memo decided not to "make a national coverage determination on surgical remedies" for gender dysphoria, and instead allow local Medicare decision-makers to "make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances" (Exhibit 9, 2016 CMS Decision Memo, at 2). In other words, the CMS Memo ***mandated*** Medicare to cover gender-affirming surgery when clinically appropriate, but allowed local decision-makers discretion to establish medically necessity criteria for surgery, rather than establishing one uniform set of national criteria, *see id.* Dr. Laidlaw completely ignores the prior, 2014 decision, of an Administrative Appeals Board in the U.S. Department of Health & Human Services (which CMS falls within) to remove a ban on coverage of gender-affirming surgery in Medicare, finding "a consensus among researchers and mainstream medical organizations that [gender-

affirming] surgery is an effective, safe and medically necessary treatment for" gender dysphoria (Exhibit 10, 2014 Department Appeals Board Decision, at 20). That 2014 decision explicitly found that gender-affirming surgery was safe, effective, and not experimental (*id.* at 11, 15, 21).

Indeed, Dr. Laidlaw acknowledges that his "opposition to gender-affirming care for the treatment of gender dysphoria in youth and adults is contrary to the vast majority of medical associations' recommendations" (Ex. 4 at 25:22-26:1). This includes the following: American Medical Association, American Psychological Association, American Psychiatric Association, Endocrine Society, Pediatric Endocrine Society, American Academy of Pediatrics, American Academy of Family Physicians, American College of Obstetricians and Gynecologists, American College of Physicians, (Ex. 4 at 29:16- 36:18). *See e.g., Kadel v. N. Carolina State Health Plan for Tchrs. & State Emps.*, 12 F.4th 422, 427–28 (4th Cir. 2021), *as amended* (Dec. 2, 2021) (noting the WPATH Standards of Care "have been adopted by health organizations across the country" and that gender-affirming treatments, including hormone therapy and surgical care, "are safe, effective, and often medically necessary"), *cert. denied*, 142 S. Ct. 861 (2022); *Edmo v. Corizon, Inc.*, 935 F.3d 757, 771 (9th Cir. 2019) (the provision of

gender-affirming medical care, consistent with the WPATH Standards of Care, represents "the ***broad medical consensus*** in the area of transgender health care," which "requires providers to individually diagnose, assess, and treat individuals' gender dysphoria.") (emphasis added); *see also Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The ***consensus*** recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care.") (emphasis added), *aff'd*, 47 F.4th at 671; *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1018 (W.D. Wis. 2019); Exhibit 16, Nat'l Academies of Science, Engineering, and Medicine (2020), at 361 ("A major success of [WPATH's] guidelines has been identifying evidence and ***establishing expert consensus that gender-affirming care is medically necessary*** and, further, that withholding this care is not a neutral option. A number of professional medical organizations have joined WPATH in recognizing that gender-affirming care is medically necessary for transgender people because it reduces distress and promotes well-being, while withholding care increases distress and decreases well-being.") (emphasis added) (citations omitted).

Dr. Laidlaw's opinions regarding the effectiveness of gender-affirming medical care are wholly outside the mainstream, and he can cite to no authoritative

sources in support of his opinion. While undoubtedly Dr. Laidlaw "has strong beliefs," the fact that his opinions are "not generally accepted by the scientific community, and [are] unsupported by other studies" means that "his testimony is based more on personal opinion than on scientific knowledge," making it unreliable. *Allison*, 184 F.3d at 1319. These opinions should be excluded.

B. Several of Dr. Laidlaw's opinions about the supposed harms caused by gender-affirming treatment to Plaintiffs deliberately misrepresent the facts and evidence, and are therefore unreliable

Dr. Laidlaw offers several opinions about the potential for infertility and bone density loss resulting from the use of puberty-delaying medication in general, and as to the Plaintiffs in this litigation specifically (Ex. 1 ¶¶ 92-97, 100-09; Ex. 2 ¶¶ 35-43, 52-54). These opinions are entirely unreliable. In the first place, as discussed above, since he does not practice pediatric endocrinology, and has only ever treated one adult for gender dysphoria, Dr. Laidlaw's opinions with respect to the harms posed by puberty-delaying treatment for youth should be regarded with skepticism, (Ex. 4 at 8:14-16, 11:22-12:16 & Ex. 5 at 43:11-43:17 (fewer than 5% of Dr. Laidlaw's patients are under 18, and he has only treated one patient for gender dysphoria, more than a decade ago)).

In any event, Dr. Laidlaw's testimony that puberty-delaying medications "alter or block normal human development," deliberately misrepresents the facts and

data in order to obfuscate rather than elucidate (Ex. 1 ¶ 199). While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts' omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case here where Dr. Laidlaw omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation. It is appropriate to exclude expert testimony, like these opinions of Dr. Laidlaws, that is "confusing or misleading." *Hull v. Merck & Co*., 758 F.2d 1474, 1478 (11th Cir. 1985).

One. Dr. Laidlaw misconstrues the effect of puberty-delaying treatments on fertility. He speculates at length about the potential impacts of these treatments on fertility in general, and on named Plaintiffs in particular (Ex. 1 ¶¶ 92-97, 246-47, 280, 287; Ex. 2 ¶¶ 35-43). In doing so, he ignores multiple studies that have made clear that these treatments do not have long-term implications on fertility (*e.g.,* Exhibit 11, Guaraldi et al. (2016) at R83; Exhibit 12, Marinerie et al. (2021), at 529). Dr. Laidlaw correctly points out that progression through puberty – at some point – is needed for biological reproduction (Ex. 1 ¶¶ 92-97; Ex. 2 ¶¶ 35-43). But Dr. Laidlaw then reaches far beyond this well-established fact to posit that gender-

affirming hormones could possibly damage immature gonads (Ex. 1 ¶¶ 92, 94, 97), providing no data or studies to support his speculation.[5]

Two. Dr. Laidlaw speculates about the impact of puberty-delaying treatment on bone density – again, both in general, and for the Plaintiffs specifically (Ex. 1 ¶¶ 100-09, 250, 266, 289; Ex. 2 ¶¶ 52-54). His analysis of the studies regarding the impacts of these medications on bone density completely ignores that youth given puberty-delaying medications will take those medications for a relatively short period of time, and then either resume puberty associated with their birth-assigned sex, or begin hormone treatment, either of which will ameliorate any impact on bone density caused by puberty suppressing medications. Not to mention, that exact same concerns with respect to bone density are present for youth who take these medications to treat precocious puberty, a use Dr. Laidlaw approves (Ex. 1 ¶¶ 100-09).

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The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr.

[5] Dr. Laidlaw's testimony ignores that as long as a person retains their gonads, they have the potential for fertility. And he does not account for the fact that the same risks with respect to fertility are present when these medications are used to treat other conditions, which he approves (*See* Ex. 1 ¶¶ 74-75 (discussing the use of these medications to treat prostate cancer and precocious puberty)).

Laidlaw has misrepresented or omitted information that goes to the heart of his opinions and calls into question the reliability of his opinions. By omitting key information, or worse, misrepresenting facts that if properly disclosed would contradict his opinions and undermine their foundation, Dr. Laidlaw's testimony is not reliable but "misleading" and "quite speculative, and . . . [s]uch potentially confusing testimony is at odds with the purposes of expert testimony." *Hull*, 758 F.2d at 1478, 1477.

C. Dr. Laidlaw's other opinions about the harms posed by gender-affirming medical care are based solely on ipse dixit and conjecture and are unreliable.

Dr. Laidlaw also raises, without any research or evidentiary support, the specter of several other harms that could be posed by puberty suppressing treatment. These include his musings about treatment's potential impact on future sexual function, for which he offers no evidence or citations to support other than anecdotal reports from a reality television show (Ex. 1 ¶¶ 98-99). They also include Dr. Laidlaw's conjecture about the "unknown, but likely negative consequences … with respect to brain development," for which he can offer no evidence or reasoning to support his speculation that any consequences would be "likely negative" (Ex. 1 ¶ 110).

These opinions are the epitome of ipse dixit that courts routinely exclude as unreliable. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only by the ipse dixit of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). "[T]he unremarkable observation that an expert may be qualified by experience does not mean that experience, standing alone, is a sufficient foundation rendering reliable any conceivable opinion the expert may express." *Frazier*, 387 F.3d at 1261; *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005) ("[P]resumptions do not make for reliable opinions."). This is one of those circumstances in which "there is simply too great an analytical gap between the data and the opinion proffered." *Id.; see also McDowell v. Brown*, 392 F.3d 1283, 1300 (11th Cir. 2004) ("[A]n expert opinion is inadmissible when the only connection between the conclusion and the existing data is the expert's own assertions.")

D. Dr. Laidlaw's opinions about desistence are completely unreliable.

Again, Dr. Laidlaw does not diagnose or treat gender dysphoria, has not conducted any original research on gender dysphoria, gender identity, gender non-conformity in children/youth, or transgender people's experience. *See* Section II, *supra*. Yet, he opines extensively on gender dysphoria and desistence (Ex. 1 ¶¶ 28-

35; Ex. 2 ¶¶ 19-21; Ex. 3 at 5-7). To be sure, Dr. Laidlaw offers a theory that can be (and has been) subjected to peer review and publication, based on generally accepted techniques. *See Frazier*, 387 F.3d at 1262. But Dr. Laidlaw's gloss on the peer reviewed literature that has been published based on generally accepted techniques draws a conclusion exactly opposite to what that literature demonstrates: contrary to the literature, he opines that the majority of youth diagnosed with gender dysphoria will, by adulthood, "desist" (that is, their gender identity will change to align with their birth-assigned sex). This testimony is incorrect and not reliable.

A closer examination of Dr. Laidlaw's testimony reveals that he bases these opinions on a single review of antiquated studies showing that a majority of preadolescent children diagnosed with gender identity disorder—an outmoded diagnosis distinct from gender dysphoria with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior (Ex. 1 ¶¶ 28-35; Ex. 2 ¶¶ 19-21; Ex. 3 at 5-7).[6] Yet Dr. Laidlaw's opinions stretch far beyond

[6] Dr. Laidlaw also cites his own, non-peer reviewed "commentary" (i.e., opinion) article on this topic, co-authored with two well-known critics of providing medical care to people with gender dysphoria, one of whom has also been retained by Defendants as an expert in this case. However, this commentary cites the same Ristoria & Steensma review as the source for its statistics (Exhibit 17, Laidlaw et al. (2019), at 76). The article is co-authored by Michelle Cretella, who has been

the "explicit[] findings, conclusions, and implications" of the Ristoria & Steensma review he cites to improperly "extrapolate from this information a finding, conclusion, or implication [that] authors themselves did not make." *In re Abilify (Aripiprazole) Prod. Liab. Litig.*, 299 F. Supp. 3d 1291, 1351 (N.D. Fla. 2018). The Ristoria & Steensma review examined outcomes from 10 studies on children with gender dysphoria or gender identity disorder conducted from 1968 to 2012 (Exhibit 13, Ristoria & Steensma (2016), at Table 1). It acknowledges that:

> The lower persistence rates in the earlier studies, compared to the more recent studies after 2000, may be the result of the inclusion of less extreme cases in the earlier studies than in later studies. For example, before . . . 1980 there was no formal diagnosis of GD for children. It could therefore be that the children included in the studies before 1980 would in retrospect not meet the full criteria for a diagnosis. Also, the recent studies consisted of clinically referred samples of children, which was not the case for the earlier studies.

Id. at 15-16. Despite the fact that the very paper on which he relies to claim that as many as 98% of children who present with gender dysphoria later "desist" makes clear that it supports no such conclusion, Dr. Laidlaw states that, "[b]ecause the

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criticized by the Society for Adolescent Health and Medicine for "pushing political and ideological agendas not based on science and facts" (Exhibit 18, Sct'y Adol. Health & Med. (2017), at 4). The other co-author is Kevin Donovan, whom Defendants have retained as an expert in this case, and who has described not only "transgender conversion surgeries" but "homosexual marriage," "homosexual behavior," contraception, cohabitation, and divorce, as "sinful" (Exhibit 19, Donovan & Sotomayor (2020), at 135).

rate of desistance is so high, gender affirmative therapy will necessarily cause serious and irreversible harm to many children and adolescents who would naturally outgrow the condition if not affirmed" (Ex. 1 ¶ 33). This opinion is based on faulty propositions. *See, e.g., Kilpatrick v. Breg, Inc*., 613 F.3d 1329, 1338 (11th Cir. 2010) (study that explicitly limited its findings to rabbits could not be the basis of expert testimony regarding humans); *McClain v. Metabolife Int'l, Inc*., 401 F.3d 1233, 1247 (11th Cir. 2005) (expert could not reasonably rely on a study to prove causation where the study concluded that the supplement at issue "*may* pose health risks to *some* persons" and the authors had specifically written "a letter to the editor explaining that the study did not prove causation") (emphasis in original).

In fact, Dr. Laidlaw has previously admitted that the "desistance" studies on which he relies speak only to preadolescent youth who were diagnosed with gender identity disorder under the DSM-III or the DSM-IV, and do not pertain to "desistance" of youth diagnosed with gender dysphoria under the DSM-5 (Ex. 5 at 103:4-104:4). He has similarly admitted that he is unaware of any studies documenting "desistance" among adolescents (people over the age of 12) or adults (*id*. at 109:2-109:14. Dr. Laidlaw's attempts to rehabilitate his asserted desistence rates in his Rebuttal Report do not hold water. He notes that the three most recent

studies included in the Ristoria & Steensma review he relies on included children aged 3 to 13, and that those studies showed desistance rates of 61-88% (Ex. 2 ¶ 21). From that information he extrapolates that "this would include children in the age range of 8-12 years old, many of whom were already adolescents going through puberty based on their age and were therefore not pre-pubertal. Therefore we can infer that a high proportion of adolescents do in fact desist" (*id.* (citation omitted)). But of course, this is pure speculation and guesswork. Dr. Laidlaw fails to acknowledge that it is just as likely that the desistence rates of older youth were much lower than those of younger children. And the studies included in the Ristoria & Steensma review, the most recent of which is over 10 years old (and some of which rely on data from the 1950s, 1960s, and 1970s), do not comport with more recent literature, which has uniformly found that youth who have a diagnosis of gender dysphoria in adolescence overwhelmingly continue to identify as transgender as they age (Exhibit 14, Olson et al. (2022), at 4; Exhibit 15, de Vries et al. (2011), at 1).[7] In any event, the fact that younger, preadolescent

[7] Notably, Thomas D Steensma, who co-authored the study on which Dr. Laidlaw improperly cites for the proposition that most youth with gender dysphoria "desist" in their gender identity, also co-authored the de Vries study, which looked 70 youth in the Netherlands referred for treatment of gender dysphoria between 2000 and 2008, found that all of them decided to continue their medical transition after 1-2 years, confirming that "young adolescents who had been carefully diagnosed

children may have a concept of their gender identity that is still changing is of no consequence to whether medical interventions are appropriate for adolescents and adults, for whom research confirms gender dysphoria usually persists (Ex. 14; Ex. 15).[8] Dr. Laidlaw's opinions with respect to desistence do not use a "reliable and sound" methodology, and the one study on which he purports to rely does not support his "ultimate conclusion." *Kilpatrick*, 613 F.3d at 1337; *Rink*, 400 F.3d at 1293 (using unsound underlying data results in "flawed methodology"). This testimony should be excluded.

E. Dr. Laidlaw's opinions about informed consent are unreliable

Dr. Laidlaw does not offer any new information or evidence to support his opinion that:

> [I]t is not possible for the parent or guardian to make a true informed consent decision for the child because of the poor quality of evidence of benefit, the known risks of harm, and the many unknown longterm risks of harm which could only truly be known after years and decades of gender affirmative therapy. A parent or guardian cannot consent to dubious treatments which result in irreversible changes to their child's body, infertility, sexual dysfunction, and in many cases eventual sterilization.

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show persisting gender dysphoria into late adolescence or young adulthood." Ex. 15 at 2281.

[8] In addition, "a discussion of risks to prepubescent children is irrelevant to this case and would likely serve only to confuse." *Kadel*, 2022 WL 3226731, at *9.

(Ex. 1 ¶ 181; *see also id.* ¶¶ 179-83, 307-08, 310; Ex. 3, at 26-27; Ex. 2 ¶¶ 86-90). Instead, his opinions regarding informed consent are simply cumulative of the same unreliable opinions he offers regarding the effectiveness and potential harm caused by gender-affirming treatments. They completely misrepresent the concept of informed consent, which can, and does allow people (including parents and guardians making decisions about their children's medical care) to authorize necessary care, even when it may result in irreversible changes to the body, including impacts on fertility and sexual function, when they have been educated about "the burdens, risks, and expected benefits of all options, including forgoing treatment" such that they are able to "make an independent, voluntary decision" about treatment (Exhibit 20, AMA Code of Medical Ethics, at § 2.1.1). Indeed, it is common for parents to make these decisions, even when not all the risks of a particular intervention are fully known. For example, many antidepressants have both known and unknown impacts on fertility, yet they are commonly prescribed, including to youth.[9] Dr. Laidlaw's opinions on informed consent lack any

[9] *See, e.g.,* Exhibit 21, Beeder & Samplaski (2020), at 45 ("At this point, it is difficult for clinicians to counsel patients on the effect that these medications might have on their fertility. We would recommend an informed discussion with patients attempting parenthood and taking these medications. Checking a baseline semen analysis and sperm DNA fragmentation might provide some level of guidance."); Exhibit 22, Casilla-Lennon et al. (2016), at 314.e1 ("Our data suggest that

"grounding in the methods and procedures of science," such that they are nothing "more than subjective belief or unsupported speculation." *Daubert*, 509 U.S. at 590. They amount to nothing more than "unscientific speculation offered by a genuine scientist," and should be excluded. *Allison,* 184 F.3d at 1317 (*quoting Rosen v. Ciba–Geigy Corp*., 78 F.3d 316, 318 (7th Cir. 1996)).

F. Dr. Laidlaw's opinions about WPATH are unreliable

Dr. Laidlaw's opinions about the WPATH Standards of Care for gender-affirming medical care should similarly be disregarded as unreliable. In particular he offers the completely unfounded, and therefore unreliable "professional opinion WPATH SOC 8 represents a grave and immediate danger to minors, young adults, and adults and should not be followed by any physician, mental health care provider, or other medical professional" (Ex. 1 ¶ 198; *see also id.* ¶¶ 184-85, 192-98, 309; Ex. 3 at 27, 29-30; Ex. 2 ¶¶ 28-30).[10] Dr. Laidlaw is not privy to the actual

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antidepressants may reduce the probability of a woman with a history of depression to conceive naturally. Future studies are needed to differentiate the extent to which this association is due to the antidepressant itself versus the underlying depression.").

[10] When pressed on the basis for his opinions regarding WPATH in another case, Dr. Laidlaw did not cite any literature, study, or publication but rather stated that it was based on his opinion that "one would expect them [WPATH] not to exclusively follow one, say, politically based point of view," and that (again, in his opinion) WPATH is not "open to a variety of points of view" Ex. 5 at 89:7-89:18. When pressed further for his basis for this opinion, Dr. Laidlaw simply stated that

internal conversations of WPATH, has not participated in WPATH conferences, is not a member of WPATH, and has not participated in any of its internal discussions (Ex. 5 at 90:1-90:16). He therefore lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). In short, Dr. Laidlaw does not have "any experience with . . . WPATH. . . upon which to base his criticisms," nor does he cite to any meaningful data or evidence to support them, making his speculation as WPATH's credibility completely unreliable. *Kadel,* 2022 WL 3226731, at *10.

G. Dr. Laidlaw's testimony is motivated by bias, rendering it unreliable

"In evaluating the reliability of an expert's method . . . a district court may properly consider whether the expert's methodology has been contrived to reach a particular result." *Rink*, 400 F.3d at 1293, n.7. Here, Dr. Laidlaw has already confirmed the basis for all his opinions offered: He opposes affirmation of a transgender person's identity in any circumstances (Ex. 4 at 87:15-87:21; *id.* at 39:22-40:19). In other words, the entire basis for all his opinions offered rests on his non-scientific opposition to treatment for gender dysphoria, especially for

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his opinion is based on a conversation with one psychologist and the fact that WPATH published the Standards of Care. *Id.*, at 92:2-92:12.

children. *But see Brandt,* 551 F. Supp. at 891 ("[G]ender-affirming care for transgender minors may be medically appropriate and necessary to improve the physical and mental health of transgender people."). While Plaintiffs are cognizant of the fact that bias in an expert witness's testimony is usually an issue of credibility as opposed to one of admissibility, when an expert's opinions are based on bias as opposed to scientific or medical knowledge, then the question of bias becomes one of reliability and admissibility. Indeed, reliability is a flexible inquiry wherein "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis v. Overhead Door Corp.,* 10 F.4th 268, 281 (4th Cir. 2021). Here, there is ample evidence that Dr. Laidlaw's testimony is so permeated and tainted by his unscientific views and personal bias as to render it unreliable. *Cf. Sanchez v. Esso Standard Oil de Puerto Rico, Inc.,* No. CIV 08-2151, 2010 WL 3809990, at *4 (D.P.R. Sept. 29, 2010).

IV. DR. LAIDLAW OFFERS SEVERAL UNHELPFUL AND IRRELEVANT OPINIONS.

"The gatekeeping inquiry must be tied to the facts of a particular case." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150 (1999) (quotations omitted). The proponent of the expert testimony bears the burden of proving that the

testimony is relevant and "logically advances a material aspect" of the case. *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir. 2009) (citations omitted). Here, Dr. Laidlaw offers several opinions that simply are not relevant to this inquiry as they will not "help the trier of fact to understand the evidence or to determine a fact in issue." Fed. R. Ev. 702(a); *Id.* 401, 402 & 403; *Daubert*, 509 U.S. at 591 ("Expert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful.") (cleaned up).

The primary issues before this Court, among others, are: (1) whether medical treatment for gender dysphoria is experimental, such that it could be appropriately excluded from Medicaid coverage, *Rush v. Parham*, 625 F.2d 1150, 1156 (5th Cir. 1980); *K.G. ex rel. Garrido v. Dudek*, 864 F. Supp. 2d 1314, 1321 (S.D. Fla. 2012), *aff'd in part, rev'd in part sub nom. Garrido v. Dudek*, 731 F.3d 1152 (11th Cir. 2013); and (2) whether the process Florida underwent to exclude coverage of such care in its Medicaid program made "classifications that are 'arbitrary or irrational' and that reflect a 'bare desire to harm a politically unpopular group,'" *Glenn v. Brumby*, 663 F.3d 1312, 1315 (11th Cir. 2011) (*quoting City of Cleburne v. Cleburne Living Ctr., Inc.*, 473 U.S. 432, 446-47 (1985)). Because this case is about gender-affirming medical care, much of the testimony offered by Dr. Laidlaw has no bearing on the issues:

- He offers unsupported musings on the increased number of people diagnosed with gender dysphoria (Ex. 1 ¶¶ 29-31; *see* Ex. 3 at 5-6). His ideas in this regard are based only on his conjecture, and ignore several plausible alternative explanations for the increased number of people diagnosed with gender dysphoria. In any event, the number of people diagnosed with gender dysphoria (increasing or not) is simply not pertinent to the question of what treatment for the condition is medically appropriate, or whether refusing to cover treatment is discriminatory. Dr. Laidlaw does not and cannot dispute that gender dysphoria is a legitimate medical condition (Ex. 4 at 16:14-23).
- Similarly, Dr. Laidlaw takes pains to establish that gender dysphoria is a psychological condition and not an endocrine one (Ex. 1 ¶¶ 23-26; Ex. 2 ¶¶ 13-14; *see* Ex. 3 at 4-5). But again, it is not relevant to the issues in this case whether gender dysphoria is a psychological condition, an endocrine condition, or a health condition. Dr. Laidlaw does not and cannot dispute that gender dysphoria is a legitimate condition for which treatment is indicated (Ex. 4 at 16:14-23).

- He provides speculation about human sexual development (Ex. 1 ¶¶ 41-55; *see* Ex. 3 at 8-11). Again, human sexual development is entirely irrelevant to the legal questions presented in this case.
- He opines, without citing studies or data, as to the difference between gender identity and "biological sex," including as to whether "biological sex" can be changed (Ex. 1 ¶¶ 36-40, 53-55, 306; Ex. 2 ¶¶ 3-12; *see* Ex. 3 at 5-7). But this case is not about changing one's sex. It is about treatment for gender dysphoria. His unsupported speculation is irrelevant.
- His ideas about "social transition" are also irrelevant, since this case does not address social transition, but medical treatment for gender dysphoria (Ex. 1 ¶¶ 61-65; *see* Ex. 3 at 12-13).
- Dr. Laidlaw's opinions about the policies of other countries are similarly irrelevant, since what other countries cover in their state health care programs has no relation to Florida Medicaid's obligation to cover services under U.S. Law (Ex. 1 ¶¶ 29-31, 222-27; Ex. 2 ¶¶ 72-77; *see* Ex. 3 at 36-37).[11]

[11] Dr. Laidlaw does not have first-hand knowledge of these countries' policies, and misrepresents them, since none of the identified countries wholly exclude coverage for gender-affirming medical care. *See Brandt by & through Brandt v. Rutledge*, 47 F.4th 661, 671 (8th Cir. 2022) (discussing Finland's policy); Ex. 4 at 106:2-108:5.

Because each of these opinions offered lacks any "valid scientific connection to the disputed facts in the case," they should be excluded. *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999).

V. THE OPINION OF DR. LAIDLAW LACKS PROBATIVE VALUE AND IS THEREFORE NEITHER HELPFUL TO THE FACT-FINDER NOR ADMISSIBLE UNDER FEDERAL RULE OF EVIDENCE 403.

Finally, the Court should exclude the majority of the opinion and testimony of Dr. Laidlaw because its introduction will result in unfair prejudice, confusion of the issues, or in duplicative or misleading testimony. Fed. R. Evid. 403. As articulated above, the majority of opinions offered by Dr. Laidlaw are irrelevant, speculative, and unreliable. In addition, Defendants have proffered two other endocrinologists to provide testimony in this case, and making Dr. Laidlaw's proposed testimony largely "cumulative or needlessly time consuming." *Hendrix*, 255 F.R.D. at 579. His testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender-confirming care based on speculation, irrelevant, misleading, and biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude the reports, opinions, and testimony of Dr. Laidlaw, except as they relate to "to the risks associated with puberty blocking medication and hormone therapy." *Kadel*, 2022 WL 3226731, at *10.

Dated: April 7, 2023

Respectfully Submitted,

/s/ Abigail Coursolle

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April, 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for Plaintiffs and counsel for Defendants conferred regarding the instant motion during a Zoom conference on April 6, 2023. Defendants indicated they do not consent to the relief requested herein

CERTIFICATE OF WORD COUNT

According to Microsoft Word, the word-processing system used to prepare this Motion and Memorandum, there is a combined total of 7,381 words in the Motion and the Memorandum of Law.

/s/ Abigail K. Coursolle
Attorney for Plaintiffs

TAB 136

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*,

Plaintiffs,

v.

JASON WEIDA, *et al.*,

Defendants.

Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. PAUL W. HRUZ AND SUPPORTING MEMORANDUM OF LAW

TABLE OF CONTENTS

Pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and Rule 702, Plaintiffs move to partially exclude certain testimony of Defendants' expert Dr. Paul Hruz, on the grounds that he fails to meet the qualification, reliability, and helpfulness requirements imposed by Fed. R. Evid. 702 and *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

Dr. Hruz is a pediatric endocrinologist. Many of the opinions he purports to offer in this case have previously been excluded. *See Kadel v. Folwell,* No. 1:19CV272, 2022 WL 3226731, at *9-10 (M.D.N.C. Aug. 10, 2022). He has no experience treating or diagnosing gender dysphoria; he has never provided gender-affirming care, has never done any original research on the issue, has never published any peer-reviewed literature on the matter, and holds opinions that are purely speculative and far afield from the mainstream of the medical and scientific communities. Indeed, as he does here, in *Kadel,* Dr. Hruz "offer[ed] a wide range of conclusions that fall into five main categories: mental healthcare, medical and surgical care, informed consent, criticism of medical associations, and political criticisms." *Kadel,* 2022 WL 3226731, at *8. Despite the broad ranging categories on which he was offered to testify, after reviewing his qualifications, the *Kadel* Court limited Dr. Hruz's testimony to "the risks associated with puberty blocking medication and hormone therapy." *Id.* at *9.

The Court here should similarly impose the same limitation on Dr. Hruz's

testimony. Accordingly, Dr. Hruz is not a qualified expert on gender dysphoria or its treatment, and his opinions and testimony are neither relevant nor reliable. Additionally, his opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403. In support of this motion, Plaintiffs state as follows:

MEMORANDUM OF LAW

LEGAL STANDARD

Federal Rule of Evidence 702 places gatekeeping obligation on a trial court, to ensure that an expert's testimony "both rests on a reliable foundation and is relevant to the task at hand." *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993); *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of Daubert's gatekeeping requirement cannot be overstated."). In determining the admissibility of expert testimony under Rule 702, courts engage in a "rigorous" three-part inquiry and must consider whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d

548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999).

The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). The party offering the expert testimony has the "burden of establishing qualification, reliability, and helpfulness." *Frazier*, 387 F.3d at 1260. As detailed below, Dr. Hruz's proposed opinions fail to meet these requirements and should be excluded.

ARGUMENT

I. Dr. Hruz is not qualified to offer an expert opinion on the diagnosis and the mental health treatment of gender dysphoria.

A witness must be "qualified to testify competently regarding the matter he intends to address." *Frazier*, at 1260. "A witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*, 326 F.3d at 1342. However, credentials are not dispositive when determining qualification. Each of the three analytical prongs (including qualifications) is assessed in reference to the matter to which the expert seeks to testify—i.e., "to the task at hand." *Daubert*, 509 U.S. at 597. It is for that reason that "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014)

(holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). Rather, an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Id.* at 1369. "A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Dura Automotive Systems of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002). If a proposed expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," such expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

Therefore "[d]etermining whether a witness is qualified to testify as an expert requires the trial court to examine the credentials of the proposed expert in light of the subject matter of the proposed testimony." *Banuchi v. City of Homestead*, 606 F.Supp.3d 1262, 1272 (S.D. Fla. 2022) (cleaned up). Here, Dr. Hruz does not have the medical specialty required to discuss the diagnosis and treatment for gender dysphoria, particularly the diagnosis and assessment of gender dysphoria and non-endocrine treatments that are wholly outside his expertise as an endocrinologist.

The Court in *Kadel* succinctly determined based on Dr. Hruz's deposition

testimony that:

> Hruz is not qualified to offer expert opinions on the diagnosis of gender dysphoria, the DSM, gender dysphoria's potential; causes, the likelihood that a patient will "desist," or the efficacy of mental health treatments. He has never diagnosed a patient with gender dysphoria, treated gender dysphoria, treated a transgender patient, conducted any original research about gender dysphoria diagnosis or its causes, or published any scientific, peer reviewed literature on gender dysphoria.

Kadel, 2022 WL 3226731, at *9; Ex. A at ¶142 Hruz Expert Report[1] ("I have never personally engaged in the delivery of gender affirming medical interventions to children with gender dysphoria"); Ex. C at 88:18-89:8, 89:17-25 (Dr. Hruz discussing his lack of qualifications and treatment for gender dysphoria); Ex. E at 24:11-24:14, 25:20-25:23. Indeed, Dr. Hruz has also not sat in on a meeting with a patient discussing the treatment options for gender dysphoria. Ex. C at 40:6-40:11. Nor has he conducted any original research about transgender people or gender dysphoria. Ex. C at 35:5-36:1; Ex. E at 62:25-63:9; Ex. F at 25:24-28:13. He has not published any scientific, peer-reviewed literature on gender dysphoria or transgender people either. Ex. C at 42:14-49:19; Ex. E at 61:17-64:7, 295:19-

[1] Unless otherwise specified, all exhibits cited herein are attached to the contemporaneously filed Declaration of Shani Rivaux.

295:23.[2] Dr. Hruz is neither a psychiatrist[3], a psychologist, nor a mental health care provider of any kind qualified to diagnose gender dysphoria or to opine on the reliability of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition ("DSM-5"). Ex. C at 112:9-11, 55:23-56:15; Ex. E at 41:21-42:2, 42:11-42:18.

Like the Court in *Kadel,* this Court should exclude Dr. Hruz on these topics due to his lack of expertise. *See Dura Auto. Sys. of Indiana, Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("The *Daubert* test must be applied with due regard for the specialization of modern science. A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty. That would not be responsible science."). Instead, Dr. Hruz bases his opinions solely on his review of literature and conversations he has had with others. The fact that Dr. Hruz has read about gender dysphoria and

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[2] Dr. Hruz's only publication relating to gender dysphoria in a peer-reviewed journal is a letter to the editor not based on any original research or scientific study, and for which it is unclear if letters to the editor are subjected to peer-review. Ex. C at 43:9-45:15. *See also* Ex. P (noting that letters to the editor are typically not peer reviewed). His other publications pertaining to gender dysphoria are all in non-scientific, non-medical, non-peer-reviewed journals affiliated with religious organizations.

[3] In his rebuttal report, Dr. Hruz claims that his opinions are supported by his "professional experience as a psychiatrist." Ex. B at ¶3. However, none of his qualifications or his prior testimony have demonstrated any credentials of a psychiatrist.

transgender people does not qualify him as an expert on these issues, however. That is precisely the sort of "generalized knowledge of a particular subject" that courts have rejected as a qualification under Rule 702. As with the disqualified expert in *Lebron* who "reached his opinion instead by relying on studies," this is insufficient to serve as an expert witness. *Lebron*, 772 F.3d at 1369.

Aside from his lack of expertise, Dr. Hruz is the definition of a manufactured "expert witness" as his involvement originates from and dates back to a conference by the Alliance Defending Freedom ("ADF")[4] organized specifically to cultivate professional "experts" who would testify against the gender-affirmation of transgender people. Ex. C at 241:10-246:20; Ex. E at 92:21-93:24; Ex. F at 147:11-21; *cf.* Ex. O at 84:3-85:12, 90:13-91:13 (Dr. Lappert testifying that he attended the same ADF conference as Dr. Hruz in 2017 where the "poverty of [experts] who are willing to testify" against gender-confirming policies was discussed and that attendees "were asked whether they would be

[4] ADF is well-known for pushing anti-LGBT policies across the country and internationally. *See*, *e.g.*, Nico Lang, *A Hate Group Is Reportedly Behind 2021's Dangerous Wave of Anti-Trans Bills*, them. (Feb. 19, 2021), https://bit.ly/3HEqCR9; Julie Compton, *Activists take aim at anti-LGBTQ 'hate group,' Alliance Defending Freedom*, NBC News (Nov. 14, 2018), https://nbcnews.to/3oEe9Es. The Southern Poverty Law Center has designated ADF a hate group. *See* S. Poverty Law Ctr., *Why is Alliance Defending Freedom a Hate Group?* (Apr. 10, 2020), https://bit.ly/3HE6LS1 (accessed Nov. 19, 2021).

willing to participate as expert witnesses"); Ex. Q at 169:18-171:4. Like the disqualified expert in *Lebron*, Dr. Hruz "developed his opinions expressly for purposes of testifying" in an area outside his specialty. *Lebron*, 772 F.3d at 1369.

In sum, Dr. Hruz is not qualified to serve as an expert on the diagnosis or the mental health treatment paradigms for gender dysphoria and his testimony should be limited to "the risks associated with puberty blocking medication and hormone therapy." *Kadel,* 2022 WL 3226731, at *9.

II. Dr. Hruz's opinions and testimony are not relevant to this case.

To satisfy the helpfulness requirement, the testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Id.* at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* The "court must satisfy itself that the proffered testimony is relevant to the issue at hand, for that is a precondition to admissibility." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 282 (4th Cir. 2021) (cleaned up). "The touchstone of this inquiry is the concept of relevance." *Prosper v. Martin*, 989 F.3d 1242, 1249 (11th Cir. 2021). Thus, "expert testimony which does not relate to any issue in the case is not relevant and non-helpful." *Knight v. Boehringer Ingelheim*

Pharms., Inc., 323 F.Supp.3d 837, 846 (S.D. W.Va. 2018). In order to be relevant, an opinion needs to "fit" with the facts at issue. *Simmons v. Augusta Aviation, Inc.*, 596 F. Supp. 3d 1363, 1374 (S.D. Ga. 2022) "To satisfy this requirement, the testimony must concern matters beyond the understanding of the average lay person and logically advance a material aspect of the proponent's case." *Id.* Testimony that "offers nothing more than what lawyers for the parties can argue in closing arguments" or that consists of "subjective portrayals of factual information" "generally will not help the trier of fact." *Giusto v. Int'l Paper Co.*, 2021 WL 3603374, at *4 (N.D. Ga. Aug. 13, 2021).

This case is about whether Defendants' exclusion of coverage for medically necessary gender-affirming health care treatments violates Plaintiffs' rights. Many of Dr. Hruz's opinions are not relevant to this inquiry as they do not have a "valid scientific connection to the pertinent inquiry" *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir.2009). His opinions do not "fit" because they are not sufficiently tied to the facts of the case so that they will aid a factfinder.

A. Dr. Hruz's opinions about "desistance" are irrelevant.

Take for example Dr. Hruz's opinions about purported "desistance" rates as a reason to question the provision of gender-confirming care. Another subject matter area in which the *Kadel* Court excluded Dr. Hruz's testimony. *Kadel*, 2022

WL 3226731, at *9. Dr. Hruz spends considerable time on (and builds most of his testimony questioning the propriety of gender-affirming health care upon) antiquated studies showing that a majority of *prepubertal* children diagnosed with *gender identity disorder*—an outmoded diagnosis *distinct from gender dysphoria* with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior. *See*, *e.g.*, Ex. A at ¶¶63-64; 141. But not only are such opinions based on faulty propositions, they simply do not fit the facts of this case.

Dr. Hruz's testimony that focuses on the risks associated with providing hormone therapy to prepubescent children—children who have not begun puberty—is not relevant. Ex. C at 125:23-126:5. By his own admission, "no medical and surgical interventions are initiated until after the onset of puberty" under any model of treatment. *Id.* But again, no hormonal or surgical care is recommended for or provided to *prepubertal* children, nor are any of the plaintiffs prepubertal children. Accordingly, Dr. Hruz's opinions regarding "desistance" are thus irrelevant to this case.

B. Dr. Hruz's opinions about an "international response" in other countries is irrelevant.

Dr. Hruz's opinions about a purported "international response" regarding the provision of gender-confirming care in Finland, Sweden, and the United Kingdom are both misleading and wholly irrelevant. Ex. A at ¶¶123-126; Ex. D at 91-96. In the first place, Dr. Hruz has offered no firsthand knowledge of other

countries' policies, so he is not qualified to testify about them. And his testimony is false, or at best, misleading, since, each of these countries *provides and covers* some gender-confirming hormonal and surgical treatment for gender dysphoria for adolescents and adults, whereas AHCA excludes treatment completely from Medicaid coverage. *See*, *e.g.*, Ex. C at 183:23-184:4, 185:3-10, 189:14-190:7; *see also Brandt by & through Brandt v. Rutledge*, 47 F.4th 661, 671 (8th Cir. 2022) ("Similarly, the WPATH Standards of Care and the Finnish council both recommend that cross-sex hormones be considered only where the adolescent is experiencing persistent gender dysphoria, other mental health conditions are well-managed, and the minor is able to meet the standards to consent to the treatment."). Moreover, how care is provided and covered in countries with nationalized health care systems is not relevant to whether gender-confirming care should be covered by Medicaid in Florida.[5]

C. Dr. Hruz's musings about the causes of gender dysphoria are irrelevant.

Dr. Hruz opines, without any evidence, that gender dysphoria *may be* caused by social contagion and social pressure. Ex. A at ¶¶ 31, 91, 116-118; Ex. D at 40-43, 99. But whether gender dysphoria is caused by social contagion is both wholly

[5] For example, in Sweden standards of care are developed through legislation and thus part of a political process, which contrasts with the process in the Florida. *See* Socialstyrelsen, *About the National Board of Health and Welfare*, https://www.socialstyrelsen.se/en/about-us/ (accessed Nov. 19, 2021) (noting that standards are based on legislation).

unsupported, as described below, and irrelevant to the case at hand. It is undisputed that gender dysphoria is a recognized medical condition that necessitates medical treatment. *See*, *e.g.*, Ex. C at 57:24-58:9 ("Q. Would you agree there are transgender people in this world? A. … That's undeniable that … there are individuals that have this experience of discordance between their gender identity and their sex."); *see also Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 594-95 (4th Cir. 2020). Likewise his musings about as to the difference between gender identity and "biological sex," including as to whether "biological sex" can be changed, are immaterial since this case is about access to gender-affirming care, not changing sex. Ex. A at ¶¶ 14, 58, 66. Because each of these opinions offered lacks any "valid scientific connection to the disputed facts in the case," they should be excluded. *Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999).

D. Dr. Hruz's Opinions about WPATH Standards of Care are irrelevant.

Dr. Hruz opines that WPATH should be disregarded as an "advocacy group" and that its recommendations "represent ideological positions devoid of rigorous scientific evidence"[6] and that the Endocrine Society Guidelines should be rejected because some of the committee members are also WPATH members. Ex. A at ¶¶

[6] Without any support, Dr. Hruz also claims that the American Academy of Pediatrics is a "politically influenced, non-science association." Ex. A at ¶140.

88-97. However, Dr. Hruz has not demonstrated any personal knowledge regarding the internal conversations at WPATH, has not participated in WPATH conferences, is not a member of WPATH and therefore lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). In short, Dr. Hruz does not have "any experience with . . . WPATH. . . upon which to base his criticisms[and] is therefore not qualified to testify about the credibility of th[at] organization[]." *Kadel,* 2022 WL 3226731, at *10.

E. Dr. Hruz's Hypothetical and Speculative opinions are irrelevant.

Finally, and perhaps most crucially, essentially all of Dr. Hruz's opinions are irrelevant because they are not based on fact, let alone "fit" within the facts of case. Dr. Hruz's report in this case is substantially similar to the report he submitted in *Kadel*. *Compare* Ex. A and Ex. D. Two years ago, when asked about his opinions in the report submitted in *Kadel*, he testified that they were hypotheses. More specifically, he testified that the entirety of his opinions is based on *hypotheses*, meaning they are based on speculation. Ex. C at 154:4-8 ("A. You know, all along here, … I've been stating, and I hope very clearly, that much of my opinion is based upon hypotheses and alternative hypotheses, because there is no definitive answer to this question."); *id.* at 57:1-3 ("A. Because I present many things in my report as hypotheses. And without making definitive statements.").

Indeed, Dr. Hruz purportedly has no view as to what modality of treatment should be provided to transgender people suffering gender dysphoria. *Id.* at 61:21-62:2. Such "speculation is unreliable evidence and is inadmissible." *Dunn*, 275 F.Supp.2d at 684; *see Allison v. McGhan Medical Corp.*, 184 F.3d 1300, 1312 (11th Cir. 1999). In other words, Dr. Hruz lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). And opinions based on "subjective belief or unsupported speculation" should be rejected. *Daubert*, 509 U.S. at 589-590.

* * *

The opinions expressed by Dr. Hruz are insufficiently tied to the facts of this case so that they will aid a factfinder and should be excluded as irrelevant.

III. Dr. Hruz's opinions and testimony are unreliable.

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "At this stage,

the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010). In making this determination the court can consider a variety of factors, including whether the purported expert's theory has been tested, whether it has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291-92 (11th Cir. 2005).[7] To be reliable the expert's testimony must always be based on "good grounds." *Daubert,* 509 U.S. at 590. Moreover, *Daubert* requires that reliable expert testimony be more than scientifically unsupported "leaps of faith." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d at 1202. Here, Dr. Hruz's opinions fail all indicia of reliability. Dr. Hruz's proffered opinions are based on nothing more than rank speculation, "untested" theories, uncorroborated anecdotes, and assumptions that are obsolete, flawed, unethical, and expressed opinions based upon "unsettled science." What is more, some of his opinions are patently false.

[7] Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. Hendrix, 255 F.R.D. at 578-79.

A. Dr. Hruz's opinions are unreliable because they are based on untested hypotheses and speculation.

As noted above, ***Dr. Hruz's opinions are hypotheses***; hypotheses that he himself has not tested or studied. *See, e.g.,* Ex. A at ¶¶31; 76; 90-91; 116-118; 130-131. And "[w]hile hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination." *Dunn v. Sandoz Pharms. Corp.*, 275 F.Supp.2d 672, 684 (M.D.N.C. 2003). "[T]he courtroom is not the place for scientific guesswork, even of the inspired sort." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Indeed, "[w]here an expert's opinion testimony is founded on an unsupported premise, it gives rise to an inference that is based on speculation and has no evidentiary value." *Walker v. Blitz USA, Inc.*, 663 F. Supp. 2d 1344, 1364 (N.D. Ga. 2009). At bottom, such speculation is unreliable evidence and is inadmissible.

B. Dr. Hruz's opinions are unreliable because they are misleading and therefore do not serve to enlighten the trier of fact.

In addition, some of Dr. Hruz's opinions are misleading at best, or flat out false. For example:

One. Dr. Hruz opines that the literature around gender-affirming care is "in a state insufficient to enable sound conclusions about the efficacy of "affirming treatments." Ex. A at ¶¶93; 122; 142; Ex. D at 100 ("treatments – hormones and

surgery – for gender dysphoria and 'transitioning' have not been accepted by the relevant scientific communities (biology, genetics, neonatolgy [sic], medicine, psychology, etc.)."). Not true. It is the official, consensus, evidence-based position of the National Academies of Science, Engineering, and Medicine that, "[a] major success of these guidelines has been identifying evidence and establishing expert consensus that gender-affirming care is medically necessary and, further, that withholding this care is not a neutral option." Ex. H at 361;[8] Ex. C at 205:20-206:22. Indeed, "[a] number of professional medical organizations have joined WPATH in recognizing that gender affirming care is medically necessary for transgender people." Ex. H at 361. This includes, among others, the American Medical Association, American Psychiatric Association, American Psychological Association, American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, and the Endocrine Society. *Id.*; Ex. E at 58:21-61:9. It also includes Dr. Hruz's own employer, Washington University in St. Louis. Ex. C at 85:14-86:11.

Two. In his report, Dr. Hruz presented a number of modalities of treatment for the care of patients with gender dysphoria, including: (1) "conversion" or "reparative therapy"; (2) "watchful waiting"; and (3) the "affirming" approach, as

[8] Ex. H, a report of the National Academies, is self-authenticating as a publication issued by a public authority, Fed. R. Evid. 902(5), and is appropriate for judicial notice, *United States v. Doe*, 962 F.3d 139, 147 n.6 (4th Cir. 2020).

if these did not endorse the provision of gender-affirming medical care for adolescents and adults. Ex. A at ¶¶54-65; Ex. D at 49-50. In doing so, Dr. Hruz opined that the approach advocated by Dr. Kenneth Zucker and the "watchful waiting" model use "modern psychotherapeutic approaches to address suicidal ideation in children with gender dysphoria." Ex. A at ¶¶63-64; *see also* Ex. D at 50-51 (Dr. Hruz explaining that treatment "involve[] no medical treatment and is currently the best scientifically supported intervention."). But Dr. Hruz misrepresents these approaches by failing to explain that Dr. Zucker's approach and the "watchful waiting" model, which recommends the provision of gender-affirming medical care if a patient's gender dysphoria persists into adolescence. Ex. G; Ex. C at 121:6-12, 125:11-17. For example, with regards to Dr. Zucker, his approach has been described as follows by the APA:

> For adolescent patients (including those who first came to the clinic as young children), Dr. Zucker follows the Standards of Care Guidelines of the World Professional Association for Transgender Health. The treatment options include helping patients make a satisfactory transition to the opposite sex, including the institution of hormonal treatment to facilitate transition. In some cases, treatment may include helping an interested adolescent obtain sex-reassignment surgery.

Ex. R; Ex. G at 61. Indeed, "All of the three models of care … share in common the administration of hormonal treatment in adolescence." *Id.* at 64.

Three. In that same vein Dr. Hruz falsely presented "reparative therapy" as if it was an accepted modality of treatment. Ex. A at ¶60. Nothing could be further

from the truth, however. The provision of conversion/reparative therapy represents a fringe view completely contrary to the mainstream medical and scientific community in the United States. As Dr. Hruz has previously acknowledged in deposition, the American Psychiatric Association and the American Psychological Association oppose "reparative therapy" or gender identity change efforts as unethical and harmful. Ex. C at 164:1-170:8. The same position adopted by the National Academies. *Id.* at 176:9-177:24; Ex. H at 361-363. Indeed, per the American Psychological Association's Resolution on Gender Identity Change Efforts, "individuals who have experienced pressure or coercion to conform to their sex assigned at birth or therapy that was biased toward conformity to one's assigned sex at birth have reported harm resulting from these experiences such as emotional distress, loss of relationships, and low self-worth." Ex. S. What is more, Dr. Hruz cites to no authority—let alone any original, peer-reviewed study, in support of this so-called approach to treatment.[9]

Four. Dr. Hruz's misrepresents "desistance" rates as a reason to question the provision of gender-confirming care. This is a subject matter area in which the *Kadel* Court excluded Dr. Hruz's testimony. *Kadel v. Folwell,* 2022 WL 3226731at *9.

[9] Hruz cites to Dr. Ken Zucker's work as supportive of this therapeutic approach. However, as outlined above, Dr. Hruz grossly misrepresents Dr. Zucker's approach. What is more, the citation to Dr. Zucker is to an opinion article not any peer-reviewed original research.

Dr. Hruz spends considerable time on (and builds most of his testimony questioning the propriety of gender-affirming health care upon) antiquated studies showing that a majority of *prepubertal* children diagnosed with *gender identity disorder*—an outmoded diagnosis *distinct from gender dysphoria* with different diagnostic criteria—"desisted" from their gender nonconformity or cross-gender behavior. Ex. A at ¶¶ 63-64. But, his presentation of this literature is extremely misleading since, not only due to his reliance on outdated studies, but also because he ignores the more recent literature which has uniformly found that youth who have a diagnosis of gender dysphoria in adolescence overwhelmingly continue to identify as transgender as they age.[10] Moreover, as Dr. Hruz has previously admitted that absolutely no gender-affirming medical or surgical care is provided to *prepubertal* children. Ex. C at 125:23-126:5. That is true for each of the treatment paradigms Dr. Hruz discusses (apart from "conversion" or "reparative therapy"), a fact Dr. Hruz did not disclose.

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[10] *See, e.g.,* Kristina R. Olson, *Gender Identity 5 Years After Social Transition*, 150 Ped. e2021056082 (2022) (of 300 youth with gender dysphoria, at the end of the five years, 94% of participants still identified as transgender); Annelou L C de Vries et al., *Puberty Suppression in Adolescents with Gender Identity Disorder: A Prospective Follow-Up Study*, 8 J. Sex. Med. 2276 (2011). Notably, Thomas D Steensma, who co-authored the study on which Dr. Laidlaw improperly cites for the proposition that most youth with gender dysphoria "desist" in their gender identity, also co-authored the de Vries study, which looked 70 youth in the Netherlands referred for treatment of gender dysphoria between 2000 and 2008, found that all of them decided to continue their medical transition after 1-2 years, confirming that "young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood." *Id.* at 2281.

Id. at 119:22-140:12. His opinions are therefore not only misleading, but also irrelevant, since this case is about the coverage for medically necessary gender-affirming medical care, and none of the plaintiffs are prepubertal children.

Five. Dr. Hruz provides no scientific bases for his conclusions that "A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity" or that "A currently unknown percentage and number of patients reporting gender dysphoria may be manipulated by a social contagion and social pressure processes, including peer group, social media, YouTube role modeling, and parental pressures." Ex. A at ¶¶ 130-131. But "Hruz is not a statistician and does not discuss in his report how he came to those conclusions, what data he relied upon, or what methodology he applied to that data." *Kadel*, 2022 WL 3226731, at *9. "This testimony will therefore be excluded as unreliable." *Id.*

* * *

The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr. Hruz has misrepresented or omitted information that goes to the heart of his opinions and calls into question the reliability of his opinions. While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts'

omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case here where Dr. Hruz omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation. In such circumstances, the "potential to mislead" rather "than to enlighten" is too great. *In re Lipitor*, 892 F.3d at 632.

C. Dr. Hruz's opinions are unreliable because they are not generally accepted in the scientific and medical community.

General acceptance in the relevant scientific community is also relevant to the reliability inquiry. *Nease*, 848 F.3d at 229. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known technique or theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Hruz's opinions are outside the mainstream of medical and scientific opinion and have been explicitly rejected by these relevant communities.

The provision of gender-confirming care has been accepted and endorsed, *inter alia*, by the: American Medical Association; American Psychiatric Association; American Psychological Association; Endocrine Society; Pediatric Endocrine Society; American Academy of Pediatrics; National Academies of Science, Engineering, and Medicine; and Dr. Hruz's own employer. Ex. C at 164:5-11; Ex. E at 70:25-71:22; *id.* 57:11-59:14; Ex. H at 361-363. The Fourth

Circuit has described it as "the consensus approach of the medical and mental health community." *Grimm*, 972 F.3d at 595; *Edmo v. Corizon, Inc.*, 935 F.3d 757, 771 (9th Cir. 2019) (the provision of gender-affirming care, consistent with the WPATH Standards of Care, represents "the ***broad medical consensus*** in the area of transgender health care," which "requires providers to individually diagnose, assess, and treat individuals' gender dysphoria.") (emphasis added); *see also Brandt v. Rutledge*, 551 F.Supp.3d 882, 890 (E.D. Ark. 2021) ("The consensus recommendation of medical organizations is that the only effective treatment for individuals at risk of or suffering from gender dysphoria is to provide gender-affirming care."), *aff'd*, 47 F.4th 661 (8th Cir. 2022); *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1018 (W.D. Wis. 2019).

In fact, another federal district court found as much when it enjoined Arkansas' state law seeking to ban gender-confirming treatment for minors. *See Brandt*, 551 F.Supp.3d 882. In doing so, the *Brandt* court explicitly found that: (a) "Gender-affirming treatment is *supported by medical evidence* that has been *subject to rigorous study*;" and (b) "*Every major expert medical association* recognizes that gender-affirming care for transgender minors may be *medically appropriate and necessary* to improve the physical and mental health of transgender people." *Id.* at 891 (emphasis added). Notably, Dr. Hruz filed an expert declaration in the *Brandt* case that is virtually identical to the report he filed in this

case. As such, the *Brandt* court's findings stand as a stark repudiation of Dr. Hruz's opinion that gender-affirming care is "experimental" and "not medically necessary." Ex. A at ¶¶137-138; Ex. D at 17. It is for these reasons that the Court in *Kadel* excluded much of Dr. Hruz's opinions in that case on these issues. *Kadel v. Folwell,* 2022 WL 3226731at *9.

Conversely, Dr. Hruz's opinions in support of reparative therapy or gender identity change efforts has also been rejected by the general scientific community, among others. Ex. C at 164:1-170:8; Ex. E at 118:7-19, 237:1-23. *See also King v. Governor of the State of New Jersey*, 767 F.3d 216, 221–22 (3d Cir. 2014); *Pickup v. Brown*, 740 F.3d 1208, 1223–24 (9th Cir. 2014). This again shows that Dr. Hruz's opinions are wildly outside the mainstream and his failure to notify the Court of the rejection of these purported alternative treatment renders his testimony unreliable.

D. Dr. Hruz's opinions are unreliable because they have no support and are based on ipse dixit.

As noted herein, Dr. Hruz's opinions are based on untested hypotheses and do not have any factual support. For example, Dr. Hruz opines that gender dysphoria *may be* caused by social contagion and social pressure. Ex. A at ¶131. But he offers no evidence for this hypothesis, which he admits has not been tested. *Id.* Of course, "nothing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence which is connected to existing data only

by the *ipse dixit* of the expert." *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997). And this is one of those circumstances in which "there is simply too great an analytical gap between the data and the opinion proffered." *Id*. In fact, the only study to have looked at this hypothesis found no support for the hypothesis. Ex. N.

* * *

Given that Dr. Hruz's opinions fail to meet the most basic indicia of reliability, the Court should exclude Dr. Hruz's opinions and testimony as unreliable.

IV. Dr. Hruz's opinions are so tainted by his personal bias as to render his opinions unreliable.

While Plaintiffs are cognizant of the fact that bias in an expert witness's testimony is usually an issue of credibility as opposed to one of admissibility, when an expert's opinions are based on bias as opposed to scientific or medical knowledge, then the question of bias becomes one of reliability and admissibility. Indeed, reliability is a flexible inquiry wherein "courts must ensure that an expert's opinion is based on scientific, technical, or other specialized knowledge and not on belief or speculation." *Sardis*, 10 F.4th at 281. Here, there is ample evidence that Dr. Hruz's testimony is so permeated and tainted by his unscientific views and personal bias as to render it unreliable. *See Kadel*, 2022 WL 3226731, at *9 ("Plaintiffs have offered evidence that calls Hruz's motivations—and thereby, his reliability—into serious question."); *cf. Sanchez v. Esso Standard Oil de Puerto*

Rico, Inc., No. CIV 08-2151, 2010 WL 3809990, at *4 (D.P.R. Sept. 29, 2010).

More specifically, Dr. Hruz's testimony appears to be motivated by his personal and religious views regarding transgender people. To be clear, Plaintiffs do not seek to impugn or malign whatever moral or religious views Dr. Hruz may hold. However, to the extent Dr. Hruz's moral and religious views have influenced his purported expert opinions— indeed, they seem to be the motivating factor— that is something the Court must be aware of and should consider as it assesses the reliability of his testimony.

In his report, Dr. Hruz discusses meeting with Dr. Norman Spack, a noted pediatric endocrinologist and the co-founder of Boston Children's Hospital Gender Management Service Program, as someone he consulted when he first began to study issues relating to gender dysphoria from a scientific standpoint. Ex. Ex. A at ¶9; D at 6. But Dr. Spack's account of this encounter is quite different. Dr. Spack asserts that "Dr. Hruz did not discuss or mention that his issues or concerns were based on science." Ex. K at ¶ 13. To the contrary, Dr. Hruz expressed to Dr. Spack that he had "a significant problem with the entire issue" and "whole idea of transgender," and that for him, it was "a matter of [his] faith." *Id.* at ¶¶ 11-12. When confronted with Dr. Spack's account, Dr. Hruz notably did not deny he made such statements. Ex. C at 247:10-251:4.

Similarly, Dr. Hruz misrepresents the nature of his conversations with

"dozens of parents of children with gender dysphoria" as that of seeking "to understand the unique difficulties experienced by this patient population." Ex. A at ¶9; Ex. D at 6. One of these parents gives quite a different account of meeting with Dr. Hruz, however. Dr. Hruz met with Kim Hutton, the mother of a transgender child, in 2013. Ex. E 102:24-103:9, 126:12-129:25. Dr. Hruz says he met with the parent of a transgender child who was affiliated with an organization called TransParent, during a "very early investigative phase" of his study of gender dysphoria. Ex. E 103:25-104-7, 102:24-103:9. By Ms. Hutton's account, the nature of Dr. Hruz's conversation with her revealed that that he was firmly opposed to gender-affirming care, as well as opposed to a having a Transgender Center at St. Louis Children's Hospital, and that this opposition was rooted in his personal moral and religious views. Indeed, Dr. Hruz reportedly told Ms. Hutton, "there will never be a pediatric gender center at St. Louis Children's Hospital. I won't allow it." Ex. L at 30:8-30:11. Dr. Hruz also told Ms. Hutton that her "child was not normal and would never be normal," Ex. L at 28:20-28:23; that "the idea of doing surgeries on transgender people is -- is wrong," *id.* at 21:21-27:24; and repeatedly encouraged Ms. Hutton to "read Pope John Paul II's writings on gender," because it would explain everything. *id.* at 29:17-29:20. And in response to Ms. Hutton's statement that transgender children "are at a 41 percent risk of suicide if they don't have acceptance and -- and care from their parents and -- and

if they don't get their medical needs met," Dr. Hruz responded that, "Some children are born in this world to suffer and die." *Id.* at 29:21-30:4. As a result, Ms. Hutton left her conversation with Dr. Hruz—a conversation Dr. Hruz says he "was approaching [] in a purely investigative manner," Ex. E at 126:16-127:3—"perplexed" due to "the religious tone of the conversation," which she "figured [] would at least be based on science." Ex. L at 37:11-37:19.

The bias illuminated by Dr. Spack's and Ms. Hutton's testimony is further confirmed by the nature of Dr. Hruz's publications and presentations on this issue. With one exception, all of Dr. Hruz's publications pertaining to gender dysphoria have been in religiously affiliated, non-scientific publications. Ex. C at 42:10-49:19. Similarly, aside from a handful of grand rounds, Dr. Hruz has not made any presentations about this topic at scientific conferences, *id.* at 90:17-93:3; instead, presenting on this topic to religious organizations. For instance, in November 2017, Dr. Hruz gave a presentation at the Saint John Paul II Bioethics Center at the Holy Apostles College & Seminary, where he referred to being transgender as something that "probably goes back to some of the early heresies in the church," and to pictures of transgender people as "disturbing." Ex. E at 83:5-85:20. When confronted with these statements, Dr. Hruz did not disavow or deny making them. *Id.* And in February 2018, Dr. Hruz presented at an "International Conference on Gender, Sex and Education" that was billed as "the world's first great public

objection to totalitarian LGBTI laws," "a conference to oppose gender ideology," and "against the LGBTI doctrine… taking hold of Western Countries." Ex. M; Ex. C at 93:4-97:10.

The foregoing, coupled with Dr. Hruz's departure with generally accepted medical and scientific standards, demonstrates that Dr. Hruz's purported expert testimony lacks any indicia of reliability. And while the Federal Rules of Evidence state that "[e]vidence of a witness's religious beliefs or opinions is not admissible to attack or support the witness's credibility," Fed. R. Evid. 610, the Advisory Committee Notes to Rule 610 make clear that "an inquiry for the purpose of showing interest or bias because of them is not within the prohibition." Advisory Committee Notes to Rule 610. Indeed, "[w]ithout this critical information," the Court would be "deprived of the necessary facts from which it could appropriately draw inferences about [Dr. Hruz's] reliability." *State v. Heinz*, 485 A.2d 1321, 1328 (Conn. App. 1984). Here, it is evident that Dr. Hruz has not been candid regarding his experiences or the bases for his "opinions." The record evidence demonstrates a clear bias by Dr. Hruz against transgender people generally, which infects his reliability as a purported expert witness in this case.

V. Dr. Hruz's opinions lack probative value and are therefore inadmissible under Federal Rule of Evidence 403.

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet

admissibility requirements may still be excluded under Fed. R. Evid. 403. Exclusion under Rule 403 is appropriate if the probative value of otherwise admissible expert testimony is substantially outweighed by its potential to confuse or mislead the jury, or if the testimony is cumulative or needlessly time consuming. *See, e.g., Hull v. Merck & Co., Inc.*, 758 F.2d 1474, 1477 (11th Cir.1985) (admission of speculative and "potentially confusing testimony is at odds with the purposes of expert testimony as envisioned in Fed. R. Evid. 702"); *Tran v. Toyota Motor Corp.*, 420 F.3d 1310, 1316 (11th Cir. 2005) (affirming exclusion of expert testimony as cumulative). Consequently, "the judge in weighing possible prejudice against probative force under Rule 403 . . . exercises *more* control over experts than over lay witnesses." *Daubert*, 509 U.S. at 595 (cleaned up).

Accordingly, the Court should exclude Dr. Hruz's opinions because its introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Dr. Hruz offers opinions that are irrelevant to the issues in this case, and, in any event, the opinions he offers are speculative and unreliable. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender- confirming care based on speculation, irrelevant, misleading, or biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude Dr. Hruz's report,

opinions, and testimony and limit his opinions to those permitted in *Kadel*.

Respectfully submitted this 7th day of April, 2023.

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Memorandum of Law contains 7,463 words.

/s/ Shani Rivaux
Counsel for Plaintiffs

TAB 138

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE
EXPERT TESTIMONY OF DR. KRISTOPHER KALIEBE

Now come, Plaintiffs, by and through their counsel, and respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert, Dr. Kristopher Kaliebe, pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702.

Dr. Kaliebe is not a qualified expert on gender dysphoria or its treatment, and his opinions and testimony are neither relevant nor reliable, under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible because any probative value they may have (and they have none) is substantially outweighed by the danger of unfair prejudice, confusion of the issues,

waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

Based on Dr. Kaliebe's lack of qualifications and the unreliability and unhelpfulness of his testimony and opinions, at minimum, the Court should exclude any portions of the expert report, opinions, and testimony of Dr. Kaliebe that go beyond his experience regarding the diagnosis of gender dysphoria in children and adolescents.

A memorandum of law is filed contemporaneously herewith.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Omar Gonzalez-Pagan

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that he attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

TAB 139

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT TESTIMONY OF DR. KRISTOPHER KALIEBE

TABLE OF CONTENTS

Plaintiffs respectfully submit this memorandum of law in support of their motion to exclude the expert testimony of Dr. Kristopher Kaliebe.[1]

INTRODUCTION AND STATEMENT OF THE CASE

Plaintiffs are transgender Medicaid beneficiaries who have been diagnosed with gender dysphoria. In August 2022, Defendants adopted a rule, Florida Administrative Code 59G-1.050(7) (the "Challenged Exclusion"), prohibiting Medicaid coverage of services for the treatment of gender dysphoria. Defendants adopted the Challenged Exclusion after undergoing a process with a predetermined outcome that concluded that the provision of medical treatment for the treatment of gender dysphoria, including puberty blockers, hormone therapy, and surgery, "do not conform to GAPMS [("generally accepted professional medical standards")] and are experimental and investigational." Defendants thus deny equal treatment to Plaintiffs based on sex because they are transgender.

In response, Defendants have put forward an expert, Dr. Kristopher Kaliebe, a child and adolescent psychiatrist, who has no experience regarding the treatment of gender dysphoria, nor has ever studied or written any literature—alone scientific, peer-reviewed literature—on gender identity or gender dysphoria. However, Dr. Kaliebe is not a qualified expert on gender dysphoria or its treatment, and his

[1] Unless otherwise specified, all exhibits cited herein are attached to the contemporaneously filed Declaration of Omar Gonzalez-Pagan.

opinions and testimony are neither relevant nor reliable, under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny.

Accordingly, and for the reasons set forth below, the Court should exclude the expert report, opinions, and testimony of Dr. Kaliebe. At minimum, based on Dr. Kaliebe's lack of qualifications and the unreliability and unhelpfulness of his testimony and opinions, the Court should exclude any portions of the expert report, opinions, and testimony of Dr. Kaliebe that go beyond his experience regarding the diagnosis—not treatment—of gender dysphoria in children and adolescents.

LEGAL STANDARD

"The admission of expert evidence is governed by Federal Rule of Evidence 702, as explained by *Daubert* and its progeny." *Rink v. Cheminova, Inc.*, 400 F.3d 1286, 1291 (11th Cir. 2005). "District courts are [thus] charged with [a] gatekeeping function." *Id.*; *see also United States v. Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of *Daubert*'s gatekeeping requirement cannot be overstated.").

In conducting their gatekeeping function, courts must "engage in a rigorous three-part inquiry" and determine whether

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of

> fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, 387 F.3d at 1260 (quoting *City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998)). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized they are "distinct concepts that courts and litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). "The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence." *Rink*, 400 F.3d at 1292.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592 (emphasis added). "Rule 702 applies whether the trier of fact is a judge or a jury." *UGI Sunbury LLC v. A Permanent Easement for 1.7575 Acres*, 949 F.3d 825, 832 (3d Cir. 2020). Even rigorous cross-examination is not a substitute for the court's gatekeeping role. *See Nease v. Ford Motor Co.*, 848 F.3d 219, 231 (4th Cir. 2017). As such, the court's gatekeeping role and the test for admissibility of expert testimony are applicable even at a bench trial or at the summary judgment stage. *See, e.g.*, *Rink*, 400 F.3d at 1294 (finding no abuse of discretion by the district court in motions to exclude in the context of summary judgment); *Kadel v. Folwell*, 2022

WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (granting motions to exclude in the context of summary judgment); *Lo v. United States*, 2022 WL 1014902, at *12 (W.D. Wash. Apr. 5, 2022) (excluding unqualified expert evidence in the context of a bench trial); *cf. UGI Sunbury*, 949 F.3d at 833 (holding the district court abused its discretion in a bench trial when it "ignored rule [702]'s clear mandate" by "sidestepping Rule 702 altogether and declining to perform any assessment of [expert]'s testimony before trial").

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, on occasion expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403.

ARGUMENT

I. Qualification – Dr. Kaliebe is not qualified to offer expert opinions on the treatment or causes of gender dysphoria, nor on the development of clinical practice guidelines.

An expert witness may be qualified "by knowledge, skill, experience, training, or education." Fed. R. Evid. 702. "Determining whether a witness is qualified to testify as an expert requires the trial court to examine the credentials of the proposed expert in light of the subject matter of the proposed testimony." *Banuchi v. City of Homestead*, 606 F.Supp.3d 1262, 1272 (S.D. Fla. 2022) (cleaned up). "Whether [an expert] is qualified is a threshold question, and vigorous cross-examination is no substitute." *Griffin v. Coffee Cnty.*, 608 F.Supp.3d 1363, 1373 (S.D. Ga. 2022),

objections overruled, 2022 WL 2805037 (S.D. Ga. July 18, 2022). If not qualified, the expert's testimony is unreliable. *See Reliastar Life Ins. Co. v. Laschkewitsch*, 2014 WL 1430729, at *1 (E.D.N.C. Apr. 14, 2014).

However, "qualifications alone do not suffice." *Clark v. Takata Corp.*, 192 F.3d 750, 759 n.5 (7th Cir. 1999); *see also Patel ex rel. Patel v. Menard, Inc.*, 2011 WL 4738339, at *1 (S.D. Ind. Oct. 6, 2011). Even "[a] supremely qualified expert cannot waltz into the courtroom and render opinions unless those opinions are based upon some recognized scientific method and are reliable and relevant under … *Daubert*." *Clark*, 192 F.3d at 759 n.5.

Moreover, "an expert's qualifications must be within the same technical area as the subject matter of the expert's testimony; in other words, a person with expertise may only testify as to matters within that person's expertise." *Martinez v. Sakurai Graphic Sys. Corp.*, 2007 WL 2570362, at *2 (N.D. Ill. Aug. 30, 2007); *see also Lebron v. Sec. of Fla. Dept. of Children and Families*, 772 F.3d 1352, 1369 (11th Cir. 2014) ("Expertise in one field does not qualify a witness to testify about others."). "Generalized knowledge of a particular subject will not necessarily enable an expert to testify as to a specific subset of the general field of the expert's knowledge." *Martinez*, 2007 WL 2570362, at *2.

This is particularly true in medicine where "no medical doctor is automatically an expert in every medical issue merely because he or she has graduated from

medical school or has achieved certification in a medical specialty." *O'Conner v. Commonwealth Edison Co.*, 807 F.Supp. 1376, 1390 (C.D. Ill. 1992), *aff'd*, 13 F.3d 1090 (7th Cir. 1994); *see also*, *e.g.*, *Hartke v. McKelway*, 526 F.Supp. 97, 100-101 (D.D.C. 1981). For example, a clinical psychologist may not be necessarily qualified to testify about stress worsening a preexisting heart condition, and a pediatrician experienced as a children's accident preventionist may not be qualified to testify to the conduct of an adult driver. *See Diviero v. Uniroyal Goodrich Tire Co.*, 919 F.Supp. 1353, 1355–56 (D. Ariz. 1996) (citing *Kloepfer v. Honda Motor Co.*, 898 F.2d 1452, 1458–59 (10th Cir. 1990), and *Edmonds v. Illinois Central Gulf Railroad*, 910 F.2d 1284, 1287 (5th Cir. 1990), as examples).

Here, Dr. Kaliebe opines that: gender dysphoria has been rare until the last two decades; there is no consensus in the field regarding the treatment of gender dysphoria, nor is there an evidence-base sufficient to lead to any confident recommendations; the evidence for affirmative treatment is low-quality; spread of ideology combined with technologically induced contagion effects leading the recent increase in gender dysphoria; and on criticisms of medical associations as well as political criticisms. Ex. A, at ¶ 4. But Dr. Kaliebe, a child and adolescent psychiatrist, is not qualified to render most, if any, of the opinions he proffers.

Dr. Kaliebe (1) has never conducted any original, peer-reviewed research about gender identity, transgender people, or gender dysphoria, Ex. B, at 43:17-44:1;

(2) has not published any literature, let alone scientific, peer-reviewed literature, on gender dysphoria or transgender people, Ex. B, at 25:5-14; (3) has never treated a patient for gender dysphoria, Ex. B, at 33:18-21 ("So you wouldn't be providing treatment for the dysphoria at Silver Clinic? A. I think we would not be directly addressing gender dysphoria in psychotherapy."); *id.* at 33:15-16 ("A. … I don't know that we would say we were giving therapy for gender dysphoria"); *id.* at 138:24-139:1 ("Q. You do not provide medical treatment for gender dysphoria; is that right? A. Medicines, correct.");[2] and (4) is not an endocrinologist, pediatrician, adolescent medicine doctor, surgeon, or other kind of physician qualified to medically treat gender dysphoria. Ex. B, at 44:2-8; Curriculum vitae attached to Ex. A.

Given the above, the district court's decision in *Kadel*, 2022 WL 3226731, at **5-17, is most instructive here. Like other experts in *Kadel*, Dr. Kaliebe "has never … treated gender dysphoria, … conducted any original research about gender dysphoria diagnosis or its causes, or published any *scientific*, *peer-reviewed*

[2] At most, Dr. Kaliebe can claim that he has supervised psychiatric residents (Ex. B, at 29:9-10) in overseeing the care of twelve (12) patients with gender dysphoria (Ex. B, at 28:15-20) for "comorbidities," like "depression or anxiety or trauma or personality disorders or whatever," by "trying to provide them skills and sort of basic coping mechanisms, self-regulation, all the standard things you provide to someone who has emotional dysregulation or behavioral problems or, you know, emotional problems, standard care." Ex. B, at 33:21-34:5. But as Dr. Kaliebe has acknowledged, "[p]roviding treatment for comorbidities doesn't necessarily address a patient's gender dysphoria." Ex. B, 35:10-16.

literature on gender dysphoria." *Kadel*, 2022 WL 3226731, at *9 (emphasis added). Dr. Kaliebe "is not an endocrinologist, nor has he ever treated a patient with hormone therapies." *Id.* at at *13; Ex. B, at 32:15-17 ("A. … nor are we involved with providing hormones or those type of things."); *id.* at 138:24-139:4. In fact, Dr. Kaliebe had to consult his wife, an adult endocrinologist, ahead of his deposition in order to familiarize with the effects of puberty-delaying medications and hormone therapy. Ex. B, at 12:24-13:11, 139:5-8. Thus, Dr. Kaliebe "is not qualified to render opinions about … the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for … endocrinologists." *Kadel*, 2022 WL 3226731, at *13. Additionally, Dr. Kaliebe "is not a surgeon and has no experience with surgery for gender dysphoria and, therefore, is not qualified to testify to the risks associated with surgery or the standard of care used by surgeons for obtaining informed consent for surgery." *Id.* at *9.

Moreover, Dr. Kaliebe is not qualified to opine on the diagnosis and treatment of gender dysphoria in adults. During his deposition, Dr. Kaliebe acknowledged that he "definitely ha[s] more expertise and more experience in child psychiatry" and that "would be more where I'm comfortable." Ex. B, at 44:16-17, 45:1. While Dr. Kaliebe "was asked to review and opine generally," he "did [his] best to try to catch up on adult literature and know more about adult issues." Ex. B, at 44:21-22. But

that is not enough. *See* Ex. B, at 86:1-2 ("And I will admit that I know less about and am less up to date everything about adult transgender care.").

Dr. Kaliebe "is also not qualified to opine on the efficacy of randomized clinical trials, cohort studies, or other longitudinal, epidemiological, or statistical studies of gender dysphoria." *Kadel*, 2022 WL 3226731, at *13; *see*, *e.g.*, Ex. A, at ¶¶ 47, 163, 164. "He is not a statistician or epidemiologist, and there is no evidence in his report or deposition that he has any experience, specialized training, or knowledge about crafting a research study, analyzing data, or conducting a clinical trial." *Id.* A psychiatrist "with little to no research experience is not qualified to opine on the veracity of statistical studies." *Id.*

In large part, Dr. Kaliebe bases his opinions on his review of other people's scholarship—in fact, on non-primary sources, those being non-peer reviewed reports about the scientific literature. But "[m]erely reading literature in a scientific field does not qualify a witness—even an educated witness—as an expert." *Kadel*, 2022 WL 3226731, at *9; *see also Dura Auto. Sys. of Ind., Inc. v. CTS Corp.*, 285 F.3d 609, 614 (7th Cir. 2002) ("The *Daubert* test must be applied with due regard for the specialization of modern science. A scientist, however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty. That would not be responsible science."). Indeed, this is precisely the sort of "generalized knowledge of a particular subject" that courts have rejected as a qualification under

Rule 702. As with the disqualified expert in *Lebron* who "reached his opinion instead by relying on studies," this is not a sufficient qualification to serve as an expert witness. 772 F.3d at 1369.

Nor can Dr. Kaliebe claim to be qualified based on his conversations with the twelve (12) transgender minor patients, to whom he has provided no treatment for gender dysphoria and only supervised others' psychotherapeutic care of the patients. Such "reliance on anecdotal evidence" is a "red flag[] that caution[s] against certifying an expert." *Newell Rubbermaid, Inc. v. Raymond Corp.*, 676 F.3d 521, 527 (6th Cir. 2012).

Moreover, Dr. Kaliebe, who opines at length about the development of clinical practice guidelines by WPATH and the Endocrine Society (*see*, *e.g.*, Ex. A, at ¶¶ 62-63; Ex. C, at ¶¶ 19-26, 31-33), admits he is not an expert on the development of clinical practice guidelines. Ex. B, at 101:3-10; s*ee Solaia Tech. LLC v. ArvinMeritor, Inc.*, 361 F.Supp.2d 797, 813–14 (N.D. Ill. 2005) (finding expert was not qualified "to testify about areas in which he has admitted he has no expertise"); *accord Lifewise Master Funding v. Telebank*, 374 F.3d 917, 928 (10th Cir. 2004) (affirming trial court's ruling that purported expert could not testify where the court noted, inter alia, that witness admitted that he was not expert in areas pertinent to damages modeling). And Dr. Kaliebe does not profess any training or experience on the development of clinical practice guidelines.

The Court should find that Dr. Kaliebe is not qualified to testify about gender dysphoria and its treatment, the conduct and efficacy of scientific studies and the weighing of these, and the promulgation of clinical practice guidelines. At most, based on his purported experience diagnosing twelve (12) patients with gender dysphoria over his career, Dr. Kaliebe could testify to the diagnosis of gender dysphoria in children and adolescents.

II. Reliability – Dr. Kaliebe's opinions and testimony are unreliable.

An expert's testimony should only be admitted if it is sufficiently reliable. The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). It must be based on "good grounds," *Daubert,* 509 U.S. at 590, and cannot be based on "leaps of faith." *Rider*, 295 F.3d at 1202.

Thus, when determining the reliability of proposed expert testimony, courts "consider, to the extent possible: (1) whether the expert's theory can be and has been tested; (2) whether the theory has been subjected to peer review and publication; (3) the known or potential rate of error of the particular scientific technique; and (4)

whether the technique is generally accepted in the scientific community." *Quiet Tech.*, 326 F.3d at 1341. Other factors which may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *See Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578-79 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

"At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Id.* at 578. And "proffered evidence that has a greater potential to mislead than to enlighten should be excluded." *In re Lipitor (Atorvastatin Calcium) Mktg., Sales Pracs. & Prod. Liab. Litig. (No II) MDL 2502*, 892 F.3d 624, 632 (4th Cir. 2018).

Here, Dr. Kaliebe's report, testimony, and opinions fail all indicia of reliability. Dr. Kaliebe's proffered opinions are based on nothing more than speculation, "untested" theories, uncorroborated anecdotes, and assumptions that are obsolete, flawed, unethical, or expressed opinions based upon "unsettled science." What is more, some of his opinions are patently false.

A. Dr. Kaliebe's opinions are unreliable because they are based on unsupported premises, untested hypotheses, and speculation.

"While hypothesis is essential in the scientific community because it leads to advances in science, speculation in the courtroom cannot aid the fact finder in making a determination." *Dunn v. Sandoz Pharms. Corp.*, 275 F.Supp.2d 672, 684 (M.D.N.C. 2003). "[T]he courtroom is not the place for scientific guesswork, even of the inspired sort." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). Indeed, such "speculation is unreliable evidence and is inadmissible." *Dunn*, 275 F.Supp.2d at 684. "Where an expert's opinion testimony is founded on an unsupported premise, it gives rise to an inference that is based on speculation and has no evidentiary value." *Walker v. Blitz USA, Inc.*, 663 F.Supp.2d 1344, 1364 (N.D. Ga. 2009).

Here, several of Dr. Kaliebe's opinions are based on speculation, unsupported premises, or mere guesswork. Take the following examples:

One. Dr. Kaliebe opines that "Significant evidence points to a spread of ideology combined with technologically induced contagion effects leading the recent increase in gender dysphoria." Ex. A, at ¶ 4(e); *id.* at ¶¶ 30, 39-41. But Dr.

Kaliebe admits there is no evidence to support this opinion,[3] rather, in his words, "We are all *hypothesizing*, obviously." Ex. B, at 58:23-59:3 (emphasis added).[4]

Two. Dr. Kaliebe repeatedly opines about a purported failure of the scientific and medical community to study what he calls "body affirmation" as a psychotherapeutic approach to treatment. Ex. A, at ¶ 66(a) ("SOC 8 makes no analysis of privileging gender affirmation over body affirmation."); Ex. C, at ¶ 12 ("Body positivity and body acceptance are laudable goals and should be compared against the use of hormones and surgeries in order to determine which is a more effective and humane treatment."), *id.* at ¶ 13 ("Further research may well find psychotherapies or mind-body approaches with better results than gender affirmation through hormones and surgery."). However, Dr. Kaliebe cites no literature—none—in support this hypothetical treatment modality he repeatedly proposes. In fact, he concedes there is no literature at all to support this hypothetical approach to therapy. Ex. B, at 111:20-21; Ex. C, at ¶ 13. In other words, it is a hypothesis built upon unsupported premises.

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[3] For example, the literature to which Dr. Kaliebe cites to support his opinion does not relate to gender dysphoria, Ex. B, at 58:8-11, and the Littman article to which he cites "actually doesn't reach any conclusions as to social contagions," but rather "at best … raises hypotheses," Ex. B, at 71:15-18.

[4] To the extent Dr. Kaliebe points to two unscientific polls of the attendees to two conference panel sessions and a single personal anecdote, such evidence has no indicia of reliability. *See* Section II.C, *infra*.

Upon questioning, Dr. Kaliebe clarified that what he refers to as "body affirmation" has nothing to do with treating gender dysphoria or resolving a person's incongruence. At his deposition, Dr. Kaliebe explained that what he terms "body affirmation" "is purely about [a person] being comfortable with their body," such that "somebody that identifies as female" would be "completely comfortable with their stereotypically male body, notwithstanding that they identify as female." Ex. B, at 111:11-17. However, upon questioning Dr. Kaliebe admits that "part of somebody's gender dysphoria [is] the distress associated with that incongruence due in part to how they are perceived by others in the world." Ex. B, at 113:1-5. It is thus unclear how his hypothetical approach would treat gender dysphoria.

Indeed, Dr. Kaliebe posits that "if we could help people become more comfortable in the body that they are in, you know, perhaps, that would mean that they could be somewhat more comfortable and *maybe the gender dysphoria never goes away*, but we might be able to help them with their depression or anxiety or self-harm or other things." Ex. B, at 113:6-11 (emphasis added). But again, Dr. Kaliebe cites to nothing in support of this hypothetical, and until now unheard of, approach to treating gender dysphoria.

Three. Dr. Kaliebe repeatedly makes broad assertions that "in private, but not in public, most psychiatrists will acknowledge their doubts regarding affirmative care," Ex. A, at ¶ 123; "[m]ost psychiatrists are willing to admit we don't have

enough research to really know how to proceed," *id.*; and "[m]ost physicians have doubts about a gender medicine," Ex. C, at ¶ 36. However, Dr. Kaliebe fails to cite to any study, literature, or evidence in support of such broad assertions in every instance in which he makes them. Instead, Dr. Kaliebe bases these opinions on a few conversations he has had and then extrapolates them to the population of physicians and psychiatrists at large. *See*, *e.g.*, Ex. B, at 60:17-61:6, 63:19-64:4, 127:8-10, 146:10-25. But when Dr. Kaliebe's opinions are based on a select few anecdotes, it is a circumstance where "there is simply too great an analytical gap between the data and the opinion proffered," such that the expert testimony must be excluded. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 144 (1997).

Four. Dr. Kaliebe suggests that cognitive behavioral therapy (CBT) or yoga could be effective modes of psychotherapy for gender dysphoria. Ex. A, at ¶¶ 136, 142. But he admits he does not know if CBT could be effective to treat gender dysphoria (it cannot), because according to him it has not been studied. Ex. B, 152:7-22. Likewise, Dr. Kaliebe admits there are no studies on yoga as treatment of any mental health conditions, let alone gender dysphoria. Ex. B, at 164:21-165:9, 166:5-11. Such speculative opinions are wholly unreliable.

Similarly, Dr. Kaliebe suggests that "more specific and nuanced approaches for gender dysphoria exist," such as gender exploratory therapy. Ex. A, at ¶ 137 (citing to https://genderexploratory.com/). However, not only does he not cite to any

literature in support for this modality of treatment, but he admits that there is no evidence that gender exploratory therapy is safe or effective. Ex. B, at 159:2-4. Again, his opinion about gender exploratory therapy is speculative, at best.[5]

Five. Dr. Kaliebe opines in his rebuttal report that "[i]n childhood, most gender dysphoria spontaneously resolves without treatment." Ex. C, at ¶ 16. He provides no citation or evidence for this opinion, making it an unsupported premise that should be excluded as unreliable.

Six. Dr. Kaliebe opines that "it is clear the SOC 8 guidelines are at odds with the stated policies of most countries." Ex. C, at ¶ 6. He provides no citation or support for this extremely broad statement. What is more, he concedes he has no awareness "of which countries have adopted SOC 8." *Id.* The Court should reject this wholly unsupported opinion as unreliable.

Seven. Dr. Kaliebe's opinions about the innerworkings of WPATH or the motivations and opinions of its membership is wholly speculative and unreliable. *See*, *e.g.*, Ex. C, at ¶¶ 3-4. The same holds true for his criticisms of the Endocrine

[5] "Whereas gender-affirmative approaches follow the client's lead when it comes to gender, gender-exploratory therapy discourages gender affirmation in favor of exploring through talk therapy the potential pathological roots of youths' trans identities or gender dysphoria." Ex. D, at 472. "The surge of gender-exploratory therapy coincides with ongoing attempts to criminalize gender-affirming care for trans youths, sometimes masquerading as a compromise between gender-affirmative care and conversion practices and at other times functioning as the intellectual arm of political movements calling for the criminalization of gender-affirming care." *Id.* at 473.

Society. *E.g.*, Ex. A, at ¶ 105 ("While I have little direct experience with the Endocrine Society, my assessment is that many endocrinologists, and perhaps most, also believe their professional organization is also too strongly influenced by activist physicians."). Dr. Kaliebe has no experience with these organizations upon which to base his criticisms. "He is therefore not qualified to testify about the credibility of those organizations." *Kadel*, 2022 WL 3226731, at *10. Indeed, Dr. Kaliebe can "not offer[] any reliable testimony on this subject that will help the trier of fact." *Id.*

* * *

Dr. Kaliebe lacks knowledge "of facts which enable him to express a reasonably accurate conclusion as opposed to conjecture or speculation." *Jones v. Otis Elevator Co.*, 861 F.2d 655, 662 (11th Cir. 1988). Indeed, much of Dr. Kaliebe's testimony and opinions "appears to be based more on supposition than science." *O'Neill v. Windshire-Copeland Assocs.*, 372 F.3d 281, 285 (4th Cir. 2004). And opinions based on "subjective belief or unsupported speculation" should be rejected. *Daubert*, 509 U.S. at 589-590.

B. Dr. Kaliebe's opinions are unreliable because they are misleading, employ flawed methodologies, and do not serve to enlighten the trier of fact.

In addition, many of Dr. Kaliebe's opinions are misleading at best, or flat out false. Take the following examples:

One. Dr. Kaliebe spends much ink criticizing the development of the WPATH Standards of Care, Version 7 and Version 8. Dr. Kaliebe does so by quoting

and repeating criticisms made by others. *See*, *e.g.*, Ex. A, at ¶¶ 62-63; Ex. C, at ¶¶ 19-26, 31-33. But these criticisms are unreliable for, at least, two independent reasons.

First, Dr. Kaliebe admits that he is not an expert in the development of clinical practice guidelines. Ex. B, at 101:3-10. And an expert, "however well credentialed he may be, is not permitted to be the mouthpiece of a scientist in a different specialty." *Dura Auto. Sys.*, 285 F.3d at 614. Indeed, because Dr. Kaliebe is not qualified "to testify about areas in which he has admitted he has no expertise," such testimony is unreliable. *Solaia Tech.*, 361 F.Supp.2d at 813–14.

Second, while an expert may properly rely on the opinion of another expert, an expert cannot simply repeat or adopt the findings of other experts without investigating them. *See In re Polypropylene Carpet Antitrust Litig.*, 93 F.Supp.2d 1348, 1357 (N.D. Ga. 2000) (citing *In re TMI Litig.*, 193 F.3d 613, 715–16 (3d Cir. 1999) (finding blind reliance by expert on other expert opinions demonstrates flawed methodology under *Daubert*); *TK–7 Corp. v. Estate of Barbouti*, 993 F.2d 722, 732–33 (10th Cir. 1993) (excluding expert opinion relying on another expert's report because witness failed to demonstrate a basis for concluding report was reliable and showed no familiarity with methods and reasons underlying the hearsay report)).

Two. Dr. Kaliebe opines throughout his reports on the efficacy of gender-affirming medical treatment. However, Dr. Kaliebe does not discuss any single

original, peer-reviewed study in detail and in fact, only cites four original studies in the references for his original report. *See* Ex. B, at 88:2-22; Ex. A, at 69-75. Specifically, he cites to four studies Branstrom, et al. (2020), Chen, et al. (2023), Dhejne, et al. (2011), and Kaltiala, et al. (2020). However, the universe of original peer-review research looking into the safety and effectiveness of gender-affirming medical treatments is orders of magnitude larger.

For example, a systematic literature review of peer-reviewed studies published in English between 1991 and 2017 looked at 56 original peer-reviewed studies into whether gender transition, including medical treatments such as hormone therapy and surgeries, improves the overall well-being of transgender adults. *See* Exs. E and F.[6] Similarly, a review from 1998 looked at data from 80 studies spanning 30 years. Ex. G (Expert Report of Johanna Olson-Kennedy, M.D., M.S.), at ¶ 44. In other words, *a meta-analysis review from 25 years looked at 20 times the number of studies that Dr. Kaliebe reviewed for his report*. There is likewise a multitude of original peer-reviewed studies looking into the effect of gender-affirming medical treatment on the mental health and well-being of transgender adolescents with gender dysphoria. *See*, *e.g.*, Ex. G, at ¶¶ 25-30, 33-39,

[6] Though not relevant for purposes of this Motion to Exclude, it is worth noting that this systematic literature review "found a robust international consensus in the peer-reviewed literature that gender transition, including medical treatments such as hormone therapy and surgeries, improves the overall well-being of transgender individuals." Ex. E.

46 (discussing over 13 original peer-reviewed studies looking specifically at transgender adolescents); Ex. H (Expert Report of Daniel Shumer), at ¶¶ 82, 86 (discussing over 15 original peer-reviewed studies looking specifically at transgender adolescents); Ex. I (discussing 16 original peer-reviewed studies examining the impacts of gender-affirming medical care for transgender adolescents).

Plaintiffs do not point to the aforementioned vast expanse of scientific literature to argue the merits of Dr. Kaliebe's opinions (as wrong as they are), but to illustrate the lack of reliability of Dr. Kaliebe's opinions based on his methodology (or lack thereof). Dr. Kaliebe is unfamiliar with and does not reference—let alone, discuss—the original peer-reviewed studies that he criticizes. Rather, Dr. Kaliebe parrots the criticisms of others. His references are primarily opinion pieces and literature reviews by others, not original peer-reviewed studies. *See generally* Ex. A, at 69-75. But Dr. Kaliebe cannot serve as a mouthpiece for others. His criticisms of the scientific evidence supporting gender-affirming medical care must be based on his own review of that evidence. The fact that Dr. Kaliebe is unfamiliar with the expansive universe of literature at issue here demonstrates the lack of reliability for his opinions about the effectiveness of gender-affirming medical care.

Three. Dr. Kaliebe disputes that gender identity has a biological basis. He cites to an article by Marianowicz-Szczygiel (2022) outlining an apparent rise of

people presenting to gender clinics and an article by Littman (2018) discussing the perceptions of the non-affirming parents of transgender adolescents. Ex. C, at ¶ 10. But neither article disputes there is a biological basis for gender identity. For example, Dr. Kaliebe conceded that "the fact that more people have been showing up at clinics could be explained by the fact that, A, the care is more available; and, B, more people feel comfortable seeking the care." Ex. B, at 54:5-10. And Dr. Kaliebe conceded that the Littman article, given its multiple limitations, could not reach any conclusions regarding social contagion and, at most, raised hypotheses. Ex. B, at 71:16-18. What is more, scientific, peer-reviewed literature that Dr. Kaliebe has encountered shows the opposite, namely, that "there is empirical evidence that there is a biological basis for a person's gender identity." Ex. J; *see also* Ex. B, at 150:17 ("A. I've seen it cited.").

Dr. Kaliebe's opinions about whether there is a biological basis for gender identity are unreliable because (a) he employed a flawed methodology that omitted discussion of existing, on point peer-reviewed scientific literature, and (b) his opinions are based on unproven hypotheses and not any data. While usually the factual basis of an expert opinion goes to credibility, "it is possible for an experts' omission of articles to render his or her opinion inadmissible on reliability grounds." *Huggins v. Stryker Corp.*, 932 F.Supp.2d 972, 994 (D. Minn. 2013). Such is the case

here where Dr. Kaliebe omits key information, or worse, misrepresents facts that if properly disclosed would contradict his opinions and undermine their foundation.

* * *

The Court "must ensure that any and all scientific testimony or evidence admitted is not only relevant, but reliable." *Daubert*, 509 U.S. at 589. Here, Dr. Kaliebe has employed flawed methodologies and misrepresented or omitted information that goes to the heart of his opinions, all of which calls into question the reliability of his opinions. In such circumstances, the "potential to mislead" rather "than to enlighten" is too great. *In re Lipitor*, 892 F.3d at 632.

C. Dr. Kaliebe's opinions are unreliable because they are based on facts or data not typically relied on by physician or scientists.

Rule 703 requires that "[t]he facts or data … upon which an expert bases an opinion or inference" must be "of a type reasonably relied upon by experts in the particular field in forming opinions or inferences upon the subject." Fed. R. Evid. 703.

One. Based on his alleged "review of the research," Dr. Kaliebe opines "that the evidence base for gender dysphoria treatment is mixed and generally low quality." Ex. A, at ¶ 45. However, Dr. Kaliebe bases his opinions on his review of reports of government entities in Finland, Sweden, and the United Kingdom, as well as the GAPMS Report. Ex. B, at 86:25-87:8. But, as Dr. Kaliebe acknowledges, none of those are published, peer-reviewed literature. *Id.*; *see also* Ex. B, at 99:17-25. And

such unpublished, non-peer-reviewed reports *are not* the types of materials reasonably relied upon by experts in any field of medicine. When asked what actual peer-reviewed, original studies he reviewed, he could not identify any and his original report cites to only four (4) original studies (none of which relate to the provision of puberty-delaying medications as treatment for an adolescent's gender dysphoria). Ex. B, at 86:21-88:22.

Two. As noted above, Dr. Kaliebe *hypothesizes* that "direct social influences and online and social media contagion" are "major contributors" to a rise in gender dysphoria. *E.g.*, Ex. A, at ¶ 30; *see also id.* at ¶¶ 40, 41. However, he points to no *reliable* evidence to support his *hypothesis* (which itself is an unreliable basis for an expert opinion, *see* Section II.A, *supra*). For example, Dr. Kaliebe points to a single case anecdote in support for his hypothesis. Ex. B, 59:13-16. But such "anecdotal information … is scientifically unreliable and not supported by any … scientifically reliable studies." *Soldo v. Sandoz Pharms. Corp.*, 244 F.Supp.2d 434, 571 (W.D. Pa. 2003);[7] *see also McClain v. Metabolife Int'l, Inc.*, 401 F.3d 1233, 1252, 1253-54 (11th Cir. 2005).

In addition, Dr. Kaliebe relies on two non-published, non-peer-reviewed, unscientific polls of the attendees of two conference panel sessions to support his

[7] In *Soldo*, the excluded expert's testimony was based on anecdotal evidence contained *in published case reports*. Here, Dr. Kaliebe has not even attempted to publish his anecdotal evidence as a case report.

opinion that "Psychiatrists also believe social media has significantly contributed to the rise in gender dysphoria." Ex. A, at ¶ 41; *see also id.* at ¶¶ 42-43. Dr. Kaliebe admits that he did not do any regression or statistical significance analysis regarding these polls, Ex. B, at 66:15-19, and that all the polls tell us "is the views of the attendees of that particular seminar." Ex. B, at 67:1-4. Indeed, there are about 45,000 psychiatrists in the United States, Ex. B, at 63:15-18, and as Dr. Kaliebe admits his "conversations are not a representative sample of all childhood adolescent psychiatrists." Ex. B, at 64:8-11.

Dr. Kaliebe also cites as a support a *press release* from the French Academies, Ex. A, at ¶ 40, but admits that "a press release is not peer-reviewed or scientific literature." Ex. B, at 68:7-13.

Of course, it should be noted that, as Dr. Kaliebe admits, "it is not shocking that teens find like-minded teens online and they speak to each other about their similar experiences," and "that, in particular, small populations that tend to be isolated and/or discrete tend to turn to social media actually as a way to connect and find one another." Ex. B, at 67:21-68:6.

In sum, none of the sources upon which Dr. Kaliebe relies for his opinions are of reliable or of the type upon which any serious physician or scientist would rely on.

Three. Dr. Kaliebe also spends much ink discussing the apparent politicized nature of conversations surrounding the treatment of gender dysphoria and *hypothesizes* that such politicization and moralization has led to the silencing of contrary views. *See*, *e.g.*, Ex. A, at ¶¶ 71-89 (discussing apparent "lack of consensus"); *id.* at ¶¶ 90-124 (discussing "breakdown in scholarly dialogue"). Dr. Kaliebe bases these opinions on conjecture and anecdotes he has purportedly collected based on a few conversations. However, neither of these are the type of "facts or data" other experts in psychiatry or medicine "would reasonably rely on … in forming an opinion in the subject." Fed. R. Evid. 703. Indeed, "broad opinions [that] are based solely on … generalized views, anecdotal accounts, and speculation … are not reliable." *In re 3M*, 2021 WL 684183, at *3 (N.D. Fla. Feb. 11, 2021). Similarly, opinions "based on mere conjecture, assumption, credibility calls, and amounting to no more than ipse dixit" are "neither reliable nor helpful." *Day v. Edenfield*, 2022 WL 972430, at *10 (N.D. Fla. Mar. 31, 2022).

What is more, in some instances, some of these opinions are demonstrably false. For example, Dr. Kaliebe states that "skeptical voices have been difficult to find within any of the journals of the Endocrine Society, American Academy of Pediatrics, American Psychiatric Association or American Academy of Child and Adolescent Psychiatry" and that he "ha[s] not found a single skeptical or even ideologically balanced article in any of these journals." Ex. A, at ¶ 82. But

notwithstanding that Dr Kaliebe was aware of two letters to the editor published in the *Journal of the Endocrine Society* that were critical of gender-affirming medical care, he still made the false statement.[8] *See* Ex. B, at 131:15-132:13.

In sum, none of Dr. Kaliebe's "opinions" about the politicized nature of the debate surrounding transgender issues and the treatment of gender dysphoria are medical or scientific opinions. They do not require "the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue." *Frazier*, 387 F.3d at 1260. To the contrary, they are at best personal opinions and gripes with those with whom he disagrees. They are both unreliable and irrelevant, and at times, outright false. Allowing Dr. Kaliebe to testify "based on limited personal accounts and information relayed to [him] by an unspecified number of third parties would be to sanction [his] use as a vehicle for introducing hearsay testimony." *In re 3M*, 2021 WL 684183, at *2.

* * *

Dr. Kaliebe's opinions are thus "unsupported by reliable principles and methods and lack[s] hallmarks of scientific rigor: peer-reviewed research, studies, or experiments in support of his opinions." *United States v. Geanakos*, 2017 WL 4883294, at *3 (E.D. Cal. Oct. 30, 2017).

[8] To be sure, neither of these two letters were based on original research or were peer-reviewed.

D. Dr. Kaliebe's opinions are unreliable because they are not generally accepted in the scientific and medical community.

General acceptance in the relevant scientific community is also relevant to the reliability inquiry. *Nease*, 848 F.3d at 229. Not only is widespread acceptance an important factor in assessing the reliability of an expert's opinions, but the fact that a known technique or theory "has been able to attract only minimal support within the community may properly be viewed with skepticism." *Daubert*, 509 U.S. at 594. Here, Dr. Kaliebe's opinions are outside the mainstream of medical and scientific opinion and have been explicitly rejected by these relevant communities.

The provision of gender-affirming medical care has been accepted and endorsed, *inter alia*, by the: American Medical Association; American Psychiatric Association; American Psychological Association; Endocrine Society; Pediatric Endocrine Society; American Academy of Pediatrics; and the National Academies of Science, Engineering, and Medicine. *See* Ex. K at 361.

In fact, another federal district court found as much when it enjoined Arkansas' state law seeking to ban gender-confirming treatment for minors. *See Brandt v. Rutledge*, 551 F.Supp.3d 882 (E.D. Ark. 2021), *aff'd*, 47 F.4th 661 (8th Cir. 2022). In doing so, the *Brandt* court explicitly found that: (a) "Gender-affirming treatment is *supported by medical evidence* that has been *subject to rigorous study*;" and (b) "*Every major expert medical association* recognizes that gender-affirming care for transgender minors may be *medically appropriate and necessary* to improve

the physical and mental health of transgender people." *Id.* at 891 (emphasis added). The *Brandt* court's findings stand as a stark repudiation of Dr. Kaliebe's opinion that the provision of gender-affirming medical care to adolescents with gender dysphoria is an "experiment," for which "there is clearly no consensus of opinion." Ex. A, at ¶¶ 11, 21-22.

* * *

Given that Dr. Kaliebe's opinions fail to meet the most basic indicia of reliability, the Court should exclude Dr. Kaliebe's opinions and testimony as unreliable.

III. Helpfulness – Dr. Kaliebe's opinions and testimony are not relevant to this case.

Helpfulness "goes primarily to relevance." *Daubert*, 509 U.S. at 580; *see also Prosper v. Martin*, 989 F.3d 1242, 1249 (11th Cir. 2021) ("The touchstone of this inquiry is the concept of relevance."). Under the helpfulness prong, the "court must satisfy itself that the proffered testimony is relevant to the issue at hand, for that is a precondition to admissibility." *Sardis v. Overhead Door Corp.*, 10 F.4th 268, 282 (4th Cir. 2021) (cleaned up). Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). Thus, "expert testimony which does not relate to any issue in the case is not relevant and non-

helpful." *Knight v. Boehringer Ingelheim Pharms., Inc.*, 323 F.Supp.3d 837, 846 (S.D. W.Va. 2018).

In order to be relevant, an opinion needs to "fit" with the facts at issue. *Simmons v. Augusta Aviation, Inc.*, 596 F.Supp.3d 1363, 1374 (S.D. Ga. 2022) "To satisfy this requirement, the testimony must concern matters beyond the understanding of the average lay person and logically advance a material aspect of the proponent's case." *Id.* Testimony that "offers nothing more than what lawyers for the parties can argue in closing arguments" or that consists of "subjective portrayals of factual information" "generally will not help the trier of fact." *Giusto v. Int'l Paper Co.*, 2021 WL 3603374, at *4 (N.D. Ga. Aug. 13, 2021).

This case is about whether Defendants' exclusion of coverage for medical treatments for gender dysphoria violates Plaintiffs' rights under the equal protection clause, Section 1557 of the Affordable Care Act, and the Medicaid Act. Dr. Kaliebe's opinions are not relevant to this inquiry as they will not help the trier of fact to understand the evidence or to determine a fact in issue. His opinions do not "fit" because they are not sufficiently tied to the facts of the case so that they will aid a factfinder.

A. Dr. Kaliebe's opinions about "desistance" are irrelevant.

Dr. Kaliebe's opinion that "[i]n childhood, most gender dysphoria spontaneously resolves without treatment" is wholly irrelevant. Ex. C, ¶ 16. But no

medical or surgical treatment is recommended or provided to *prepubertal* children. And this case is about the coverage for medical treatment for gender dysphoria. Dr. Kaliebe's (unsupported) opinions about "spontaneous desistance" are thus irrelevant to this case.[9]

B. Dr. Kaliebe's opinions about supposed controversies in other countries are irrelevant.

Likewise, Dr. Kaliebe's opinions about "controversies" regarding the provision of medical treatment for gender dysphoria in other countries, such as Finland, Sweden, and the United Kingdom, are both misleading and wholly irrelevant. *See*, *e.g.*, Ex. A, at ¶¶ 49-60, 160, 161. Dr. Kaliebe failed to disclose that each of these countries *provides and covers* gender-affirming hormonal and surgical treatment for gender dysphoria for adolescents in certain circumstances and adults, without any restriction, whereas Defendants exclude coverage for treatments for both these populations categorically. *See*, *e.g.*, Ex. B, at 100:17-101:2; Ex. L; *see also Brandt*, 47 F.4th at 671; *Eknes-Tucker v. Marshall*, 603 F.Supp.3d 1131, 1146 (M.D. Ala. 2022) ("According to Dr. Cantor, Defendants' own expert witness, no state or country in the entire world has enacted a blanket ban of these medications other than Alabama.").

[9] These opinions are methodologically flawed and unreliable because Dr. Kaliebe cites to no authority and provides no basis for his opinion.

Moreover, each of the reports and reviews of the provision of gender-affirming care in these three countries pertained to medical care for minors and not adults, unlike the Challenged Exclusion. Ex. B, at 100:1-16.

In the end, how care is provided and covered in countries with nationalized health care systems is not relevant to whether coverage of gender-affirming medical care should be provided by Medicaid in Florida.[10]

C. Dr. Kaliebe's musings about the causes of gender dysphoria are irrelevant.

As noted above, Dr. Kaliebe *hypothesizes*, without any evidence, that gender dysphoria *may be* caused by social contagion and social pressure. But whether gender dysphoria is caused by social contagion is both wholly unsupported, as described above, and irrelevant to the case at hand. It is undisputed that gender dysphoria is a recognized medical condition that necessitates treatment. *See*, *e.g.*, Ex. B, at 34:9-11 ("Q. … Would you agree with me that gender dysphoria is a very real condition? A. Yes."); *see also Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 594-95 (4th Cir. 2020); *Eknes-Tucker*, 603 F.Supp.3d at 1138 ("Gender dysphoria is a clinically diagnosed incongruence between one's gender identity and assigned gender. If untreated, gender dysphoria may cause or lead to anxiety,

[10] For example, in Sweden standards of care are developed through legislation and thus part of a political process. *See* Socialstyrelsen, *About the National Board of Health and Welfare*, https://www.socialstyrelsen.se/en/about-us/ (accessed Apr. 7, 2023) (noting that standards are based on legislation).

depression, eating disorders, substance abuse, self-harm, and suicide." (citations omitted)).

* * *

The opinions expressed by Dr. Kaliebe are insufficiently tied to the facts of this case so that they will aid a factfinder and should be excluded as irrelevant.

IV. Dr. Kaliebe's opinions lack probative value and are therefore inadmissible under Rule 403.

Finally, the Court should exclude Dr. Kaliebe's opinions because their introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Dr. Kaliebe offers no opinions relevant to the issues in this case, and, in any event, the opinions he offers are unfounded, speculative, and unreliable. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the propriety of gender-confirming care based on speculation, irrelevant, misleading, or biased opinions.

CONCLUSION

For the foregoing reasons, the Court should exclude Dr. Kaliebe's report, opinions, and testimony. More specifically, at minimum, the Court should limit Dr. Kaliebe's opinions and testimony solely to those regarding the diagnosis of gender dysphoria in children and adolescents, and otherwise exclude Dr. Kaliebe's report, opinions, and testimony in full.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Omar Gonzalez-Pagan

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that he attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

LOCAL RULE 7.1(F) WORD COUNT CERTIFICATION

As required by Local Rule 7.1(F), I certify that this Opposition contains 7,948 words.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan
Counsel for Plaintiffs

TAB 141

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF
FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION TO EXCLUDE EXPERT TESTIMONY OF STEPHEN B. LEVINE, M.D.

Now come, Plaintiffs, by and through their counsel, and respectfully move this Court to exclude the expert report, opinions, and testimony of Defendants' proposed expert, Stephen B. Levine, M.D., pursuant to Federal Rules of Civil Procedure 26 and 37, and Federal Rules of Evidence 104, 403, and 702.

Dr. Levine's opinions should be excluded because (1) many are unhelpful as they are not opposed to the relief Plaintiffs seek and (2) the remaining opinions are unreliable because they are not based on scientifically valid principles, reasoning, and methodology as required under Federal Rule of Evidence 702 and the standards set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), and its progeny. His opinions and testimony are likewise inadmissible because any

probative value they may have is substantially outweighed by the danger of unfair prejudice, confusion of the issues, waste of time, undue delay, and needless presentation of cumulative evidence. *See* Fed. R. Evid. 403.

Based on the unhelpfulness and unreliability of Dr. Levine's testimony and opinions, at minimum, the Court should exclude any portions of his expert report, opinions, and testimony that go beyond (1) identifying risks associated with prescribing medication and surgery to adolescents, (2) and criticizing the quality of the research on treatments for gender dysphoria.

A memorandum of law is filed contemporaneously herewith.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Carl S. Charles

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LOCAL RULE 7.1(B) CERTIFICATION

The undersigned certifies that Plaintiffs' counsel attempted in good faith to resolve the issues raised in this motion through a meaningful conference with Defendants' counsel, including through a meet and confer Zoom conference on April 6, 2023.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

TAB 145

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH MAF

PLAINTIFFS' MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE EXPERT TESTIMONY OF STEPHEN B. LEVINE, M.D.

TABLE OF CONTENTS

I. INTRODUCTION

Plaintiffs are transgender Medicaid beneficiaries who have been diagnosed with gender dysphoria. In August 2022, Defendants adopted a rule, Florida Administrative Code 59G-1.050(7) (the "Challenged Exclusion"), prohibiting Medicaid coverage of services for the treatment of gender dysphoria. Defendants adopted the Challenged Exclusion after undergoing a process with a predetermined outcome that concluded that the provision of medical treatment for the treatment of gender dysphoria, including puberty blockers, hormone therapy, and surgery, "do not conform to GAPMS [("generally accepted professional medical standards")] and are experimental and investigational." Defendants thus deny equal treatment to Plaintiffs based on sex because they are transgender.

In response, Defendants have put forward an expert, Dr. Stephen Levine, a psychiatrist, whose opinions other federal courts have significantly narrowed, excluded in part, and in one case, dismissed altogether. The same is true here. Dr. Levine's opinions should be excluded because (1) many are unhelpful because they are not opposed to the relief Plaintiffs seek and (2) the remaining opinions are unreliable because they are not based on scientifically valid principles, reasoning, and methodology. The Court should therefore, with narrow exception, exclude Dr.

Levine's opinions.[1]

II. LEGAL STANDARD

The admission of expert testimony is governed by Federal Rule of Evidence 702, as explained by *Daubert* [v. *Merrell Dow Pharm*., *Inc*., 509 U.S. 579, 597 (1993)] and its progeny." *Rink* v. *Cheminova*, Inc., 400 F.3d 1286, 1291 (11th Cir. 2005). "District courts are [thus] charged with [a] gatekeeping function." *Id*.; see also *United States* v. *Frazier*, 387 F.3d 1244, 1260 (11th Cir. 2004) ("The importance of *Daubert*'s gatekeeping requirement cannot be overstated."). In conducting their gatekeeping function, courts must "engage in a rigorous three-part inquiry and determine whether:

> (1) the expert is qualified to testify competently regarding the matters he intends to address; (2) the methodology by which the expert reaches his conclusions is sufficiently reliable as determined by the sort of inquiry mandated in *Daubert*; and (3) the testimony assists the trier of fact, through the application of scientific, technical, or specialized expertise, to understand the evidence or to determine a fact in issue.

Frazier, at 1260; *see also City of Tuscaloosa v. Harcros Chems., Inc.*, 158 F.3d 548, 562 (11th Cir. 1998), *cert. denied*, 528 U.S. 812 (1999). The Eleventh Circuit refers to these three considerations separately as "qualification," "reliability," and "helpfulness" and has emphasized that they are "distinct concepts that courts and

[1] Excerpts of the Expert Disclosure of Stephen B. Levine, M.D., signed February 16, 2023, is attached as Exhibit A to the concurrently filed Declaration of Carl S. Charles ("Charles Decl.")

litigants must take care not to conflate." *Quiet Tech. DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). "The party offering the expert has the burden of satisfying each of these three elements by a preponderance of the evidence." *Rink*, 400 F.3d at 1292.

To be sure, "[i]mplementing Rule 702, *Daubert* requires district courts to ensure that any and all scientific testimony or evidence admitted is both relevant and reliable." *Claire v. Fla. Dep't of Mgmt. Servs.*, 2021 WL 5982330, at *1 (N.D. Fla. Oct. 20, 2021). "[T]he trial judge must determine [this] ***at the outset***." *Daubert*, 509 U.S. at 592 (emphasis added). The court's gatekeeping role and the test for admissibility of expert testimony are applicable even at a bench trial or at the summary judgment stage. *See*, *e.g.*, *Rink v. Cheminova*, 400 F.3d 1286 (11th Cir.) (granting motions to exclude in the context of summary judgment); *Kadel v. Folwell*, 2022 WL 3226731, at **5-17 (M.D.N.C. Aug. 10, 2022) (same); *Lo v. United States*, 2022 WL 1014902, at *12 (W.D. Wash. Apr. 5, 2022) (excluding unqualified expert evidence in the context of a bench trial); *cf. UGI Sunbury*, 949 F.3d at 833 (holding the district court abused its discretion in a bench trial when it "ignored rule [702]'s clear mandate" by "sidestepping Rule 702 altogether and declining to perform any assessment of [expert]'s testimony before trial").

It is axiomatic that "[a] witness may be qualified as an expert by virtue of his 'knowledge, skill, experience, training, or education." *Quiet Technology DC-8, Inc.*,

326 F.3d at 1342. However, credentials are not dispositive when determining qualification. In conducting the *Daubert* inquiry, each of the three analytical prongs is assessed in reference to the matter to which the expert seeks to testify—i.e., "to the task at hand." *Daubert*, 509 U.S. at 597. It is for that reason that "expertise in one field does not qualify a witness to testify about others." *Lebron v. Sec'y of Fla. Dep't of Children & Families*, 772 F.3d 1352, 1368 (11th Cir. 2014) (holding that a psychiatrist was properly prevented from opining on rates of drug use in an economically vulnerable population because he had never conducted research on the subject, and instead relied on studies to form his opinion). If a proposed expert witness does not "propose to testify about matters growing naturally and directly out of research he had conducted independent of the litigation," such an expert should be disqualified. *Lebron*, 772 F.3d at 1369 (quoting Fed. R. Evid. 702 (cleaned up)).

An expert's testimony should only be admitted if it is sufficiently reliable. "To meet the reliability requirement, an expert's opinion must be based on scientifically valid principles, reasoning, and methodology that are properly applied to the facts at issue." *In re 3M Combat Arms Earplug Products Liab. Litig.*, 3:19MD2885, 2022 WL 1262203, at *1 (N.D. Fla. Apr. 28, 2022). The requirement of reliability found in Rule 702 is "the centerpiece of any determination of admissibility." *Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1197 (11th Cir. 2002). In making this determination the court can consider a variety of factors, including whether the

purported expert's theory has been tested, whether it has been subjected to peer review and publication, and whether the theory has been generally accepted in the scientific community. *See Daubert*, 509 U.S. at 593-94; *Rink*, 400 F.3d at 1291-92.[2] To be reliable the expert's testimony must always be based on "good grounds." *Daubert,* 509 U.S. at 590. Moreover, *Daubert* requires that reliable expert testimony be more than scientifically unsupported "leaps of faith." *Rider* v. *Sandoz Pharm. Corp.*, 295 F.3d 1194, 1202 (11th Cir. 2002).

To satisfy the helpfulness requirement, the testimony must have a justified scientific relationship to the facts at issue. *Daubert*, 509 U.S. at 591. Thus, helpfulness, "goes primarily to relevance." *Id.* at 580. Relevant expert testimony "logically advances a material aspect of the proposing party's case" and "fits" the disputed facts. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004). "The relationship must be an appropriate 'fit' with respect to the offered opinion and the facts of the case." *Id.* Expert testimony does not "fit" when there is "too great an analytical gap" between the facts and the opinion offered. *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 147 (1997) (offering animal studies showing one type of cancer in mice to establish causation of another type of cancer in humans is "simply too great

[2] Other factors that may be relevant include (1) the nature of the field of claimed expertise, (2) the source of the expert's knowledge, (3) the expert's level of care in using the knowledge, and (4) the expert's consideration of alternative hypotheses. *Hendrix*, 255 F.R.D. at 578-79.

an analytical gap between the data and the opinion offered"); *Boca Raton Cmty. Hosp., Inc. v. Tenet Health Care Corp.*, 582 F.3d 1227, 1232 (11th Cir.2009) ("if an expert opinion does not have a 'valid scientific connection to the pertinent inquiry' it should be excluded because there is no 'fit.'").

Finally, because of the potentially misleading effect of expert evidence, *see Daubert*, 509 U.S. at 595, expert opinions that otherwise meet admissibility requirements may still be excluded under Fed. R. Evid. 403. Exclusion under Rule 403 is appropriate if the testimony is cumulative or needlessly time consuming. *See, e.g., Hull v. Merck & Co., Inc.*, 758 F.2d 1474, 1477 (11th Cir.1985) (admission of speculative and "potentially confusing testimony is at odds with the purposes of expert testimony as envisioned in Fed. R. Evid. 702"); *Tran v. Toyota Motor Corp.*, 420 F.3d 1310, 1316 (11th Cir. 2005) (affirming exclusion of expert testimony as cumulative). Consequently, because "[e]xpert evidence can be both powerful and quite misleading because of the difficulty in evaluating it…[T]he judge in weighing possible prejudice against probative force under Rule 403…exercises *more* control over experts than over lay witnesses." *Daubert,* 509 U.S. at 595 (cleaned up) (emphasis added).

III. ARGUMENT

As noted above, other federal courts have narrowed, excluded, and in one case, entirely dismissed Dr. Levine's opinions about transgender people and the

treatment of gender dysphoria.[3] This began several years ago with district court's holding in *Norsworthy v. Beard*, that "the Court gives very little weight to the opinions of Levine, whose report misrepresents the Standards of Care; overwhelmingly relies on generalizations about gender dysphoric prisoners, rather than an individualized assessment of Norsworthy; contains illogical inferences; and admittedly includes references to a fabricated anecdote." 87 F. Supp. 3d 1164, 1188 (N.D. Cal. 2015). This holding was echoed in *Edmo v. Idaho Dep't of Corr.*, 358 F. Supp. 3d 1103, 1125-1126 (D. Idaho 2018) (holding that Dr. Levine "is considered an outlier in the field of gender dysphoria" and gave "virtually no weight" to his opinions), *vacated in part on other grounds sub nom. in Edmo v. Corizon, Inc.*, 935 F.3d 757 (9th Cir. 2019). Dr. Levine's opinions were likewise excluded in *Hecox v. Little,* where the Court dismissed his opinion that "gender-affirming policies … are … harmful to transgender individuals," and instead "accept[ed] Plaintiffs' evidence regarding the harm forcing transgender individuals to deny their gender identity can cause." 479 F. Supp. 3d 930, 977 n.33 (D. Idaho 2020).

Of most relevance to this case, several of Dr. Levine's proposed opinions were

[3] Because of the numerical limitation on the parties depositions, Plaintiffs opted not to depose Dr. Levine and instead rely on his prior deposition and trial testimony in cases similar to this one, where his expert reports and proffered opinions have been nearly identical to his report submitted here. *See Brandt et al.*, v. *Rutledge et al*. No. 4:21-cv-00450-JM (E.D. Ark., 2022); *Fain et al.*, v. *Crouch et al.*, No. CV 3:20-0740, 2022 WL 3051015 (S.D.W. Va. Aug. 2, 2022); *Kadel et al.,* v. *Folwell et al.*, No. 1:19CV272, 2022 WL 3226731 (M.D.N.C. Aug. 10, 2022).

excluded based on irrelevance and unreliable methodology by the U.S. District Court for the Middle District of North Carolina in *Kadel* v. *Folwell*, No. 1:19CV272, 2022 WL 3226731 (M.D.N.C. Aug. 10, 2022). Judge Loretta C. Biggs granted in part a motion to exclude Dr. Levine's testimony, noting that he would be limited to offering opinions primarily to the following matters: (1) identifying risks associated with prescribing medication and surgery to adolescents, (2) and criticizing the quality of the research on treatments for gender dysphoria.[4] At a minimum, Dr. Levine's proposed opinions in this matter should be so limited as well, with his remaining testimony, opinions and content of reports otherwise excluded.

A. Many Of Dr. Levine's Opinions Will Not Help the Trier of Fact Because They Support Plaintiffs' Position.

Many of Dr. Levine's opinions do not "logically advance a material aspect *of the proposing party's case*" and do not "fit" the disputed facts because his proposed opinions do not oppose the relief Plaintiffs seek. *McDowell v. Brown*, 392 F.3d 1283, 1298-99 (11th Cir. 2004) (emphasis added). For that reason, Dr. Levine's opinions "fit" with the facts relevant to resolving this matter in favor of Plaintiffs' claims, not those of Defendants. *Id*. And even though several of Dr. Levine's opinions, and the clinical experience upon which they are based, do not stand in opposition to the relief

[4] The court in *Kadel* also found that Dr. Levine was permitted to testify as to his opinions of WPATH but for the reasons stated herein, infra, this Court should not so permit.

Plaintiffs seek, many do, and admitting this unreliable and unhelpful testimony wholesale would not meet the standard set forth by *Daubert* and its progeny.

Significantly, several of Dr. Levine's proposed opinions regarding gender-affirming medical care, and his clinical experience upon which those opinions are based, are not contrary to the relief Plaintiffs seek in this case: that Florida Medicaid beneficiaries diagnosed with gender dysphoria receive appropriate medical care. Charles Decl., Ex. A at ¶6. On November 28, 2022, Dr. Levine testified at length about his proposed opinions regarding gender-affirming care at the bench trial in *Brandt* v. *Rutledge,* No. 4:21-cv-00450-JM (E.D. Ark., 2022).[5] There, as here, Dr. Levine was Defendants' only expert witness to have ever treated patients for gender dysphoria, and he testified that removing gender affirming medical care from patients currently receiving it would have "shocking and devastating" psychological consequences. Charles Decl. Ex. B at 912:3-19. Dr. Levine testified there, as he does in his report in this matter, that "there is no evidence beyond anecdotal reports that psychotherapy can enable a return to male identification for genetically male boys, adolescents, and men, or return to female identification for genetically female girls, adolescents, and women." Charles Decl., Ex. A at ¶49; Charles Decl., Ex. B at 920:18-24. And to be sure, "broad opinions [that] are based solely on … anecdotal accounts, and speculation … are not reliable." *In re 3M Combat Arms Earplug Prod.*

[5] The Plaintiffs in *Brandt* did move to exclude or limit Dr. Levine's testimony.

Liab. Litig., 2021 WL 684183, at *3. Dr. Levine also testified that reliance on self-report from the patients and information from parents is not unique to the diagnosis of gender dysphoria and is "ideally" how psychiatry works. Charles Decl. Ex. B at 894:24-895:6. He also testified that the use of medications to treat gender dysphoria is off-label—meaning not FDA approved for this specific indication—does not mean the drugs are experimental. Charles Decl. Ex B. at 930:14-17. And while Dr. Levine agreed that the "overwhelming majority" of his patients have been adults, he testified that he has written letters of authorization for hormone therapy for some patients under 18 and, going forward, would consider doing so on a case-by-case basis. Charles Decl. Ex. B at 886:13-18, 897:1-898:18, 900:21-902:15, 902:25-903:6.

Similarly, in *Fain* v. *Crouch*, No. CV 3:20-0740, 2022 WL 3051015 (S.D.W. Va. Aug. 2, 2022), where plaintiffs challenged a Medicaid coverage restriction of gender-affirming care in West Virginia, similar to the one at issue in this case, Dr. Levine testified at deposition that in the previous seven months he had provided several letters of approval for gender-affirming surgeries for transgender people incarcerated at Framingham, a correctional institution in Massachusetts. Charles Decl. Ex. C at 84:4-85:4. Dr. Levine has also previously testified that he has written similar letters for gender-affirming hormones and surgery in accordance with the medical community's widely accepted and authoritative guidance for transgender care, World Professional Association of Transgender Health ("WPATH") Standards

of Care ("SOC"). Charles Decl., Ex. C. at 139:14-19; Ex. D at 55:13-17; 56:2-5; 112:16-21; 176:8-16; Ex. E at 1-90:15-22. He also testified that he does not provide such letters unless he has sufficiently informed his patients of possible risks and received a reasonable assurance that they understand. Charles Decl., Ex. D at 176: 8-16; 225:24-226:17. For almost 50 years, Dr. Levine's clinical practice has generally adhered to the WPATH SOC. Charles Decl. Ex. C at 136:8-11. And, as WPATH's former Chairman of the SOC Committee, Dr. Levine helped to write Version 5 of the SOC, recognized his own writing in Version 7, and asked if he could help draft the recently published Version 8. Charles Decl., Ex. A at ¶5; Ex. C at 147:12-149:18. He testified at deposition in *Fain*, and under oath previously, that he "is not advocating denying endocrine treatment or surgical treatment" to transgender people, a position he described as "draconian."[6]

Finally, Dr. Levine testified at deposition in *Fain* and that he was not offering

[6] Charles Decl., Ex. C at 88:10-13; Ex. D at 73:4-7 ("Q: Is the worrisomeness about a patient's future health, is that a reason to ban all medical care for gender dysphoria? A: Absolutely not."); 84:21-85:1 ("Q: Given all those concerns you have, is that a reason to deny all medical interventions to people with gender dysphoria? A: No …."); 85:4-11 ("Q: Are those concerns you raised justifications in your mind for denying medical interventions to people who have gender dysphoria? A: You know, I'm not advocating denying endocrine treatment or surgical treatment."); 152:1-6 ("Q: Do you think because that study showed that some people committed suicide after gender affirming surgery that no patient should be able to access gender affirming surgery? A: That would be illogical"); 154:3-5 ("Q: But you're not recommending total bans on gender affirming surgery? A: I'm not recommending total bans."); 160:23-25 ("I did not say that gender affirming treatment in general should be stopped. I've never said that.").

any opinions about whether Defendants should have an exclusion in their Medicaid program for coverage of gender-affirming medical care. Charles Decl. Ex. C at 86:25-87:19. He also testified that he does not feel his "expertise extends to how the insurance industry works and how governments and legislatives work," nor "does he consider himself an expert" on whether the West Virginia Medicaid exclusion should exist. Charles Decl., Ex. C at 87:14-22. Nevertheless, Dr. Levine has testified that he is "an agent of the patient, I want what's best for the patient, and especially if the patient couldn't otherwise afford it, I would wish for my patient to have it, yes." Charles Decl., Ex. F at 157:7.

At bottom, Dr. Levine has repeatedly and consistently testified in federal court that he does not support banning the provision or coverage of gender-affirming medical care, that for 50 years he has and continues to provide letters of authorization for gender affirming medical treatments for adult and minor patients, and that he is not an expert about insurance coverage of gender-affirming medical care. *See* e.g. Charles Decl., Ex. D at 86:1-8. Many of his opinions do not "logically advance a material aspect *of the proposing party's case*," do not "fit" the disputed facts, and will ultimately not assist the trier of fact because his proposed opinions do not oppose the relief Plaintiffs seek. *McDowell*, 392 F.3d at 1298-99 (emphasis added).

B. Dr. Levine's Opinions That Do Not Support Plaintiffs' Position Are Methodologically Unreliable and Scientifically Unsupported.

An expert's opinion should only be admitted if it is based on scientifically

valid methodology that is properly applied to the facts. *In re 3M*, 2022 WL 1262203, *at *1*. Dr. Levine's opinions fall far short of the reliability standard, a reality he has admitted to as recently as November 2022. Dr. Levine admits in his report submitted here, at trial in *Brandt*, and at deposition in *Fain* and other recent cases, that theories upon which he relies lack *any* scientific support and have not been tested or subjected to peer review or publication. Charles Decl., Ex. A at ¶49; Ex. B 797:8-19, 887:19-888:25, 921:21-922:7, 924:12-25, 949:24-954:22; Ex. C at 140:12-143:2, 145:19-25; Ex. D at 109:20-25; 116:4-7, 122:8-124:22, 200:11-201:25.

Even putting that aside, although Dr. Levine claims many times that his "experience" is sufficient foundation for his opinions, he fails to address how this purported experience leads to his conclusions and how such experience is reliably applied to the facts here. Afterall, "At this stage, the court must undertake an independent analysis of each step in the logic leading to the expert's conclusions; if the analysis is deemed unreliable at any step the expert's entire opinion must be excluded." *Hendrix v. Evenflo Co., Inc.*, 255 F.R.D. 568, 578 (N.D. Fla. 2009), *aff'd sub nom. Hendrix ex rel. G.P. v. Evenflo Co., Inc.*, 609 F.3d 1183 (11th Cir. 2010).

1. Dr. Levine's Assertion that the WPATH SOC Version 8 Is Not the Widely Accepted and Authoritative Protocol for the Treatment of Gender Dysphoria Is Misleading and Unreliable Because It Is Demonstrably False.

Chief among Dr. Levine's many unreliable opinions is his assertion that the

widely-accepted and utilized WPATH SOC are not widely-accepted and considered to be authoritative treatment protocols for gender dysphoria. Contradicting himself, Dr. Levine has repeatedly testified that he generally adheres to the WPATH SOC in his own clinical practice. Charles Decl., Ex. C at 136:8-11; Ex. D at 55:13-17; 56:2-5; 112:16-21; 176:8-16; 225:24-226:17; Ex. F at 29:10-18; 37:2-13; 47:22-49:3; 103:11-19. Nevertheless, Dr. Levine's attempt to undermine the WPATH SOC fail because he lacks evidence to support his assertions, contradicts his assertions with other binding testimony, misrepresents sources in his report, and fails to include relevant information that is contrary to his assertion—ultimately undermining the reliability and overall admissibility of his opinions.

First, Dr. Levine alleges that "reviews" of the 7th Version of the SOC ("SOC 7") "published in 2021 by Dahlen et al [sic] and Sapir in 2022 have clarified the low reliability and bias inherent in its recommendations. (Dahlen et al 2022)." The Dahlen et al. 2021 article does not characterize the SOC 7 as having "low reliability" or "inherent bias." Charles Decl., Ex. A at ¶69; Ex. G. The article does state that the SOC 7 are due for an update and acknowledges that evaluations of clinical practice guidelines in other medical areas including cancer, diabetes, pregnancy, and depression "tend to show room for improvement," and that "finding poor quality CPGs is not confined to this area of healthcare." Charles Decl., Ex. G at 8. Again, without evidence, Dr. Levine claims the 8th Version of the SOC ("SOC 8") has "not

gained additional confidence in its scientific merit." Charles Decl., Ex. A ¶69. He also claims that the presence of transgender participants at WPATH meetings "makes it difficult for professionals to raise their concerns." Charles Decl., Ex. A ¶69. But Dr. Levine admits he has not been a member of WPATH for more than 20 years and does not provide evidence to support these claims. *Id*. at ¶66.[7] The reality is that no one, not transgender people or other health professionals (whether transgender or cisgender), are preventing Dr. Levine from "raising his concerns." As Dr. Levine testified, he presented alongside other panelists with dissenting views, without interruption, at an American Psychiatric Association conference in 2022. Charles Decl., Ex. B at 925:16-926:23, 927:10-17.

Second, Dr. Levine makes inaccurate statements about other countries' treatment protocols for gender dysphoria in youth to support his claim that "opinions

[7] Dr. Levine claims in his report that "Two groups of individuals that I regularly work with have attended recent and separate WPATH continuing education sessions. There, questions about alternative approaches were quickly dismissed with 'There are none. This is how it is done.'" Charles Decl. Ex. A at ¶68. But Dr. Levine fails to name these groups he works with, the people who attended the WPATH sessions, the dates, times and other identifying information about the alleged sessions, or the people who supposedly "quickly dismissed" questions. This assertion is mere conjecture, and methodologically unreliable. Not only is such "reliance on anecdotal evidence" a "red flag[] that caution[s] against certifying an expert," *Newell Rubbermaid, Inc. v. Raymond Corp.*, 676 F.3d 521, 527 (6th Cir. 2012), but the Court should not countenance Dr. Levine testifying "based on limited personal accounts and information relayed to [him] by an unspecified number of third parties," as doing so "would be to sanction [his] use as a vehicle for introducing hearsay testimony." *In re 3M Combat Arms Earplug Prod. Liab. Litig.*, 2021 WL 684183, at *2.

and practices vary widely with respect to puberty blockers and hormones" and as evidence that the WPATH SOC 8 are not authoritative. Charles Decl., Ex. A at ¶82. However, Dr. Levine admitted in his *Brandt* trial testimony that in Finland, gender affirming medical care is provided to adolescents with gender dysphoria when indicated under their guidelines. Charles Decl., Ex. B at 938:16-939:3. He also testified that France does not have a prohibition on minors receiving gender affirming medical care, nor does Canada. Charles Decl., Ex. B at 939:23-940:9, 944:2-5. And Dr. Levine conceded he does not know how the provision of gender affirming care for minors works in Sweden but agreed that the Swedish National Board of Health stated puberty blockers and cross sex hormones may be given in exceptional cases in accordance with their guidelines criteria. Charles Decl., Ex. B at 960:1-17, 961:11-962:1. Dr. Levine has admitted these facts when asked at deposition in *Fain*. Ex. C at 106:4-108:8. Dr. Levine also acknowledged that the United Kingdom's Cass Review, which is still underway and not final, begins from the premise that some youth experience gender dysphoria and will need clinical support and medical interventions and that such care is not prohibited in their health system. Charles Decl., Ex H; Ex. C at 191:20-192:16.

Dr. Levine's own testimony at trial and at deposition contradict the opinions offered by his expert report here, which underscores serious flaws in his methodology and demonstrates that his opinions about the WPATH SOC do not

meet the reliability burden under *Daubert* or related standards for admissibility of expert testimony.

2. Dr. Levine's Opinions That Gender-Affirming Medical Care Is Experimental, Is Provided Without Mental Health Assessments or Sufficiently Informed Consent and Is Without Lasting Benefit are Inaccurate and Unsupported.

Dr. Levine opines that gender-affirming medical care is experimental, is provided without mental health assessments or sufficiently informed consent and is without lasting benefit. Charles Decl., Ex. A at VIII, X, ¶73, ¶176. But Dr. Levine has, and continues to, write letters authorizing gender affirming medical care for his patients, including for hormone therapy for some patients under 18 and, going forward, would consider doing so on a case-by-case basis. Charles Decl., Ex. B at 897:1-898:18, 900:21-902:15, 902:25-903:6. The *Kadel* court cites to an opinion that Dr. Levine has identically asserted here: that it is impossible "to make a single, categorical statement about the proper treatment of children presenting with gender dysphoria or other gender-related issues." Charles Decl., Ex. A at ¶61. As a result, the *Kadel* court observed, "Notably, Levine does not testify that medical or surgical care for gender dysphoria is categorically inappropriate." *Kadel*, 2022 WL 322673, at *15. And when asked if based on his publication from March 2022 "Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults," he claimed that "gender affirming medical care, specifically hormone therapy or

blockers or surgeries, should be categorically prohibited for minors," he replied "No, I don't." Charles Decl., Ex. B at 905:11-16. Dr. Levine is "not motivated to prohibit care." *Id*. at 906:11-14.

Dr. Levine asserts repeatedly that gender-affirming medical care is provided by doctors who encourage patients to identify as transgender and provide hormones without assessing patients and addressing other mental health conditions or without informing patients and their parents of the risks and limitations of the evidence regarding treatments. Charles Decl. Ex. A at ¶¶50, 64, 74, 83. As an initial matter, Dr. Levine admits in his report that he cannot confirm if any practitioners engage in this "affirmation care/therapy model" he describes. Charles Decl. Ex. A at ¶53. And he confirmed his lack of support for this assertion during his testimony in *Brandt*, when on cross-examination, he admitted that he does not know how common it is for doctors to provide care the way he described, which is contrary to WPATH SOC 8 and Endocrine Society clinical guideline, both of which require comprehensive psychological assessments prior to initiation of any medical treatment for adolescents. Charles Decl., Ex. B at 887:19-888:21, 890:24, 933:2-7; Charles Decl. Ex. I at 3870, 3876-3878; Charles Decl., Ex. J at S48-51.

Finally, the *Kadel* court also recognized that Dr. Levine's assertions that healthcare providers are prescribing treatment without due caution or informed consent were not admissible:

> Fourth, as discussed, it does not appear that he offers any categorical opinion as to the medical necessity of medical and surgical treatments of gender dysphoria, nor does he testify that healthcare providers are prescribing such treatment without due caution and informed consent beyond his anecdotal "experience." To the extent that Defendants seek to introduce testimony from Levine to that effect, he has not provided the Court with any data or methodology from which such claims could be made. Levine has conducted no research to identify which physicians are proceeding as he does, and which do not, rendering any broader opinion about the practice of such healthcare providers pure speculation.

Kadel, 2022 WL 322673, at *17. This is no less true here.

Dr. Levine's opinions that gender-affirming medical care is without lasting benefit also fail the reliability test because he ignores studies contrary to his personal belief or distorts studies' findings beyond the authors' explicit intentions, conclusion, or study design. Significantly, he omits recent studies demonstrating that medical treatments for transgender adolescents and adults have favorable outcomes across many measures. Charles Decl., Ex. K at ¶55. A plethora of studies show that transgender people experience pervasive stigma and discrimination, resulting in health disparities. But Dr. Levine omits any reference to that evidence and instead suggests that "long-term life in a transgender identity, however, correlates with very high rates of completed suicide," and goes on to discuss four studies that reviewed the rate of suicide among transgender adults who received gender-affirming medical care. Charles Decl., Ex. A at ¶¶166-171. While Dr. Levine admits, as he must, that "None of the studies demonstrated the hormonal or surgical intervention *caused* [sic]

suicide," he goes on in the same paragraph to assert a different unsupported conclusion, that "what these studies demonstrate" is that transgender people "are in need of extensive psychological care they don't receive," and that "neither hormonal nor surgical transition and 'affirmation' resolve their underlying problems and put them on the path to a stable and healthy life." *Id*. at ¶172. This is unreliable methodology at its finest. First, none of the four studies purport to analyze the efficacy of "hormonal or surgical transition," or whether gender-affirming medical care "resolves underlying problems" or "puts [people] on a path to a stable and healthy life." As least one of the studies' authors, Cecilia Dhejne, has explicitly said as much, both in the study itself (it is not designed to "address whether sex reassignment is an effective treatment or not.") and in direct response to Dr. Levine's misuse of her work. Charles Decl., Ex. L at 2; Charles Decl., Ex. M at 65. Another major flaw in Dr. Levine's methodology is that three of the studies' control groups were comprised of the general Dutch population, not of other transgender people with gender dysphoria who did not receiving any gender-affirming medical care. In other words, it is comparing apples to oranges. But Dr. Levine has acknowledged that the Dhejne study does not lend the study to be used to draw any conclusions about the efficacy of gender-affirming care. Charles Decl., Ex. D at 156:7-11. Finally, Dr. Levine's description of the Hall et al. 2021 study obscures the study's actual rate of suicide for the cohort by, without explanation but presumably to

support his description of a "rather shocking result," focusing on the number of transgender women in the group who died by suicide, rather than the total number of deaths by suicide for the entire cohort—which was 3 out of 175 participants, or 1.7%. Charles Decl., Ex. A at ¶171.

Furthermore, as the *Kadel* court observed, Dr. Levine himself has conceded that:

> he does not know how often medical or surgical care helps alleviate symptoms of gender dysphoria and does not offer an opinion as to the portion of these procedures that are necessary and unnecessary. (*Id.* at 67:24–68:3 ("It is not our [clinic's] knowledge base to know who's going to do better and who's going to do worse and who is not going to have any difference at all with hormones or with surgery.").)

Kadel, 2022 WL 322673, at *15.

Ultimately, Dr. Levine fails to cite any literature or clinical experience of his own to support this opinion, and regardless, he has testified that studies like these should not prevent youth and adults with gender dysphoria from receiving gender affirming care. When asked recently if he believes that because a study showed that some people committed suicide *no patient* should be able to access gender-affirming surgery, Dr. Levine responded, "that would be illogical." Charles Decl., Ex. D at 151:25-152:6. And when asked if his concerns justify denying medical interventions to all people with gender dysphoria, he responded "I'm not advocating denying endocrine treatment or surgical treatment." *Id.* at 85:4-11.

At bottom, Dr. Levine's report and the opinions contained therein are wildly

inconsistent with his oral testimony, making both unreliable.

3. Dr. Levine's Opinions About Gender Dysphoria "Naturally Resolving" in Children and Adolescents Are Not Based In Fact.

Another unreliable opinion presented by Dr. Levine is that "the large majority" of *prepubertal* children diagnosed with gender dysphoria will, absent intervention, cease to be transgender (or "desist") through puberty. Charles Decl., Ex. A at ¶¶109-111, 113-114. Putting aside that Dr. Levine has almost no clinical experience with children during his 50-year career treating patients with gender dysphoria to support this opinion, it is unreliable and methodologically unsound for other reasons.

First, Dr. Levine has conceded that some children are and will continue to be transgender and that as they progress into adolescence and adulthood, they would need medical care that he has, and would, authorize. Charles Decl., Ex. D. at 173:7-15, 137:14-23, 173:22-174:5, 53:2-10. Second, as the scholarly basis for this opinion, Dr. Levine cites three articles that share the same core characteristic that reveals the methodological flaw in Dr. Levine's analysis: they rely on previous studies whose underlying data included gender non-conforming children who never identified as a sex different from their birth-assigned sex in the first place. In other words, they included children who were never transgender. That is because the diagnosis at the time these studies were conducted— "Gender Identity Disorder in

Children" —did not include a cross-gender identification or clinically significant distress requirement for the diagnosis. *See*, *e.g.*, Diagnostic Statistical Manuals ("DSM") III, III-R, IV, and IV-R. Under these outdated diagnostic criteria, most of the children diagnosed with "Gender Identity Disorder in Children" were not actually transgender but were gender non-conforming boys who grew up to be gay or bisexual. Because the years of initial visits in the study samples were from 1952-2008, none of these children were diagnosed under the current, and relevant to the case at hand, diagnostic criteria for "Gender Dysphoria in Children," in the DSM 5, published in 2013, which requires for diagnosis "a strong desire to be of the other gender or an insistence that one is the other sex" and "clinically significant distress or impairment in social, school, or other important areas of functioning."[8] Charles Decl., Ex. N at 452. Dr. Levine confirmed this fact as to these and others of the "11 studies," at his deposition in *Fain*. Charles Decl., Ex. C at 221:2-229:14. Therefore, the "desistance rates" from the studies upon which Dr. Levine bases his opinion reflect children who, while they exhibited gender non-conforming behaviors, were

[8] Based on Dr. Levine's failure to identify at deposition in *Kadel* any of the underlying "11 studies" upon which this opinion is based, the court found his methodology to be unreliable and therefore inadmissible: "Levine's testimony regarding desistance rates does not appear to be based on reliable methodology. During deposition, Levine was unable to recall many of the studies that purportedly support his conclusion. (ECF No. 213-3 at 191:20-192:14.)" *Kadel*, 2022 WL 322673, at *16.

not transgender, or suffering from gender dysphoria.

4. Dr. Levine's Assertion that "Rapid Onset Gender Dysphoria," as a Cause of Gender Dysphoria or the Concept of "Detransition" Justifies Denying Treatment to Florida Medicaid Beneficiaries Is Unsupported By Scientific Evidence.

A stark example of one of Dr. Levine's opinions failing to meet methodological reliability is the assertion that "rapid onset gender dysphoria" is a credible phenomenon caused by "social influences through friend groups or through the internet." Charles Decl., Ex. A at II(1)(f), ¶38, ¶96, ¶114. Dr. Levine admitted at the *Brandt* trial, just six months ago, that such a conclusion is based on speculation, not science. Ex. B at 797:8-19. Furthermore, "rapid onset gender dysphoria" ("ROGD") is a scientifically unsupported hypothesis and the only article Dr. Levine routinely cites or discusses regarding ROGD was withdrawn and republished with a significant correction. Dr. Levine testified at deposition in *Kadel* he had not read the correction. Charles Decl., Ex. D at 116:22-117:9. Had he done so, Dr. Levine would be forced to acknowledge the correction's explicit disclaimers that "rapid onset gender dysphoria is not a formal mental health diagnosis," "the report did not collect data from adolescents and young adults or clinicians and therefore does not validate the phenomenon," and "the use of the term, 'rapid onset gender dysphoria' should be used cautiously by clinicians and parents to describe youth." Charles Decl., Ex. O at 1. Despite this, at deposition in *Fain*, Dr. Levine attempted to conflate an

increased number of transgender young people presenting to clinics for care with the theory of "rapid onset gender dysphoria" and asserted, without evidence, it is not a hypothesis but "a fact," that he "assumes everyone understands [this] is true." Charles Decl. Ex. C at 151:18-152:6, 152:22-153:5. When pressed to provide peer-reviewed articles, sources, or studies as scientific support he referenced presentations without title or date, admitted he could not remember the names of "authors from Europe" but asserted it had been documented by "DiAngelo and Clayton in Australia." To date, the only peer-reviewed study that interrogates this hypothesis using adolescent clinical data "did not support the ROGD hypothesis." Charles Decl., Ex. P at 1.

Similarly, Dr. Levine's opinions that there is "a growing number of detransitioners [sic]," or that the number of detransitioners is "accelerating," are also methodologically unreliable, largely because he lacks any evidence to support this belief. Charles Decl., Ex. A at ¶120. The three papers he cites for support of this assertion, "Entwistle 2020, Littman 2021, and Vandenbussche 2021," are purely descriptive, not statistical, or quantitative studies. These, respectively, include a description of anecdotal experiences of "detransitioners," describe the results of "a survey of 100 detransitioners," and report on responses from an online survey about the needs and support for people who detransition. None of the three articles purports to establish that the rate of detransition is growing or accelerating, a fact

Dr. Levine admitted as to two of the studies at deposition in *Fain*. Charles Decl., Ex. C at 155:8-163:24. Indeed, Dr. Levine's own clinical experience is contrary to this assertion—in 50 years of seeing patients with gender dysphoria, he is aware of only two patients who detransitioned. Charles Decl., Ex. B at 920:25-921:5. Nevertheless, Dr. Levine doubles down in his expert rebuttal report, relying on a reference to a "detransition subreddit" with 16,000 members as evidence that "the assumption that [detransition] was a rare occurrence began to lose traction." Ex. Q at ¶30. When confronted about this so-called evidence at deposition in *Kadel*, Dr. Levine admitted he had no evidence that *even one* of the 16,000 members of the subreddit had actually "detransitioned." Charles Decl., Ex. D at 200:6-201:25. Unsurprisingly, the *Kadel* court found such testimony lacking:

> His anecdotal testimony concerning adults and adolescents who regret their transitions appears to be based on a misreading of an article that reviewed entries on the website Reddit. (See ECF No. 215-1 ¶¶ 35, 56, 98.) He admitted during deposition that the article referred to 16,000 entries—not 60,000, as he repeatedly stated in his report—and that he had no knowledge of the content of those entries or whether any of the authors actually de-transitioned or regret their transitions. (Id. at 196:3-7, 201:12-25).

Kadel, 2022 WL 3226731, at *16.

Similarly, when asked in *Fain* about his opinion that there is "evidence that *a growing number* of young people regret transition and wish to reverse it," Dr. Levine admitted he lacked any scientific support for such an opinion. Charles Decl., Ex. C at 158:8-159:2; 160:25-161:9; 163:9-24. Dr. Levine did not point to his own

experience as a basis for this opinion and conceded three times that the sources he cited in his report did not provide relevant evidence. *Id.*

Given that these hypotheses about "rapid onset gender dysphoria" and ideas about "detransition" are unverified or unsupported, Dr. Levine cannot claim the use of reliable methodology. His reliance on his own *ipse dixit* fails to establish a basis upon which to assert these opinions. Indeed, case law establishes that "broad opinions [that] are based solely on … generalized views, anecdotal accounts, and speculation … are not reliable." *In re 3M Combat Arms Earplug Prod. Liab. Litig.*, 2021 WL 684183, at *3 (N.D. Fla. Feb. 11, 2021). And that opinions "based on mere conjecture, assumption, credibility calls, and amounting to no more than ipse dixit" are "neither reliable nor helpful." *Day v. Edenfield*, 2022 WL 972430, at *10 (N.D. Fla. Mar. 31, 2022).

C. Dr. Levine Is Not Qualified To Offer Opinions About Puberty-Delaying Treatment or the Treatment of Prepubertal Children Generally.

Dr. Levine has repeatedly admitted, most recently at the *Brandt* trial six months ago, and at depositions for the last several years, that he has virtually no experience administering psychiatric treatment to prepubertal children and no experience performing research or publishing studies about them. Charles Decl., Ex. A at ¶5; Ex. B at 887:5-8; Ex. C at 26:10-13; Ex. D at 23:1-8. When asked whether he has treated any children with gender dysphoria, he admitted, "I have only on rare

occasion personally treated or directly or indirectly treated a child." Charles Decl. Ex. C at 28:23-29:6; 62:6-14. Dr. Levine also confirmed his testimony from March 30, 2022, that over the course of his nearly 50-year career, he had only seen an estimated six prepubertal children, and not for more than one visit. Charles Decl., Ex. B at 887:5-8; Ex. R at 87:1-7. When asked if he had helped to develop guidelines for the treatment of prepubertal children or adolescents with gender identity issues he responded "the answer is no." Charles Decl., Ex. C at 51:10-16. Dr. Levine is not recognized as an expert in providing treatment to prepubertal children by his private employer who by his own admission does not refer children to him as patients, nor by the University Hospitals' LGBTQ and Gender Care Program--the Cleveland hospital affiliated with Case Western Reserve University Medical School where Dr. Levine is a clinical professor—which he previously admitted did not consult with him as part of its formation or their ongoing work. Charles Decl., Ex. R at 113:19-114:4. Nor does he write or research about providing treatment to prepubertal children or deliver any psychiatric care to them in his day-to-day practice.[9]

While lacking a reliable methodology for his proposed opinions about the

[9] Notably, the *Kadel* court held that "Levine's opinions on mental health approaches to social transition are irrelevant as well, as Defendants maintain that the Plan's exclusion of coverage for mental health treatments of gender dysphoria has never been given effect and is no longer part of the Plan. (*See* ECF Nos. 137 n.2; 137-4 ¶ 27.)" *Kadel,* 2022 WL 3226731, at *16. Dr. Levine has also testified that he has counseled some parents to support their minor child's social transition. Charles Decl., Ex. B at 896:23-25.

treatment of prepubertal children, Dr. Levine does not hesitate to offer his personal beliefs about their care. Dr. Levine would "consider banning puberty blocking hormones even for children who have been cross-gender identified for four years to give them a chance to desist." Charles Decl., Ex. D at 186:20-25. But Dr. Levine acknowledges the unscientific nature of this opinion, admitting he does not know where it comes from or "to what extent it's from my politics, or from my being a parent or a doctor, I don't know." Charles Decl., Ex. D at 187:20-24.

In short, given his proposed testimony and experience, Dr. Levine is not qualified under the *Daubert* standards to offer opinions on matters relating to the care of prepubertal children, and he cannot use his personal beliefs as reliable evidence. Nor is any of this testimony relevant. This case concerns coverage of gender-affirming medical care, and no clinical practice guideline recommends the provision of medical treatments, like puberty delaying medications or hormones, until after the onset of puberty.[10]

D. Dr. Levine's Report, Opinions, and Testimony Lack Probative Value and Are Thus Inadmissible Under Federal Rule Of Evidence 403.

Finally, the Court should exclude Dr. Levine's opinions because their

[10] The *Kadel* court also found that Dr. Levine's criticism of medical or surgical treatment of gender dysphoria in prepubescent children was not relevant because "Plaintiffs conceded that such treatments are not medically necessary until the onset of puberty. *See* Section II.B, *supra*." *Kadel*, 2022 WL 322673, at *16.

introduction will result in unfair prejudice, confusion of the issues, or in misleading testimony. Fed. R. Evid. 403. Most of Dr. Levine's opinions are unreliable and unhelpful. The testimony would also result in prejudice, as the testimony seeks to sow confusion about the veracity of Plaintiffs' gender identity, gender dysphoria diagnosis, and treatment they have been undergoing for years—issues unrelated to whether the Florida Medicaid Program can deny coverage of the same kinds of treatments to transgender people that it provides cisgender people.

IV. CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request the Court grant the instant motion and limit Dr. Levine's opinions and testimony, at a minimum, to his opinions (1) identifying risks associated with prescribing medication and surgery to adolescents, and (2) criticizing the quality of the research on treatments for gender dysphoria and that Dr. Levine's report, opinions, and his testimony be otherwise excluded in full.

Dated this 7th day of April 2023.

Respectfully Submitted,

/s/ Carl S. Charles

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CERTIFICATE OF SERVICE

I hereby certify that on this 7th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Memorandum contains 7,636 words.

/s/ Carl S. Charles
Carl S. Charles
Counsel for Plaintiffs

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

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TAB 175-1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al., *Plaintiffs*, v. JASON WEIDA[1], et al., *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

DEFENDANTS' RESPONSE TO PLAINTIFFS'
FIRST SET OF REQUESTS FOR ADMISSION

Pursuant to Federal Rule of Civil Procedure 36, Defendants Secretary Weida and the Agency for Health Care Administration ("Defendants") submit their response to Plaintiffs' First Set of Requests for Admission.

GENERAL OBJECTIONS

Defendants make the following general objections to Plaintiffs' Requests for Admission, which apply to each request regardless of whether the general objections are expressly incorporated into the specific objections below:

[1] Jason Weida has succeeded Simone Marstiller as Secretary of the Agency for Health Care Administration, as reflected in ECF 78.

Pl. Trial Ex. 001

PLAINTIFFS002191

1. Defendants object to the Requests for Admission to the extent they are overly broad, unduly burdensome, not reasonably calculated to lead to the discovery of admissible evidence, and not proportional to the needs of the case.

2. Defendants object to the Requests for Admission to the extent they seek to elicit information or evidence otherwise protected by the attorney-client privilege, the work-product privilege, the First Amendment associational privilege, the legislative privilege, or any other applicable privilege recognized under federal or Florida law.

3. Defendants object to the Requests for Admission to the extent they seek to elicit information that is in the public domain or already in Plaintiffs' possession, and therefore of no greater burden for Plaintiffs than for the Secretary to obtain.

4. Defendants object to the Requests for Admission to the extent they seek publicly available information, statements, or documents that speak for themselves and require neither an admission nor a denial from any party.

5. Only to the extent that Federal Rule of Civil Procedure 36(a)(4) would be construed as requiring an admission or denial and that an objection alone is not sufficient, the Secretary deny each Request for Admission. Otherwise, Defendants stand on the foregoing General Objections

and the below-stated specific objections without expressly admitting or denying any Request for Admission.

RESPONSES TO REQUESTS FOR ADMISSION

1. Admit that gender-affirming care can be medically necessary.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants admit that certain types of behavioral health services to treat gender dysphoria can be medically necessary, but other types of treatment are not.

2. Admit that the Challenged Exclusion prohibits Florida Medicaid coverage of gender affirming care that can be medically necessary for the treatment of Gender Dysphoria.

RESPONSE: Denied insofar as the Challenged Exclusion does not preclude the coverage of behavioral health services for gender dysphoria, and the services for which coverage is precluded are not medically necessary.

3. Admit that each of the Various Services can be medically necessary for the treatment of Gender Dysphoria.

RESPONSE: Denied.

4. Admit that each Plaintiff identifies as transgender.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

5. Admit that each Plaintiff has been diagnosed with Gender Dysphoria.

RESPONSE: Admitted that each Plaintiff has been diagnosed with

Gender Dysphoria, but Defendants reserve the right to challenge such diagnoses.

6. Admit that each Plaintiff receives health care coverage through Florida's Medicaid program.

RESPONSE: Admitted.

7. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid covered "services for the treatment of gender dysphoria," as that term is defined in the Challenged Exclusion, for each Plaintiff.

RESPONSE: Admitted that the Agency did not have a policy excluding coverage for such treatments prior to the adoption of the Challenged Exclusion.

8. Admit that Florida Medicaid covers each of the Various Services when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

9. Admit that Florida Medicaid covers mastectomy, reduction mammoplasty, and breast reconstruction surgery when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

10. Admit that Florida Medicaid covers hysterectomy and oophorectomy procedures when necessary to treat at least one condition other than Gender

Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

11. Admit that Florida Medicaid covers vaginoplasty procedures when necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

12. Admit that Florida Medicaid covers orchiectomy, penectomy, and/or phalloplasty procedures when medically necessary to treat at least one condition other than Gender Dysphoria.

RESPONSE: Admitted. However, these services not medically necessary for the treatment of gender dysphoria.

13. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid did not exclude coverage of prescribed hormones for the treatment of Gender Dysphoria.

RESPONSE: Admitted that the Agency did not have a policy categorically excluding coverage for such treatments prior to the adoption of the Challenged Exclusion.

14. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

15. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for a double mastectomy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

16. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Brit Rothstein received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

17. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Susan Doe received coverage under Florida Medicaid for a GnRH antagonist as treatment for her Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

18. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff K.F. received coverage under Florida Medicaid for a GnRH antagonist as treatment for his Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

19. Admit that, prior to the enactment of the Challenged Exclusion,

Florida Medicaid gave Plaintiff Brit Rothstein prior authorization for double mastectomy as treatment for his Gender Dysphoria.

RESPONSE: Admitted that such authorization was given by the relevant Health Plan, but was not given by the Agency.

20. Admit that, following the enactment of Challenged Exclusion, Plaintiffs have not received coverage under Florida Medicaid for the services described in Requests 14 to 19 above.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

21. Admit that if Plaintiff August Dekker does not continue to receive hormone therapy, he may undergo physical changes.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

22. Admit that if Plaintiff Brit Rothstein does not continue to receive hormone therapy, he may undergo physical changes.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

23. Admit that if Plaintiff Brit Rothstein does not receive the double mastectomy previously authorized by Defendants, he may experience exacerbated distress and chest dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

24. Admit that if Plaintiff Susan Doe does not continue to receive a GnRH antagonist, she will undergo endogenous puberty.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

25. Admit that if Plaintiff K.F. does not continue to receive a GnRH antagonist, he will undergo endogenous puberty.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

26. Admit that undergoing endogenous puberty causes development of secondary sex characteristics.

RESPONSE: Admitted.

27. Admit that undergoing endogenous puberty causes irreversible physical changes.

RESPONSE: Admitted.

28. Admit that you did not prepare any criteria for determining whether to grant a variance under Florida Statutes § 120.542 to permit Florida Medicaid coverage of any of the Various Services when used to treat Gender Dysphoria.

RESPONSE: Admitted that the Agency did not prepare any such criteria, but the Florida Legislature did as set forth in the cited statute.

29. Admit that you have no existing criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid

coverage of any of the services excluded by the Challenged Exclusion.

RESPONSE: Denied.

30. Admit that you are not currently preparing any criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

RESPONSE: Admitted. The criteria are set forth in the cited statute.

31. Admit that none of the Various Services are experimental when used to treat Gender Dysphoria.

RESPONSE: Denied.

32. Admit that none of the Various Services are investigational when used to treat Gender Dysphoria.

RESPONSE: Denied.

33. Admit that licensed medical professionals with experience treating Gender Dysphoria are in the best position to make medical determinations regarding the diagnosis and treatment of patients with Gender Dysphoria.

RESPONSE: Objection. The request is vague insofar as the term "best position" is not defined and could be interpreted in a number of ways.

34. Admit that, as recently as 2016, you did not consider puberty

suppression therapy for the treatment of Gender Dysphoria to be experimental.

RESPONSE: Denied.

35. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be investigational.

RESPONSE: Denied.

36. Admit that the individuals involved in the process of creating and implementing the Challenged Exclusion were not the same individuals who are typically involved in this process on your behalf.

RESPONSE: Denied.

37. Admit that, as recently as 2016, you did not consider any of the Various Services to be experimental.

RESPONSE: Denied.

38. Admit that, as recently as 2016, you did not consider any of the Various Services to be investigational.

RESPONSE: Denied.

39. Admit that you have criteria for determining whether to grant a variance under Florida Statutes § 120.542 for any service used to treat a healthcare condition besides Gender Dysphoria.

RESPONSE: Denied.

40. Admit that the Challenged Exclusion restricts coverage for gender-affirming care that has been the subject of decades of scholarly research.

RESPONSE: Objection. This request is vague insofar as the term "scholarly research" is not defined and could be interpreted in a number of ways.

41. Admit that no major medical organization recommends or supports prohibiting coverage of the Various Services when used to treat Gender Dysphoria.

RESPONSE: Defendants are without sufficient knowledge to admit or deny; therefore denied.

42. Admit that transgender people have historically been subject to discrimination.

RESPONSE: Objection. This request is not relevant to any party's claim or defense and is not proportional to the needs of the case.

43. Admit that, prior to the enactment of the Challenged Exclusion, you were aware that transgender people have historically been subject to discrimination.

RESPONSE: Objection. This request is not relevant to any party's claim or defense and is not proportional to the needs of the case.

44. Admit that being transgender is immutable.

RESPONSE: Denied.

45. Admit that being transgender bears no relation to one's ability to contribute to society.

RESPONSE: Objection. This request calls for an opinion, not a matter of fact. Furthermore, the request is not relevant to any party's claim or defense and is not proportional to the needs of this case.

46. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through randomized clinical trials.

RESPONSE: Objection. This request is vague and overly burdensome. Each health service is unique, and such a broad statement does not apply. To fully answer, the Agency would incur an undue burden of having to assess thousands of individual health services and determine whether they lack randomized clinical trials.

47. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through long-term longitudinal studies.

RESPONSE: Objection. This request is vague and overly burdensome. Each health service is unique, and such a broad statement should not apply. To fully answer, the Agency would incur an undue burden of having to assess thousands of individual health services and determine whether they lack long-term longitudinal studies.

48. Admit that you provide Florida Medicaid coverage for some health care services that have a risk of producing unintended, irreversible consequences.

RESPONSE: Objection. This request is vague insofar as the terms "unintended" and "consequences" are undefined and could be interpreted in a number of ways.

49. Admit that the well-established medical consensus is that gender-affirming care should be provided to transgender people with Gender Dysphoria.

RESPONSE: Denied.

50. Admit that the WPATH Standards of Care are the most widely used standards in the United States for treating Gender Dysphoria.

RESPONSE: Denied.

51. Admit that the WPATH Standards of Care are the leading standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

52. Admit that the WPATH Standards of Care are authoritative standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

53. Admit that the WPATH Standards of Care are widely accepted as the leading standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

54. Admit that the WPATH Standards of Care are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

RESPONSE: Denied.

55. Admit that the Endocrine Society's Clinical Practice Guidelines are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

RESPOSNE: Denied.

56. Admit that the Endocrine Society's Clinical Practice Guidelines are authoritative standards of care for the treatment of Gender Dysphoria.

RESPOSNE: Denied.

57. Admit that Defendants are not aware of any other widely used standards of care to treat Gender Dysphoria other than the WPATH Standards of Care or the Endocrine Society's Clinical Practice Guidelines.

RESPONSE: Denied.

58. Admit that your coverage of medical care should be made pursuant to the standards of care for a particular condition.

RESPONSE: Objection. This request calls for an opinion not a matter of fact. Furthermore, it is overly broad and lacks specificity.

59. Admit that the treatment of a medical condition should be made pursuant to the standards of care for a particular condition.

RESPONSE: Objection. This request calls for an opinion not a matter of fact. Furthermore, it is overly broad and lacks specificity.

60. Admit that persons from the Office of the Governor Ronald DeSantis were involved in your decision to promulgate the Challenged Exclusion.

RESPONSE: Denied.

61. Admit that persons from the Florida Department of Health were involved in your decision to promulgate the Challenged Exclusion.

RESPONSE: Denied.

62. Admit that you caused Chloe Cole to be invited to the July 8 Hearing.

RESPONSE: Denied.

63. Admit that you caused Sophia Galvin to be invited to the July 8 Hearing.

RESPONSE: Denied.

64. Admit that you caused Anthony Verdugo to be invited to the July 8 Hearing.

RESPONSE: Denied.

65. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Christian Family Coalition.

RESPONSE: Denied.

66. Admit that you caused to be invited to the July 8 Hearing any persons

affiliated with the Florida Citizens Alliance.

RESPONSE: Denied.

67. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Warriors of Faith.

RESPONSE: Denied.

68. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Protect our Children Project.

RESPONSE: Denied.

69. Admit that, in promulgating the Challenged Exclusion, you did not consult "evidence-based clinical practice guidelines", as that term is used in 59G-1.035.

RESPONSE: Denied.

70. Admit that, in promulgating the Challenged Exclusion, you did not consult articles "published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty association", as that term is used in 59G-1.035.

RESPONSE: Denied.

71. Admit that, in promulgating the Challenged Exclusion, you did not consult "coverage policies by other creditable insurance payor sources", as that term is used in 59G-1.035.

RESPONSE: Denied.

72. Admit that only Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman were included on the July 8 Hearing panel.

RESPONSE: Denied.

73. Admit that Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman have all taken positions that support Defendants' promulgation of exclusions for coverage of treatment of Gender Dysphoria.

RESPONSE: Objection. This request is vague insofar as the term "positions" is not defined and could be interpreted in a number of ways.

74. Admit that you did not include anyone on the July 8 Hearing panel who has taken a position that opposes Defendants' promulgation of exclusions for coverage of Gender Dysphoria.

RESPONSE: Objection. This request is vague insofar as the term "positions" is not defined and could be interpreted in a number of ways.

75. Admit that you selected the authors of the GAPMS Memo reports because of their opposition to gender-affirming care.

RESPONSE: Denied.

76. Admit that each of the authors of the GAPMS Memo have publicly taken positions in opposition to gender-affirming care.

RESPONSE: Denied.

77. Admit that you selected the panel members for the July 8 Hearing because of their opposition to gender-affirming care.

RESPONSE: Denied.

78. Admit that, prior to the GAPMS Memo's drafting and promulgation, you determined that gender-affirming care was experimental or investigational.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants deny.

79. Admit that, regardless of what information was available to you, you intended to reach the conclusion in the GAPMS Memo that gender-affirming care was experimental or investigational.

RESPONSE: Defendants object to the definition of gender-affirming care because it is contrary to the term's ordinary use. Subject to and without waiving such objection, Defendants deny.

* * *

Dated: January 12, 2023

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I hereby certify that on January 12, 2023, a true and correct copy of the foregoing document was served upon all counsel of record via email, as follows:

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TAB 175-4

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, et al., *Plaintiffs*, v. SIMONE MARSTILLER, et al., *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' FIRST SET OF REQUESTS FOR ADMISSION TO DEFENDANTS FLORIDA AGENCY FOR HEALTHCARE ADMINISTRATION AND SECRETARY SIMONE MARSTILLER

Pursuant to Federal Rules of Civil Procedure 26 and 36, Plaintiffs propound this First Set of Requests for Admission to Defendants Florida Agency for Health Care Administration and Secretary Marstiller to be answered fully and within the timeframe required under the Federal Rules and the Local Rules of this Court.

DEFINITIONS

As used herein, the following terms shall have the meanings indicated below:

1. "Defendants," "you," and "your" mean both Defendant Simone Marstiller and the Florida Agency for Health Care Administration ("AHCA"), their agents, employees, administrators, attorneys, representatives, contractors,

consultants, investigators, and all other Persons and entities working or purporting to act on behalf of, or in concert with, or in participation with AHCA.

2. The "Challenged Exclusion" means Florida Administrative Code 59G-1.050(7), which was enacted on August 21, 2022, prohibiting coverage for "services for the treatment of gender dysphoria," including "puberty blockers," "hormones and hormone antagonists," "sex reassignment surgeries," and "any other procedures that alter primary or secondary sexual characteristics."

3. "Florida Medicaid" means the same as "Medicaid" defined at Fla. Stat. 409.901(14) & 409.962(11) and includes all contractors, including health insurance plans, engaged by Defendants for the administration of Florida's Medicaid program.

4. "Florida Medicaid program" means the same as "Medicaid program" defined at Fla. Stat. 409.901(16).

5. "GAPMS Memo" refers to Defendants' June 2022 publication titled "Florida Medicaid: Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria," including by reference all attachments and exhibits.

6. Unless otherwise specified, "gender-affirming care" means any health care, physical, mental, or otherwise, administered or prescribed for the treatment of Gender Dysphoria.

7. "Gender Dysphoria" refers to the clinically significant distress or impairment related to the incongruence between one's experienced/expressed gender and their assigned sex at birth, including their primary and/or secondary sex characteristics. For purposes of these Requests, "Gender Dysphoria" shall include: (a) the diagnoses for "Gender dysphoria in adolescents and adults" and "Gender dysphoria in children," as defined within *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision* (DSM-5-TR); (b) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder in Adolescents and Adults," "Gender Identity Disorder in Children," and "Gender Identity Disorder Not Otherwise Specified," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR); (c) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder in Children," "Transsexualism," and "Gender Identity Disorder of Adolescence or Adulthood, Nontranssexual Type," and Gender Identity Disorder not Otherwise Specified," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revision* (DSM-III-TR); (d) the diagnosis for "gender identity disorder," including any subcategories such as "Gender Identity Disorder

in Children," "Transsexualism," and "Atypical Gender Identity Disorder," as defined within the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition* (DSM-III); and (e) the diagnoses for "gender incongruence of adolescence and adulthood" and "gender incongruence of childhood," as defined within the *International Classification of Diseases, Eleventh Revision* (ICD-11); and the diagnoses for "transsexualism" and "gender identity disorder," including any subcategories, as defined within the *International Classification of Diseases, Tenth Revision* (ICD-10) and *International Classification of Diseases, Ninth Revision* (ICD-9).

8. "July 8 Hearing" refers to the hearing that Defendants held on July 8, 2022 in Tallahassee, Florida regarding the Challenged Exclusion.

9. The term "major medical organization" shall mean the American Medical Association, the American Psychological Association, the American Psychiatric Association, Endocrine Society, the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the American Academy of Family Physicians.

10. "Medically necessary" shall have the same meaning as in 59G-1.010(166).

11. "Person" and "persons" mean any natural person, partnership, association, corporation, joint venture, trust, community group, government or

subdivision of any government (including any instrumentality, bureau, department, office, or agency of any government), not-for-profit enterprise, or other business entity, and all present and former officers, directors, agents, administrators, managers, representatives, contractors, consultants, employees, or other persons acting or purporting to act on behalf of such person.

12. "Plaintiffs" means the named plaintiffs in this action and any other plaintiff that is added in the future.

13. "Various Services" refers to the following procedures: penectomy, orchiectomy, vaginoplasty, feminizing genitoplasty, breast reconstruction, chondrolaryngoplasty, phalloplasty, metoidioplasty, masculinizing genitoplasty, single or double mastectomy, reduction mammoplasty, hysterectomy, oophorectomy, salpingo-oophorectomy, estradiol (in all forms, including oral/sublingual estradiol, transdermal estradiol, estradiol valerate IM, and estradiol cypionate IM), medroxyprogesterone acetate (Provera), micronized progesterone, spironolactone, finasteride, dutasteride, and testosterone (in all forms, including testosterone cypionate, testosterone enthanate, testosterone topical gel 1%, testosterone topical gel 1.62%, testosterone patches, testosterone cream, testosterone axillary gel 2%, testosterone undecanoate), and Gonadotropin-releasing hormone (GnRH) antagonists.

INSTRUCTIONS

1. These Requests are issued to each of the Defendants. Defendants' responses to these Requests shall be made within thirty (30) days of service of these Requests.

2. All responses to these Requests should be directed to: Jennifer Altman, Pillsbury Winthrop Shaw Pittman LLP, 600 Brickell Avenue, Suite 3100, Miami, FL 33131, Email: jennifer.altman@pillsbury.com, cc: soraya.garcia@pillsburylaw.com.

3. Unless otherwise specified, the time period covered by these Requests is January 1, 2015 to the present. If it is necessary to refer to periods of time prior to January 1, 2015 to respond to a Request, please do so.

4. These Requests are continuing in nature, up to and during the course of trial. Defendants' responses to these Requests are to be promptly supplemented or amended if, after the time of their initial responses, Defendants learn that any response is or has become in some material respect incomplete or incorrect, to the full extent provided for by Federal Rule of Civil Procedure 26(e). Plaintiffs will object to any attempt to introduce evidence to the Court that should have been but was not disclosed in the responses or supplementation of the responses.

5. If a Request cannot be complied with in full, it shall be complied with to the extent possible, and accompanied by an explanation of your objection to the request or other reasons you are unable to fully comply.

6. As to each Request, Defendants shall specifically admit or deny the statement contained therein. If denied, the denial must fairly meet the substance of the requested admission. If Defendants qualify their answer or deny any part of the matter for which admission is requested, Defendants shall admit so much of the statement as is true and qualify or deny the remainder.

7. If Defendants object that a term or phrase is vague or ambiguous, Defendants shall respond with their understanding of the term or phrase and specifically admit or deny the statement.

8. If Defendants object to any part of a Request, Defendants shall specify each part of the Request to which Defendants object; set forth with specificity the grounds for objecting to each such part of the Request, including the reasons, and otherwise respond to all parts of the Request to which Defendants do not object.

11. Responses to these Requests shall include all information within the custody, possession, or control of you, your employees, partners, contractors, accountants, attorneys, or other agents, or which are otherwise available to you.

12. When, after a reasonable and thorough investigation using due diligence, you are unable to admit or deny a Request or any part thereof, specify in

full the reason that you are unable to admit or deny the Request and the steps you have taken to locate information that would allow you to admit or deny the Request. If you deny any part of a matter for which admission is requested, you shall admit so much of the statement as is true.

13. For purposes of interpreting or construing the scope of these Requests, all terms shall be given their most expansive and inclusive interpretation. This includes, without limitation, the following:

a. Construing "and" as well as "or" in the disjunctive or conjunctive, as necessary to make the Request more inclusive;

b. Construing the singular form of the word to include the plural, and the plural form to include the singular;

c. Construing the masculine to include the feminine, and vice versa;

d. Construing the term "including" to mean "including but not limited to" and construing the term "all" to mean "any and all," and vice versa;

e. Construing the term "each" to include "every," and construing "every" to include "each";

f. Construing the use of a verb in any tense as applying to the use of the verb in all other tenses as is necessary to make any paragraph more, rather than less, inclusive;

g. Construing and interpreting all spelling, syntax, grammar, abbreviations, idioms, and proper nouns to give proper meaning and consistency to their context.

REQUESTS FOR ADMISSION

1. Admit that gender-affirming care can be medically necessary.

2. Admit that the Challenged Exclusion prohibits Florida Medicaid coverage of gender affirming care that can be medically necessary for the treatment of Gender Dysphoria.

3. Admit that each of the Various Services can be medically necessary for the treatment of Gender Dysphoria.

4. Admit that each Plaintiff identifies as transgender.

5. Admit that each Plaintiff has been diagnosed with Gender Dysphoria.

6. Admit that each Plaintiff receives health care coverage through Florida's Medicaid program.

7. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid covered "services for the treatment of gender dysphoria," as that term is defined in the Challenged Exclusion, for each Plaintiff.

8. Admit that Florida Medicaid covers each of the Various Services when necessary to treat at least one condition other than Gender Dysphoria.

9. Admit that Florida Medicaid covers mastectomy, reduction mammoplasty, and breast reconstruction surgery when necessary to treat at least one condition other than Gender Dysphoria.

10. Admit that Florida Medicaid covers hysterectomy and oophorectomy procedures when necessary to treat at least one condition other than Gender Dysphoria.

11. Admit that Florida Medicaid covers vaginoplasty procedures when necessary to treat at least one condition other than Gender Dysphoria.

12. Admit that Florida Medicaid covers orchiectomy, penectomy, and/or phalloplasty procedures when medically necessary to treat at least one condition other than Gender Dysphoria.

13. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid did not exclude coverage of prescribed hormones for the treatment of Gender Dysphoria.

14. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

15. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff August Dekker received coverage under Florida Medicaid for a double mastectomy as treatment for his Gender Dysphoria.

16. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Brit Rothstein received coverage under Florida Medicaid for hormone therapy as treatment for his Gender Dysphoria.

17. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff Susan Doe received coverage under Florida Medicaid for a GnRH antagonist as treatment for her Gender Dysphoria.

18. Admit that, prior to the enactment of the Challenged Exclusion, Plaintiff K.F. received coverage under Florida Medicaid for a GnRH antagonist as treatment for his Gender Dysphoria.

19. Admit that, prior to the enactment of the Challenged Exclusion, Florida Medicaid gave Plaintiff Brit Rothstein prior authorization for double mastectomy as treatment for his Gender Dysphoria.

20. Admit that, following the enactment of Challenged Exclusion, Plaintiffs have not received coverage under Florida Medicaid for the services described in Requests 14 to 19 above.

21. Admit that if Plaintiff August Dekker does not continue to receive hormone therapy, he may undergo physical changes.

22. Admit that if Plaintiff Brit Rothstein does not continue to receive hormone therapy, he may undergo physical changes.

23. Admit that if Plaintiff Brit Rothstein does not receive the double mastectomy previously authorized by Defendants, he may experience exacerbated distress and chest dysphoria.

24. Admit that if Plaintiff Susan Doe does not continue to receive a GnRH antagonist, she will undergo endogenous puberty.

25. Admit that if Plaintiff K.F. does not continue to receive a GnRH antagonist, he will undergo endogenous puberty.

26. Admit that undergoing endogenous puberty causes development of secondary sex characteristics.

27. Admit that undergoing endogenous puberty causes irreversible physical changes.

28. Admit that you did not prepare any criteria for determining whether to grant a variance under Florida Statutes § 120.542 to permit Florida Medicaid coverage of any of the Various Services when used to treat Gender Dysphoria.

29. Admit that you have no existing criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

30. Admit that you are not currently preparing any criteria for determining whether to grant a variance under Florida Statute § 120.542 to permit Florida Medicaid coverage of any of the services excluded by the Challenged Exclusion.

31. Admit that none of the Various Services are experimental when used to treat Gender Dysphoria.

32. Admit that none of the Various Services are investigational when used to treat Gender Dysphoria.

33. Admit that licensed medical professionals with experience treating Gender Dysphoria are in the best position to make medical determinations regarding the diagnosis and treatment of patients with Gender Dysphoria.

34. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be experimental.

35. Admit that, as recently as 2016, you did not consider puberty suppression therapy for the treatment of Gender Dysphoria to be investigational.

36. Admit that the individuals involved in the process of creating and implementing the Challenged Exclusion were not the same individuals who are typically involved in this process on your behalf.

37. Admit that, as recently as 2016, you did not consider any of the Various Services to be experimental.

38. Admit that, as recently as 2016, you did not consider any of the Various Services to be investigational.

39. Admit that you have criteria for determining whether to grant a variance under Florida Statutes § 120.542 for any service used to treat a healthcare condition besides Gender Dysphoria.

40. Admit that the Challenged Exclusion restricts coverage for gender-affirming care that has been the subject of decades of scholarly research.

41. Admit that no major medical organization recommends or supports prohibiting coverage of the Various Services when used to treat Gender Dysphoria.

42. Admit that transgender people have historically been subject to discrimination.

43. Admit that, prior to the enactment of the Challenged Exclusion, you were aware that transgender people have historically been subject to discrimination.

44. Admit that being transgender is immutable.

45. Admit that being transgender bears no relation to one's ability to contribute to society.

46. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through randomized clinical trials.

47. Admit that you provide Florida Medicaid coverage for some health care services that have not been studied through long-term longitudinal studies.

48. Admit that you provide Florida Medicaid coverage for some health care services that have a risk of producing unintended, irreversible consequences.

49. Admit that the well-established medical consensus is that gender-affirming care should be provided to transgender people with Gender Dysphoria.

50. Admit that the WPATH Standards of Care are the most widely used standards in the United States for treating Gender Dysphoria.

51. Admit that the WPATH Standards of Care are the leading standards of care for the treatment of Gender Dysphoria.

52. Admit that the WPATH Standards of Care are authoritative standards of care for the treatment of Gender Dysphoria.

53. Admit that the WPATH Standards of Care are widely accepted as the leading standards of care for the treatment of Gender Dysphoria.

54. Admit that the WPATH Standards of Care are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

55. Admit that the Endocrine Society's Clinical Practice Guidelines are widely accepted as authoritative standards of care for the treatment of Gender Dysphoria.

56. Admit that the Endocrine Society's Clinical Practice Guidelines are authoritative standards of care for the treatment of Gender Dysphoria.

57. Admit that Defendants are not aware of any other widely used standards of care to treat Gender Dysphoria other than the WPATH Standards of Care or the Endocrine Society's Clinical Practice Guidelines.

58. Admit that your coverage of medical care should be made pursuant to the standards of care for a particular condition.

59. Admit that the treatment of a medical condition should be made pursuant to the standards of care for a particular condition.

60. Admit that persons from the Office of the Governor Ronald DeSantis were involved in your decision to promulgate the Challenged Exclusion.

61. Admit that persons from the Florida Department of Health were involved in your decision to promulgate the Challenged Exclusion.

62. Admit that you caused Chloe Cole to be invited to the July 8 Hearing.

63. Admit that you caused Sophia Galvin to be invited to the July 8 Hearing.

64. Admit that you caused Anthony Verdugo to be invited to the July 8 Hearing.

65. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Christian Family Coalition.

66. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Florida Citizens Alliance.

67. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Warriors of Faith.

68. Admit that you caused to be invited to the July 8 Hearing any persons affiliated with the Protect our Children Project.

69. Admit that, in promulgating the Challenged Exclusion, you did not consult "evidence-based clinical practice guidelines", as that term is used in 59G-1.035.

70. Admit that, in promulgating the Challenged Exclusion, you did not consult articles "published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty association", as that term is used in 59G-1.035.

71. Admit that, in promulgating the Challenged Exclusion, you did not consult "coverage policies by other creditable insurance payor sources", as that term is used in 59G-1.035.

72. Admit that only Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman were included on the July 8 Hearing panel.

73. Admit that Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman have all taken positions that support Defendants' promulgation of exclusions for coverage of treatment of Gender Dysphoria.

74. Admit that you did not include anyone on the July 8 Hearing panel who has taken a position that opposes Defendants' promulgation of exclusions for coverage of Gender Dysphoria.

75. Admit that you selected the authors of the GAPMS Memo reports because of their opposition to gender-affirming care.

76. Admit that each of the authors of the GAPMS Memo have publicly taken positions in opposition to gender-affirming care.

77. Admit that you selected the panel members for the July 8 Hearing because of their opposition to gender-affirming care.

78. Admit that, prior to the GAPMS Memo's drafting and promulgation, you determined that gender-affirming care was experimental or investigational.

79. Admit that, regardless of what information was available to you, you intended to reach the conclusion in the GAPMS Memo that gender-affirming care was experimental or investigational.

* * *

Respectfully submitted this 12th day of December, 2022.

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* *Admitted pro hac vice.*

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing was served by email on December 12, 2022, on all counsel of record:

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COUNSEL FOR DEFENDANTS

/s/ Joe Little
Counsel for Plaintiffs

TAB 175-18

Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

June 2022

Pl. Trial Ex. 018

Ron DeSantis, Governor
Simone Marstiller, Secretary

Contents

Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term "gender" in reference to the construct of male and female identities and the term "sex" when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).[1]

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one's gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender." As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having "a strong desire to be of the other gender or an insistence that one is the other gender" or "a strong preference for cross-gender roles in make-believe or fantasy play." The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include "a strong desire to be the other gender" or "a strong desire to be rid of one's primary and/or secondary sexual characteristics." The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition "is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

[1] The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money's theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money's ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth." Additionally, the Merck Manual further states that "gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold" (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.[2]

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman's study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V's criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA's definition. They further asserted that the APA intended to "reduce pathologization" by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA's definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V's criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one's gender as a disorder. In addition, the APA considers gender as part of one's identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

[2] Following the release of the Florida Department of Health's guidelines for treating gender dysphoria, Merck removed its definition for "gender dysphoria" from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the "effort to reduce stigma" (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one's gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies "a marked incongruence between one's experienced/expressed gender and natal sex, of at least 6 months' duration" as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for "marked." This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)[3], behavioral health professionals are supposed to "find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment." WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

[3] The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as "gender affirming" surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a "standard of care" and that its grades for available services are low or very low (Endocrine Society, 2017).[4]

[4] Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient's overall behavioral health and that providing a "surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it" (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.[5]
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

[5] Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozlowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozlowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozlowska et al also cite other studies that indicate a high correlation between gender dysphoria and "adverse childhood events" and further assert that the condition "needs to be conceptualized in the context of the child's lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway" (Kozlowska et al, 2021).

For their study, Kozlowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child's developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozlowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of "adverse childhood events" such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported "instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures." These results led Kozlowska et al to conclude that gender dysphoria can be "associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion." The study also cites that treatment requires "a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child's presentation" (Kozlowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual's gravitation to the opposite sex documented over multiple years) but rather exposure to "social and peer contagion." Littman uses this term in the context of definitions cited in academic literature, stating that "social contagion is the spread of affect or behaviors through a population" and that "peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others." Examples of the latter's negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that "online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria." The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozlowska et al's study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman's research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a "maladaptive coping mechanism" for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman's study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential "gateway drug" for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who "wished they were the other sex" were more likely to become desisters and that those who "believed that they were the other sex" persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrect Gender Dysphoria Scale and Children's Global Assessment Scale)[6] to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

[6] Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is "variable." The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	**Reversible or Irreversible**
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017[7]

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

[7] This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as "irreversible" in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are "gender affirming." This decision mirrors the DSM-V's interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an "affirmation and acceptance of who they (i.e., patient) have always been" (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP's endorsement of "gender affirming" treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP's position is based on research that does not support intervention but rather supports "watchful waiting" because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites "gender affirming" interventions as the only effective method. To conclude, he states the organization is "advocating for something far in excess of mainstream practice and medical consensus" (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP's endorsement as a basis for "gender affirming" treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.[8] WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

[8] Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a "cure" to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al's study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).[9] Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden's overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al's conclusions were "too strong" and that further analysis by the authors revealed that the new "results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

[9] Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison" (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al's findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al's research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient's perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the "lifesaving" potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline "Almost half of LGBTQ youths 'seriously considered suicide in the past year'" (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that "there is great uncertainty about the effects" of sex reassignment treatments and that the "evidence alone is not sufficient to support" using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on "gender affirming" treatments. The authors noted this research had a "critical risk of bias" and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that "transgender youth who socially transitioned at early ages" will continue "to identify that way." While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their "assigned gender at birth," the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V's diagnostic criteria for gender dysphoria and that the children's families supported the decisions to transition. Instead, the authors relied on a child's chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study's publication under the headline "Few Transgender Children Change Their Minds After 5 Years" (New York Times, 2022). Such a title can add to the public's perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments "constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety." The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that "children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function" (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a "case-by-case" basis.[10] CMS specifically noted that the decision memo is not a National Coverage Determination and that "no national policy will be put in place for the Medicare program" (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that "the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up." In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo's criteria (CMS, 2017).

The basis for Medicare's decision is that the "clinical evidence is inconclusive" and that "robust" studies are "needed to ensure that patients achieve improved health outcomes." In its review of available literature, CMS sought to answer whether there is "sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria." After evaluating 33 studies that met inclusion criteria, CMS's review concludes that "not enough high-quality evidence" is available "to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively." Additionally, out of the 33 studies, just 6 provided "useful information" on the procedures' effectiveness, revealing that their authors "assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies" that "did not demonstrate clinically significant changes or differences in psychometric test results" following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).[11]

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).[12]

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[10] The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.
[11] Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.
[12] The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery. [13] The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

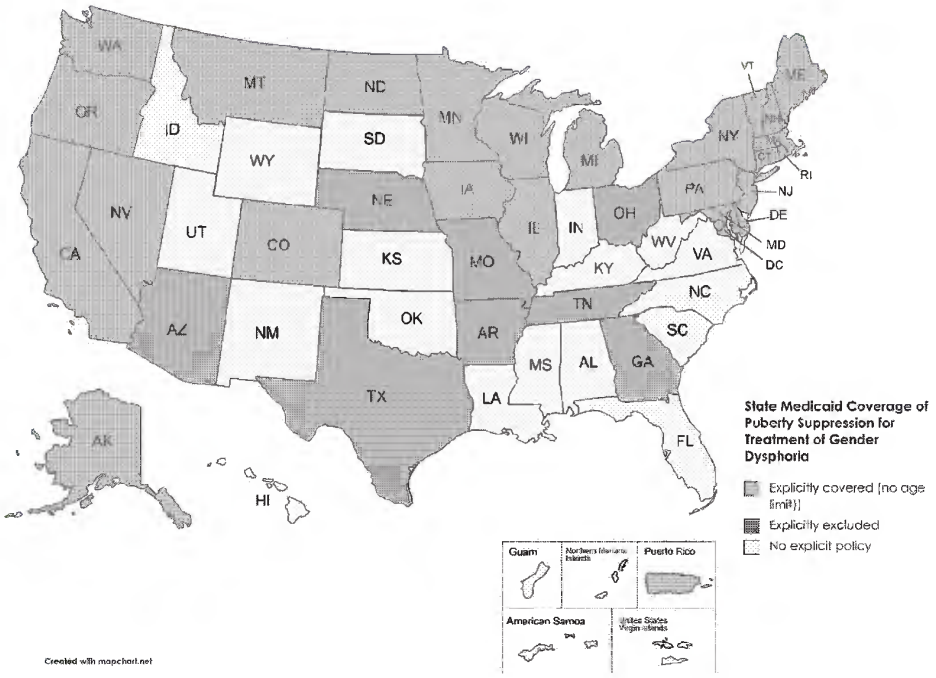
- "Social gender transition should not be a treatment option for children or adolescents."
- "Anyone under 18 should not be prescribed puberty blockers or hormone therapy."
- "Gender reassignment surgery should not be a treatment option for children or adolescents."
- "Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider."

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment's ability to improve mental health (DOH, 2022).

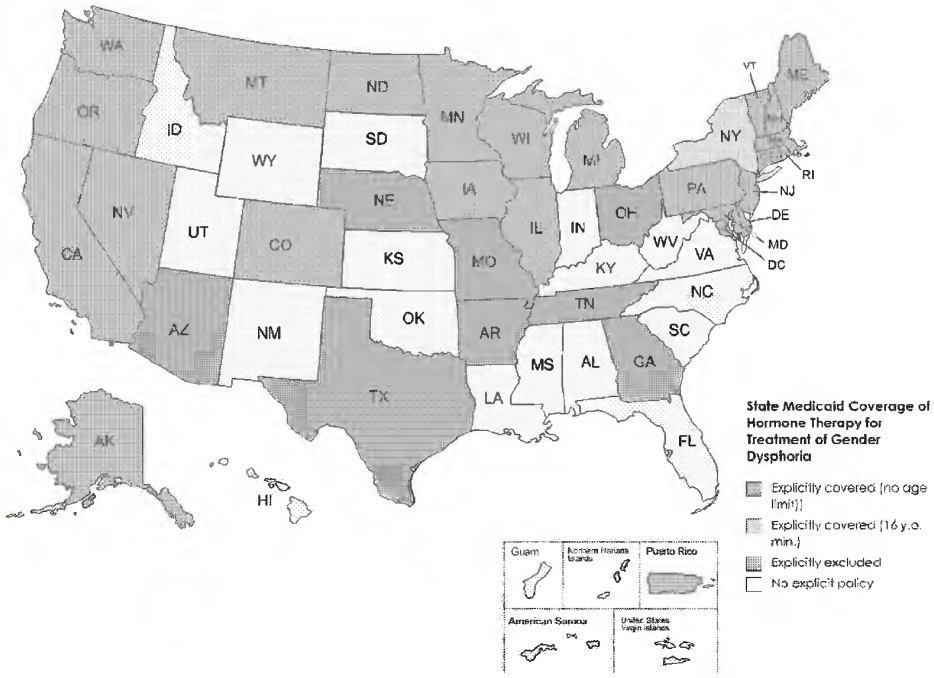
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

[13] Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida's public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

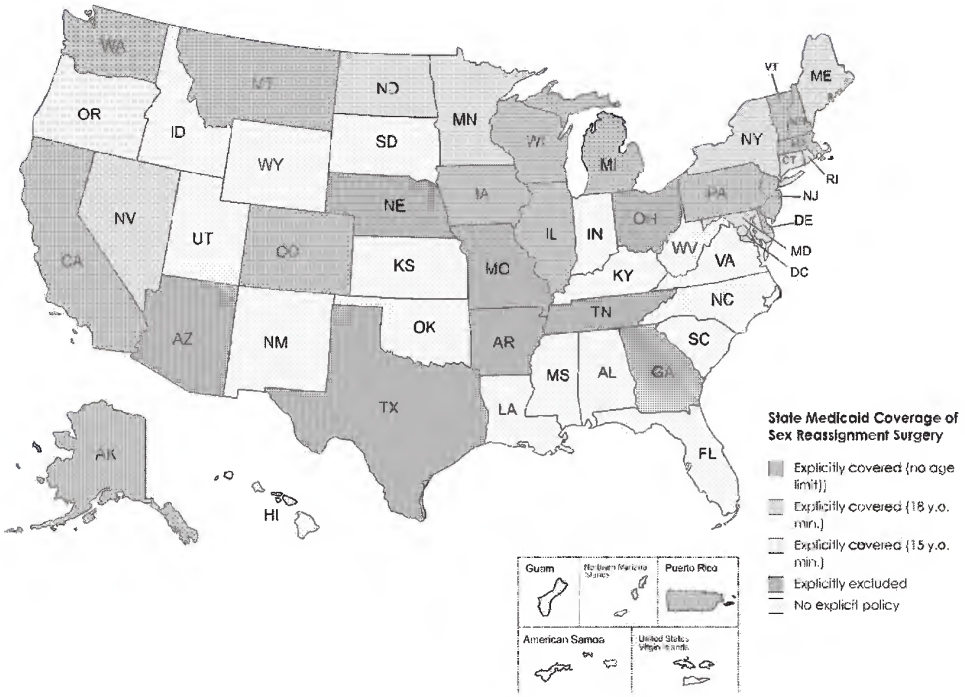
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

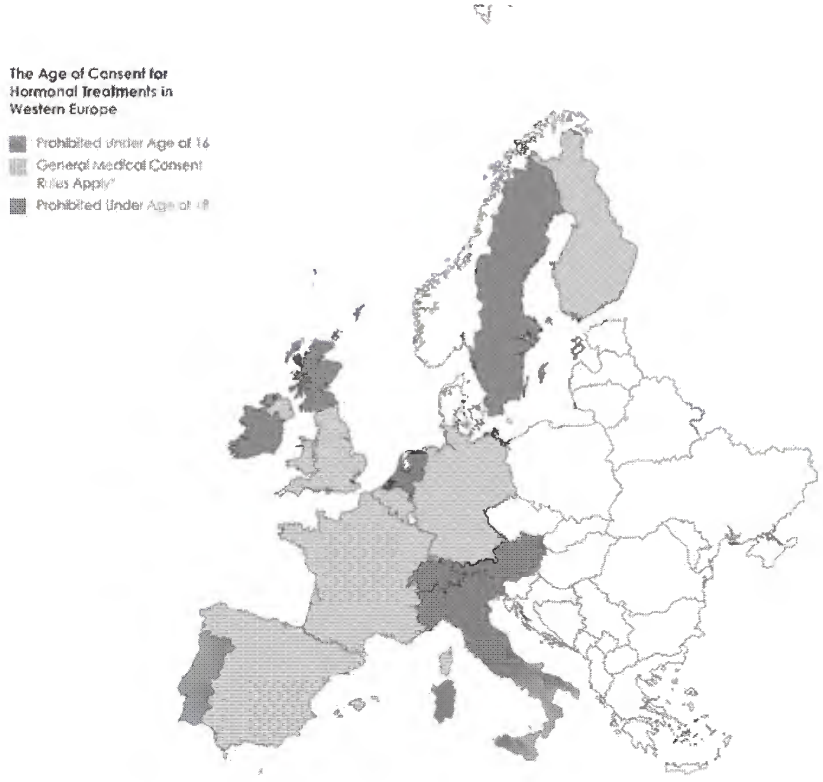
Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that "the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits." With the exception of youths who exhibited "classic" signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors "is an experimental practice" and that "no irreversible treatment should be initiated." The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.'s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:

In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

✓ **Concur** ____ **Do not Concur**

Comments:

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_____ 6/2/22

Deputy Secretary for Medicaid (or designee) *Date*

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

TAB 175-19

ATTACHMENT A

RON DESANTIS
GOVERNOR

SIMONE MARSTILLER
SECRETARY

April 20, 2022

Tom Wallace
Deputy Secretary for Medicaid
Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308

Dear Deputy Secretary Wallace:

On April 20, 2022, the Florida Department of Health released guidance on the treatment of gender dysphoria for children and adolescents.[1] The Florida Medicaid program does not have a policy on whether to cover such treatments for Medicaid recipients diagnosed with gender dysphoria. Please determine, under the process described in Florida Administrative Code Rule 59G-1035, whether such treatments are consistent with generally accepted professional medical standards and not experimental or investigational. Pursuant to Rule 59G-1035(5), I look forward to receiving your final determination.

Sincerely,

Simone Marstiller
Secretary

[1] *See* https://www.floridahealth.gov/newsroom/2022/04/20220420-gender-dysphoria-press-release.pr.html (last visited Apr. 20, 2022).

TAB 175-25

Pl. Trial Ex. 025

TESTOSTERONE

DRUGDEX Evaluations

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration
Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical

response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]

patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]

patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosing

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

FDA Uses

Testosterone

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Replacement therapy in congenital or acquired conditions associated with a deficiency or absence of endogenous testosterone, as follows:

Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals [20][22][23][25][19][27][28][24][21]
Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [20][22][23][25][19][27][28][24][21]

Limitations of Use

The safety and efficacy of testosterone therapy have not been established in men with late-onset (age-related) hypogonadism [14][5][15][1][3][16][17][2][18].

Evidence (Topical Gel)

In several randomized clinical trials in men with hypogonadism, 75% or more achieved normal serum testosterone levels with administration of testosterone gel for 2 to 3 months [29][21], with effects sustained for 6 months [30] and up to 3 years [31] in several extension studies.

Lean body mass (LBM) significantly increased with testosterone 1% gel compared with placebo at 6 months in symptomatic men 50 to 80 years old with low to low-normal testosterone levels (LBM change, 1.28 vs 0.02 kg; N=362). Fat mass decreased 1.16 kg with testosterone versus 0.14 kg with placebo, an effect that was more pronounced in patients with a BMI of 30 kg/m(2) or greater. Fat mass progressively decreased during 12 additional months of testosterone therapy, but LBM was not further affected [32].

Evidence (Buccal)

During a randomized, 12-week trial in men with hypogonadism, 86.6% of 82 evaluable patients treated with buccal testosterone twice daily had mean serum testosterone concentrations within the physiologic range [23].

Evidence (Intranasal)

In an open-label trial in hypogonadal men, 90% of 73 subjects treated with testosterone nasal gel 3 times daily had an average testosterone level within normal range after 90 days of treatment; no patients had levels above the normal range (N=306) [22].

Testosterone Cypionate

Primary hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (12 years or older)

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class IIa; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone cypionate is indicated for replacement therapy for congenital or acquired deficiency or absence of endogenous testosterone.

Primary hypogonadism: Testicular failure caused by cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy [82]
Hypogonadotropic hypogonadism: Deficiency of gonadotropin or luteinizing hormone-

releasing hormone (LHRH); pituitary-hypothalamic injury from tumors, trauma, or radiation [82]

Limitations of Use

Safety and efficacy not established in men with late-onset (age-related) hypogonadism [82].

Use androgens cautiously in the pediatric population because of adverse effects on bone maturation. The risk of compromising final mature height increases as age decreases. Assess bone age in the wrist and hand every 6 months [83].

Testosterone Enanthate

Delayed puberty, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, no; Pediatric, yes (adolescent males, IM only)

Efficacy: Pediatric, Evidence favors efficacy

Recommendation: Pediatric, Class IIb

Strength of Evidence: Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate IM injection is indicated to stimulate puberty in select male patients with delayed puberty [73].

Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

c) Pediatric:

1) Only carefully selected males should receive testosterone for the treatment of delayed puberty. Delayed puberty should not be secondary to a pathological disorder. Most patients have a familial pattern of delayed puberty and are expected to attain puberty spontaneously at a relatively late date. For patients unresponsive to psychological support, a brief treatment with conservative doses may occasionally be justified [73].

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, yes (adolescent males, IM only)

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone enanthate is indicated for testosterone replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired), including testicular failure from conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicular-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range [74].
Hypogonadotropic hypogonadism (congenital or acquired), including gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range [74].

Limitations of Use

Safety and efficacy of subQ testosterone enanthate in male patients less than 18 years old have not been established [76]

Evidence (Adult)

In a single-arm study of men with hypogonadism who received subQ testosterone enanthate, 90% achieved normal serum testosterone levels at week 12 [74].

c) Adult:

1) IM Preparation

a) Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

b) Several dosage regimens of IM testosterone enanthate were compared in the treatment of primary hypogonadism in 23 men. Patients received testosterone enanthate 100 mg weekly, 200 mg every 2 weeks, 300 mg every 3 weeks, or 400 mg every 4 weeks for 12 to 16 weeks. The 200 and 300 mg regimens appeared to be the most effective in terms of suppression of the serum luteinizing hormone (LH) concentration and infrequency of administration [77].

2) SubQ Preparation

a) In a 52-week, single-arm study of men with hypogonadism (N=150), 90% of testosterone enanthate-treated patients achieved a time-averaged serum total testosterone concentration over 7 days within the normal range (300 to 1100 nanograms (ng)/dL) at week 12. No patient had a maximum total testosterone concentration greater than 1500 ng/dL at week 12. The initial self-administered dose of 75 mg subQ once weekly was increased by 25 mg at week 7 if the week 6 total testosterone concentration at the end of the dosing interval (trough concentration [Ctrough]) was less than 350 ng/dL ,and was decreased by 25 mg if Ctrough was 650 ng/dL or greater [74].

d) Pediatric:

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

Metastatic breast cancer, Female

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (IM only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal [73].

c) Adult:

1) May be used in the palliative treatment of advancing, inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal with the primary goal of ovary ablation. Therapy may also be used in premenopausal women who have benefited from oophorectomy with hormone-responsive tumors. Androgen therapy may accelerate metastatic breast carcinoma; therefore, these patients should be monitored closely [73].

Testosterone Undecanoate

Hypogonadism, Male

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Testosterone undecanoate is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone, such as

Primary hypogonadism (congenital or acquired): Testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals; in these conditions, men have low serum testosterone concentrations and gonadotropins above the normal range [53][57][59].

Hypogonadotropic hypogonadism (congenital or acquired): Idiopathic gonadotropin deficiency, luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation; in these conditions, men have low serum testosterone concentrations and gonadotropins in the normal or low range [53][57][59].

Testosterone undecanoate IM should be used only in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59].

Limitations of Use

Safety and efficacy of testosterone capsules in males less than 18 years old have not been established [53][57]

The safety and efficacy of testosterone undecanoate IM therapy has not been established in men with late-onset (age-related) hypogonadism [58].

Evidence

Testosterone undecanoate therapy increases testosterone levels in hypogonadal male patients [61][57][62][60][59].

c) Adult:

1) Oral Capsules - Tlando(R)

a) In an open-label, single-arm study enrolling hypogonadal men, a mean 24-hour serum testosterone level within normal range (eugonadal, 300 to 1080 nanograms[ng]/dL) was achieved in 80% (95% CI, 72% to 88%) of patients receiving testosterone undecanoate capsules 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Around 19% (n=18) of subjects, majority of whom were obese, did not achieve a eugonadal range. Cmax of testosterone throughout the studied interval did not exceed 1.5 x ULN (1620 ng/dL) in 82% of patients, while 5% experienced levels between 1.8 x ULN (1944 ng/mL) and 2.5 x ULN (2700 ng/dL); no patients experienced testosterone Cmax over 2.5 x ULN. Mild to moderate adverse events were reported in 20% of the treatment population. The most frequently reported treatment-emergent adverse events were blood prolactin increase (6.3%), headache (2.1%), weight increase (2.1%), and musculoskeletal pain (2.1%). Mean age was 56 years, 16.8% were over 65 years, 69.5% had a BMI of 30 kg/m(2) or greater, and baseline total testosterone on average was 202 +/- 74 ng/dL [61].

2) Oral Capsules - Jatenzo(R)

a) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules (N=166). The percentage of patients who had Cmax 1500 nanograms (ng)/dL or less, between 1800 and 2500 ng/dL, and greater than 2500 ng/dL at the final visit were 83%, 3%, and 3%, respectively Testosterone undecanoate was taken orally at a starting dose of 237 mg twice per day with meals. The dose was adjusted on Days 21 and 56 between a minimum of 158 mg twice per day and a maximum of 396 mg twice per day on the basis of the average testosterone concentration obtained over 24 hours post-morning dose [57].

3) Intramuscular

a) In 3 studies, testosterone undecanoate therapy significantly increased testosterone levels in hypogonadal male patients [62][60][59] with injection site reactions [62][60] occurring in less than 1% in 1 study [62] and 25.9% in another study [60]

Non-FDA Uses

Testosterone

Antineoplastic adverse reaction - Leydig cell failure in adult

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy did not result in significant changes in bone mineral density, body composition, lipids, or quality of life in one study conducted in men [33].

c) Adult:

1) Testosterone was not effective in men with mild Leydig cell insufficiency following cytotoxic chemotherapy. Men (n=35) aged 40 to 49 years with the diagnosis of mild Leydig cell dysfunction due to chemotherapy were randomized to 2.5 to 5 mg transdermal testosterone daily or placebo for 1 year. Upon completion of the study, total and calculated free testosterone increased significantly with the testosterone group compared with the placebo group (p=0.05 and p=0.02, respectively). Mean total and calculated free testosterone levels increased from 13.3 nanomoles/liter (nmol/L) and 342.9 nmol/L at baseline to 17.3 nmol/L and 454.8 nmol/L during the study. No significant changes in testosterone levels were observed in the placebo group. There were no significant changes in bone mineral density or in body mass in either group.

There was a significant reduction in fatigue and a moderate improvement in activity score compared with the placebo group (p=0.008 and p=0.05, respectively). Mood or sexual function did not change with either group and only a small reduction in low density lipoprotein was reported in the testosterone treated group [33].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Successful penile enlargement to normal size for age was reported following the administration of topically applied testosterone [34][35].

c) Pediatric:

1) Eight cases of micropenis from childhood through adulthood (age range, 22 to 31 years) were followed. Diagnosis included 4 patients with hypogonadism, 2 patients with genetic or familial adiposogenital dystrophy, and 2 with miscellaneous types of endocrine abnormalities. In 5 cases, the micropenis was treated with testosterone propionate 2% in a stearin-lanolin base for a variable period of time in infancy or childhood. Topical treatment caused an increase in penis size that was disproportionate to the rest of the body. However, in adolescence and adulthood, patients with a prior history of treatment with topical testosterone during childhood had no size advantage over untreated patients. The authors felt topical testosterone only postponed the age at which an individual had to cope with a micropenis [34].

2) Parenteral (testosterone enanthate 25 mg given IM monthly for a total of 3 doses) and topical testosterone cream (2% to 10%) have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

3) Successful penile enlargement to normal size for age following the administration of topically applied testosterone 5% cream for 21 days was reported in 5 boys with normal XY karyotype who had microphallus and hypopituitarism. The cream was applied to the penis in 4 of the patients and to the right axilla in one. The investigators concluded that topical testosterone acted systemically to produce phallic growth; serum testosterone levels were equivalent to normal adult levels on the last day of therapy [35].

Coronary arteriosclerosis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Supplementation of low-dose testosterone effectively reduced exercise-induced myocardial ischemia in men with stable angina [10].

c) Adult:

1) Low-dose (5 mg/day) testosterone supplementation was effective in reducing exercise-induced myocardial ischemia in men diagnosed with stable angina. Forty-six men were randomized to transdermal testosterone or placebo for 12 weeks. Treatment with testosterone was associated with an increase in time to 1 mm ST-segment depression from 309 seconds at baseline to 343 seconds at 4 weeks and 361 seconds at 12 weeks, as measured by treadmill exercise testing. The changes were statistically

significant when compared with placebo (p=0.02). Additionally, the treatment group reported significant improvements in pain perception (p=0.026) and role limitation resulting from physical problems (p=0.024) compared with placebo [10].

Deficiency of testosterone biosynthesis, Female

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone transdermal patch demonstrated favorable results in bone density, body composition, and neurobehavioral function in women with androgen deficiency due to hypopituitarism [12].

Testosterone improved well-being, mood, and sexual function in premenopausal women with low libido and low testosterone [13].

c) Adult:

1) Transdermal testosterone application resulted in increased bone mineral density at the hip and radius, increased mean fat-free mass, increased thigh muscle area, and improved mood and sexual function in women with androgen deficiency due to hypopituitarism. The study participants (n=51, aged 19 to 50 years) had a serum free testosterone level of less than 3.1 picograms/milliliter (pg/mL) at the time of screening and were estrogen replete for at least 1 year prior to the study. Of the women participating, 59% were depressed at baseline and 46% and 68% had sexual function scores that were more than 2 or more than 1 standard deviation(s), respectively, below the normal mean (as measured by the Derogatis Interview for Sexual Function-Female Version). Participants were randomized to transdermal testosterone patches which delivered 300 mcg (in the form of 150 mcg patches) daily or placebo patches for 12 months. Study visits occurred at 1, 3, 6, 9, and 12 months after the baseline visit. At baseline, mean free testosterone was below normal for women of reproductive age, and 55% of women had undetectable levels, which increased into the normal range during testosterone administration. The dose of testosterone was decreased to 150 mcg daily in 37.8% of participants randomized to testosterone due to free testosterone levels being above the ULN for females of reproductive age. There were no changes in estradiol, insulin-like growth factor I, and sex hormone binding globulin levels with either testosterone or placebo administration. Bone density at the hip and radius increased significantly (p=0.023 and p=0.007, respectively) with mean percent changes at the hip being 0.9 +/- 0.5 and -1.2 +/- 0.6% for testosterone and placebo, respectively, and 0.8 +/- 0.2 and -0.5 +/- 0.4%, respectively, at the radius. Testosterone was associated with a 3.4 +/- 0.9% mean increase in fat-free mass compared with a 0.6 +/- 0.9% increase for placebo (p=0.04). There was a significant increase in muscle area of the thigh associated with testosterone administration compared with placebo (p=0.038). The mean increase in the testosterone and placebo groups was 6.6 +/- 1.4% and 1.5 +/-1.3%, respectively. Compared with placebo, mood significantly improved in patients receiving testosterone (p=0.029) as did sexual function (p=0.044). In women receiving testosterone, quality of life improved in the following areas: self-control (p=0.005), energy/fatigue (p=0.017), general health (p=0.026), and sleep (p=0.038). When compared with placebo, there was no improvement in spatial function or any other changes in cognitive function. Testosterone was well tolerated with increased acne being reported in one-third of patients. A mean increase in total cholesterol of 6% was reported in the testosterone group. Mild local irritation at patch site was reported in 65% of participants; the reactions were distributed equally between the testosterone and placebo groups [12].

2) Testosterone cream was effective in improving well-being, mood, and sexual function in premenopausal women in a randomized, placebo-controlled, crossover, double-blind trial. Thirty-four women completed the trial, with 31 women (mean age 39.7 years and mean serum testosterone 1.07 nanomoles/L) providing complete data. The trial

consisted of two 12-week treatment periods, separated by a 4-week washout period, in which the women were randomized to 10 mg testosterone 1% cream daily or placebo. The women using testosterone demonstrated significant improvements in scores of general well being (+12.9; 95% CI, +4.6 to +21.2; p=0.003) and of sexual self-rating (+15.7; 95% CI, +6.5 to +25; p=0.001) compared with placebo. Mean total testosterone levels during treatment were at the high end of normal and estradiol levels were unchanged. Testosterone was well tolerated with no adverse effects reported [13].

Depression

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone gel supplementation may produce antidepressant effects in depressed men with low testosterone levels [11].

c) Adult:

1) Testosterone 1% topical gel produced antidepressant effects in a small study involving 22 depressed men with low or borderline testosterone levels (morning serum levels of 350 nanograms/dL or less. The men were randomized to 1% testosterone gel (10 g/day) or placebo gel for 8 weeks. Each subject continued his existing antidepressant regimen. Testosterone-treated patients had a significantly greater rate of decrease in scores on the Hamilton Depression Rating Scale compared with placebo (p=0.0004). This improvement was noted on both the vegetative and affective subscales of the Hamilton Depression Rating Scale (p=0.01 and p=0.05, respectively). In addition, testosterone gel was associated with a significantly greater rate of decrease in the Clinical Global Impression severity scores (p=0.04). There were no significant differences between the 2 groups regarding changes in body fat percentages or changes in muscle mass. One subject receiving testosterone reported increased nocturia and difficulty initiating urination. No other subject reported adverse effects attributable to testosterone [11].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone in 3 different formulations, including transdermal gel, significantly increased testosterone levels from the physiological range for women to the normal male range by week 30 of treatment in an observational study in female-to-male transsexual individuals [9]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving

hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment		
Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **

Fat (%)	26.7 to 30.1	22.4 to 27.6 **
KEY: BMI=body mass index; ng=nanograms; pg=picograms		
* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.		
** Significant difference between baseline and week 54 values.		

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **
KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

d) Pediatric:

1) Adolescents

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible

symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
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KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus no-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Osteoporosis, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone therapy in men with osteoporosis significantly increased bone mineral density [40].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

c) Adult:

1) Transdermal testosterone gel was associated with a small but significant increase in bone mineral density (BMD) in a prospective, multicenter study involving 227 men with hypogonadism. The men were randomized to testosterone gel delivering 5 to 10 mg/day or 2 testosterone patches delivering 5 mg/day. After 90 days, the gel dose was adjusted to 75 mg/day for another 3 months. At completion of the study, the 10 mg/day gel was associated with a 1.4 and 1.9-fold higher serum testosterone concentration than the 5 mg/day gel and the patch groups. The 10 mg/day gel group was also associated with a decreased bone resorption and with small but significant increases in BMD of the hip and spine (1.1% and 2.2%, respectively; p=0.0001) [40].

Postmenopausal osteoporosis; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

The addition of testosterone to estradiol is not associated with increased benefits on bone mineral density [39].

c) Adult:

1) Testosterone 100 mg implants added to estradiol 50 mg implants had no significant effects on bone markers and may not be necessary for prevention of osteoporosis if adequate estradiol levels are maintained. Women (n=25) were given estradiol after a total hysterectomy with bilateral salpingo-oophorectomy. At 16 weeks, testosterone 100 mg was added to the treatment regimen. The bone formation marker, PICP was associated with a significant increase after estradiol alone (p=0.0032) but the addition of testosterone had no significant effects on bone markers when measured at 32 weeks. These biochemical changes confirm previous studies [39].

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Improvements in sexual function have been reported in both female and male patients [41][42][43].

c) Adult:

1) Transdermal testosterone improved sexual function and psychological well-being in women with sexual dysfunction following oophorectomy and hysterectomy. A 36-week trial enrolled 75 women, ages 31 to 56 years old, who had reported impaired sexual functioning after surgically-induced menopause, despite estrogen replacement. The 75 women received at least 0.625 mg of conjugated equine estrogens orally per day. Randomly selected, the women also received placebo, 150 micrograms (mcg) of testosterone, or 300 mcg of testosterone per day transdermally for 12 weeks each. The mean serum free testosterone concentration increased during each treatment regimen. The higher testosterone dose resulted in the greatest physical and psychological improvement [41].

2) In one 16-month, open-label, multicenter study with 4 consecutive periods, 37 men with hypogonadism received intramuscular and transdermal testosterone (nonscrotal). Period 1 consisted of 3 weeks and patients were monitored following an IM testosterone injection. During period 2, patients received no replacement testosterone for 8 weeks. During period 3, single-dose pharmacokinetic studies were performed for 3 to 4 weeks. During period 4 (12 months) efficacy and safety of the transdermal system were compared with the results obtained during periods 1 and 2. Along with other symptoms, decreased libido, impotence, fatigue, depression, and hot flushes were evaluated. After one month of transdermal treatment, the prevalence of decreased libido and fatigue had decreased to levels seen during IM treatment and remained so for the duration of transdermal treatment [42]. Similar results were found in another study [43].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection [44].

Testosterone has produced an increase in fat free mass, muscle size, and strength [45] [46].

A significant increase in weight was observed in female patients with AIDS who received 1 active testosterone patch and 1 placebo patch versus 2 placebo skin patches but did not increase significantly in patients who received 2 active testosterone patches [47].

c) Adult:

1) Transscrotal testosterone did not increase weight, body cell mass, or quality of life in patients with HIV infection. In a multicenter, randomized, double-blinded, placebo-controlled study, men infected with HIV used transdermal scrotal testosterone patches (6 mg/day) (n=67) or placebo (n=66) for 12 weeks. Patches were applied and worn for 22 to 24 hours each day. Testosterone patches were effective in increasing serum testosterone levels [44].

2) There was 1.35 kg gain in lean body mass, increased red cell count, and improvements in the subcategory of role limitation due to emotional problems in HIV-infected men treated with transdermal testosterone [45]. In a double-blind, placebo-controlled randomized study, 41 HIV-infected men received 2 placebo patches or 2 testosterone transdermal system patches applied to the abdomen, back, arms, or thighs every 24 hours (total testosterone dose 5 mg/24 hr) for 12 weeks.

3) Androgen deficiency has been shown to be prevalent among women with AIDS wasting syndrome. It may result from undernutrition generalized illness, or more direct effects of HIV on the hypothalamic-pituitary-gonadal axis. Forty-five out of 53 women with AIDS wasting syndrome finished the study. Patients were randomized into 1 of 3 groups: 2 placebo skin patches (PP group); 1 active/1 placebo patch (AP group); or 2 active patches (AA group) which were applied twice weekly for 12 weeks. The delivery rates of testosterone were 150 and 300 mcg/day for the AP and AA groups, respectively. Therapy was well tolerated with no adverse effects with regard to hirsutism, lipid profiles, or liver function tests. A significant increase in weight was observed in the AP group (1.9 +/- 0.7 kg) versus the PP group (0.6 kg +/- 0.8 kg; p=0.043), but did not increase significantly in the AA group (0.9 +/- 0.4 kg) versus the PP group [47].

4) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg intramuscularly weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared to placebo, testosterone-treated patients demonstrated a gain in fat free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

5) Sublingual testosterone 5 mg three times daily for 6 months was administered to 67 men with hypogonadism which resulted in an increase in total body (p=0.0104) and lean body mass (p=0.007), mainly in the legs. There was no significant change in bone mineral density throughout the study. Longer studies are needed in this population [48].

Testosterone Cypionate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]. Male physical characteristics were effectively achieved in an open-label time-series trial [81].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion

scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

3) Testosterone cypionate was effective in suppressing menses and increasing clitoral size and body hair in an open-label time-series trial that examined the effects of cross-sex hormones on both female-to-male and male-to-female transsexuals. Eleven of the 28 (31%) enrolled female-to-male transsexuals had previously been on testosterone in various formulations for a median duration of 24 months (range, 6 to 240 months). All previous treatment was discontinued and patients were started on testosterone cypionate (Depo-testosterone(R)) IM at doses of 50 to 200 mg every 2 weeks, with doses increased until cessation of menstruation or suppression of luteinizing hormone (LH) or follicle-stimulating hormone (FSH) in castrated patients. Some patients self-administered doses up to 400 mg per week against medical advice. Mean duration of follow-up was 16.6 +/- 15 months. Of patients who had never had any previous hormonal treatment or hysterectomy (n=12), all had reported previous normal menstrual histories. These patients all had cessation of menses by 4 months of treatment with testosterone cypionate 200 mg every 2 weeks. The mean total cholesterol level (n=28) at baseline was 209 +/- 46 mg/dL. At doses of 100 to 300 mg per month after a duration of 27 patient-months, the mean cholesterol level increased to 288 +/- 53 mg/dL, while at doses of 400 mg per month after a duration of 217 patient-months, the mean cholesterol level was 212 +/- 53 mg/dL. Significance (p less than 0.05) was reported for the change in cholesterol (all doses) from baseline. Triglycerides

were also significantly (p less than 0.05) increased to just over the ULN (normal range, 10 to 160 mg/dL). SGPT significantly (p less than 0.05) increased, but remained within the normal range. No significant changes were found in blood pressure, SGOT, bilirubin, or glucose. The amount and coarseness of hair on the chest, abdomen, and face were reported to be "strikingly" increased. No significant changes were reported for breast size, body weight, estradiol levels, or androstenedione levels. LH and FSH levels were suppressed to prepubertal levels only when the patient's testosterone level was over 1000 nanograms/deciliter or until the dose was greater than 800 mg per month. Clitoris growth increased rapidly over 1 year, with the longest clitoris measuring 6 cm [81].

d) Pediatric:

1) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

Testosterone Enanthate

Anemia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Effective in combination with other androgens for increasing the hematocrit in anemic patients who are receiving hemodialysis [67]

c) Adult:

1) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis . Patients received either testosterone enanthate 4 mg/kg IM weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; 3 courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [67].

Burn, Severe; Adjunct

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Administration of testosterone enanthate can ameliorate muscle catabolism in severe burns [78].

c) Adult:

1) Testosterone enanthate 200 mg IM per week for 2 weeks restored serum testosterone levels and ameliorated the muscle catabolism in 6 severely burned (greater than 70% total body surface area) male patients. After the second injection, protein synthetic efficiency increased 2-fold (p less than 0.01) and protein breakdown decreased almost 2-fold (p less than 0.05) [78].

Congenital hypoplasia of penis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category C

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate and topical testosterone cream have been used short term to induce temporary enlargement of a micropenis prior to surgical repair [36][37][38].

c) Pediatric:

1) Testosterone enanthate 25 mg IM given monthly for a total of 3 doses and topical testosterone cream (2% to 10%) have been used short term to induce temporary

enlargement of a micropenis prior to surgical repair [36][37][38].

Contraception, Male

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis [68].

Testosterone enanthate and cyproterone induced azoospermia more effectively than testosterone alone [69].

Testosterone enanthate plus levonorgestrel was more effective in producing azoospermia than testosterone enanthate alone [70].

Weekly injections effectively induced azoospermia in healthy fertile men [71].

Approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration during clinical trials [72].

c) Adult:

1) Testosterone Enanthate and Desogestrel

a) IM testosterone enanthate plus oral desogestrel was an effective and safe regimen for suppression of spermatogenesis in a study of 24 healthy men aged 20 to 49 years. The men were randomized to 50 mg testosterone enanthate plus 150 mcg desogestrel (n=9), 100 mg testosterone enanthate plus 150 mcg desogestrel (n=7), or 100 mg testosterone enanthate plus 300 mcg desogestrel (n=8). Additionally, these 3 groups were compared with 2 control groups receiving 100 mg testosterone enanthate alone (n=18) or 100 mg testosterone enanthate plus 125 mcg oral levonorgestrel (n=18). At the end of 6 months, azoospermia was achieved in 100% of men receiving testosterone enanthate 100 mg plus desogestrel 150 mcg, 88% of men receiving testosterone enanthate 100 mg plus desogestrel 300 mcg, and 57% of men receiving testosterone enanthate 50 mg and desogestrel 150 mcg. This was compared with 61% for testosterone enanthate 100 mg plus levonorgestrel 125 mcg and 33% for testosterone enanthate 100 mg alone. All groups tended to gain weight compared with baseline and serum HDL was moderately suppressed in all groups [68].

2) Testosterone Enanthate and Cyproterone

a) In a smaller study, all men who received testosterone and cyproterone became azoospermic compared with 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg IM weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment, baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the 3 groups [69].

3) Testosterone Enanthate and Levonorgestrel

a) Testosterone enanthate 100 mg IM weekly plus levonorgestrel 500 mcg orally daily was more effective in producing azoospermia than testosterone enanthate alone at 6 months (67% vs 33%; p=0.06). A pregnancy rate was not mentioned [70].

4) Clinical trials have indicated that approximately 50% of healthy males become azoospermic and the other 50% become severely oligospermic following administration

of testosterone enanthate. Additionally, severe oligospermia appears to be associated with effective contraception [72].

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Voice deepening, facial hair increase, cessation of menses, and significant increases in testosterone levels were achieved within 6 months of initiating IM testosterone replacement therapy in individuals with female-to-male gender dysphoria in a retrospective study [65]. Hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. In a prospective study, significant changes in several domains of psychological functioning were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls [66]

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) Significant changes in several domains of psychological functioning, as assessed using the Minnesota Multiphasic Personality Inventory second edition (MMPI-2), were observed for transgender men following 3 months of testosterone therapy compared with female controls and there were no significant differences for transgender men after therapy versus male controls (N=163; 48 transgender men, 53 male controls, 62 female

controls). The MMPI-2 contains 10 clinical scales. Transgender men were compared with female controls using the female template of MMPI-2 and compared with male controls using the male template. Higher scores on each scale equate with lower levels of psychological functioning. Relative to female controls, transgender men had a significant change from baseline on the Hypochondria (-3.14), Depression (-3.28), Hysteria (-3.66), Paranoia (-4.62), and Masculinity-femininity (+5.05) scales after 3 months of therapy. No significant differences were observed after therapy versus female controls on the Psychopathic Deviate, Psychasthenia, Schizophrenia, Hypomania, or Social Inversion scales or on any of the 10 scales relative to male controls. Testosterone was administered as 50 to 400 mg IM every 10 to 14 days (or 50% weekly) for most participants (n=32) [66].

2) Therapeutic effects of voice deepening, facial hair increase, and cessation of menses were achieved with 3 different dosages of testosterone enanthate by 6 months after initiation of therapy in individuals with female to male gender dysphoria undergoing testosterone replacement therapy in a retrospective study (N=138). At 1 month, onset of treatment effects occurred in more patients with higher doses. However, no dose dependent effects were evident at 6 months, and 96.3% to 100% of patients achieved deepening of voice, 72.7% to 97.4% achieved increase in facial hair, and 85.7% to 96.6% achieved cessation of menses. Serum testosterone levels were significantly increased to around 700 nanograms/dL and serum estradiol levels were significantly decreased from baseline to month 6, with no significant differences among the different dosages of testosterone. No significant adverse events were reported in any group and there were no clinically relevant changes in liver enzymes, coagulation parameters, or urinalysis results. Testosterone enanthate was administered as 250 mg IM every 2 weeks (n=30), 250 mg IM every 3 weeks (n=50), or 125 mg every 2 weeks (n=58) based on patient preference relating to frequency of administration and cost [65].

3) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy

Outcome	Without hormonal treatment (n=67)	With hormonal treatment (n=120)
SADS *	11	8.5 **
HAD-A ^	9	6.4 **
HAD-D ^	5.2	3.3 **

KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale

* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus without-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

Mean Social Distress, Anxiety, and Depression Scores in Transsexuals With and Without Cross-sex Hormonal Therapy		
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KEY: HAD-A=Hospital Anxiety and Depression Scale, Anxiety subscale; HAD-D=Hospital Anxiety and Depression Scale, Depression subscale; SAD=Social Anxiety and Distress Scale		
* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.		
** Significant difference versus without-hormone-therapy group		
^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.		

Sexual disorder

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone enanthate prevented the loss of potency in patients receiving concomitant luteinizing hormone-releasing hormone (LHRH) agonist therapy [79].

c) Adult:

1) Reversible oligospermia without impotence in male patients treated with an luteinizing hormone-releasing hormone (LHRH) agonist plus testosterone was reported. When an LHRH agonist is used to produce reversible oligospermia, a reduction in plasma testosterone, libido, and potency occurs. Testosterone enanthate 100 mg IM every 2 weeks prevented the loss of potency in 6 patients receiving concomitant LHRH agonist therapy [79].

Weight gain

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Testosterone has produced an increase in fat-free mass, muscle size, and strength [45] [46][80].

c) Adult:

1) Testosterone increased lean body mass and improved quality of life in androgen-deficient men with AIDS wasting syndrome. In a randomized, double-blind, placebo-controlled trial, patients received testosterone enanthate 300 mg IM weekly for 6 months (n=26) or placebo (n=25). In the testosterone-treated group, 22 patients completed the trial and 19 patients in the placebo group completed the trial. Compared with placebo, testosterone-treated patients demonstrated a gain in fat-free mass, lean body mass, and muscle mass (change, -0.6 kg and 2 kg; change, 0 kg and 1.9 kg; and change, -0.8 kg and 2.4 kg, respectively) [46].

2) Testosterone enanthate 600 mg weekly for 10 weeks produced an increase in fat-free mass, muscle size, and strength in males. A standardized exercise program was additive to the effects of testosterone. Because anabolic steroids have potentially serious adverse effects, their use in athletics is not justified; however, it is postulated that short-term administration of androgens may be advantageous for immobilized, cachectic, AIDS patients, or those with chronic wasting disease [80].

Testosterone Undecanoate

Female-to-male transsexual - Gender dysphoria

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Effective; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIa; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adult)

Testosterone undecanoate significantly increased testosterone levels in transsexual men (ie, female-to-male) from the physiological range for women to the normal male range in observational [9] and prospective studies [54]. Significant physical changes including body weight, lean body mass, body fat redistribution [55], and facial and body hair growth occurred during the first year of therapy [56]. Additionally, hormonal sex

reassignment therapy significantly reduced symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy in 1 cross-sectional study [8]. Major adverse events have not been observed, but changes in lipid profiles, hematocrit, liver enzymes [54], and fasting plasma glucose have been reported during 1-year studies [9]. Regular monitoring for adverse effects of hormone therapy is recommended [7].

Evidence (Adolescent)

In a cross-sectional study in transsexual individuals attending a gender identity unit, hormonal sex reassignment therapy was associated with significantly fewer symptoms related to social distress, anxiety, and depression compared with those not receiving hormonal therapy [8].

Guidelines (Adult)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender. Either parenteral or transdermal testosterone may be used to achieve and maintain testosterone levels in the normal male range. Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7].

Guidelines (Adolescent)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy at younger than 16 years; although, studies in this population are minimal. Initial therapy to undergo suppression of pubertal development at Tanner stages G2/B2 is suggested. Neither puberty suppression nor gender-affirming hormone therapy are recommended in pre-pubertal children [7].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) During the first year of treatment, body weight and lean body mass (LBM) were significantly increased by 3% and 10%, respectively, in transsexual men undergoing cross-sex hormonal therapy with testosterone during an observational study (n=162 transsexual men). Total body fat was decreased by a significant 9%, with redistribution of body fat significant in the leg (-16%) and gynoid (-14%), but not android regions. LBM was increased in all body parts by between 9% and 19%. Hip circumference was significantly changed by -1.9 cm, but there was no significant difference for waist circumference or the waist-to-hip ratio. Testosterone was administered as testosterone gel 50 mg/day, testosterone undecanoate 1000 mg IM once every 12 weeks, or testosterone esters 250 mg IM once every 2 weeks (not an FDA-approved product). Mean follow-up was 380 days [55].

2) Testosterone undecanoate injections significantly increased testosterone levels to the normal male range in 100% of hormone-naïve transgender men (female-to-male) in a 1-year prospective study (n=53 trans men). At baseline, serum testosterone levels were 30.2 nanograms/dL (ng/dL) and increased to a mean 595.8 ng/dL. Body weight was significantly increased from 68.4 to 70.6 kg, with an increase in lean body mass and decrease in total body fat. Waist-to-hip ratio was significantly increased (0.82 to 0.84) due to decreased hip circumference. Small, but significant, changes in total cholesterol (171.9 to 178.2 mg/dL), LDL-C (98.4 to 116.1 mg/dL), triglycerides (69 to 81.1 mg/dL), and HDL-C (56.3 to 47.8 mg/dL) occurred. Erythrocytosis was present in 2 men based on the male reference range (Hct level above 52%) and 20.1% had Hct levels above the female reference range of 48%. Liver enzyme elevations greater than 2 x ULN were reported with respect to the female reference range (1.9%), but none were 2 x the ULN of the male reference range. No cardiovascular events, venous thromboses, pulmonary

embolisms, deaths, or osteoporotic fractures were reported. Testosterone undecanoate was administered as 1000 mg IM at initiation, at 6 weeks, and then every 12 weeks thereafter. In cases of intolerance, participants could switch to testosterone esters 250 mg (not an FDA-approved product) every 2 weeks [54].

3) Testosterone in 3 different formulations significantly increased total testosterone levels from the physiological range for women to the normal male range by week 30 of treatment with no significant differences among formulations in an observational study in female-to-male transsexual individuals (N=45). At week 54, testosterone remained elevated and sex hormone-binding globulin, prolactin, and estradiol levels were significantly decreased from baseline while body weight and body mass index (BMI) were significantly increased in all groups. Results for selected hormonal and anthropometric outcomes are shown in the table below. Amenorrhea occurred at a mean 29.8 to 41 weeks. Significant changes from baseline were observed in HDL-C (decreased) and LDL-C (increased), but not total cholesterol. Fasting glucose increased significantly, but insulin and homeostasis model assessment for fasting insulin resistance (HOMA-IR) were similar to baseline. Hematocrit and hemoglobin increased from baseline. No significant changes were detected in liver enzymes, renal function, or bone mineral density. Patients were randomly assigned to testosterone enanthate 100 mg IM every 10 days, testosterone gel 50 mg once every evening, or testosterone undecanoate 1000 mg IM at week 0, week 6, and every 12 weeks thereafter. No subject had undergone sexual reassignment surgery [9].

Selected Hormonal and Anthropometric Parameters at Baseline and Week 54 Posttreatment

Parameter	Baseline Range *	Week 54 Posttreatment Range*
Testosterone (ng/mL)	0.44 to 0.54	5.89 to 7.39 **
Estradiol (pg/mL)	102.9 to 167.3	70.6 to 81.9 **
Luteinizing hormone (international units/L)	5.8 to 12.8	5.1 to 9.2
Follicle stimulating hormone (international units/L)	4.6 to 6.2	5.1 to 5.6
Prolactin (ng/mL)	15.7 to 18.2	9.8 to 15.6 **
Sex hormone-binding globulin (nmol/L)	60.3 to 65.4	31.6 to 34.3 **
Body weight (kg)	57.8 to 67.3	60.5 to 68.7 **
BMI (kg/m(2))	22.1 to 23.9	22.4 to 24.3 **
Fat (%)	26.7 to 30.1	22.4 to 27.6 **

KEY: BMI=body mass index; ng=nanograms; pg=picograms

* Range is among the 3 different testosterone formulations with no significant difference among the formulations at baseline or week 54.

** Significant difference between baseline and week 54 values.

4) Facial and body hair growth was significantly increased over time with testosterone undecanoate administration in hormone-naïve transsexual men in a prospective study (N=20). The Ferriman and Gallway score (FG; 0 to 36 scale with a score of greater than 8 in an androgen-dependent area indicating hirsutism) was a median 0.5 at baseline and increased to 12 after 12 months of therapy, but there was wide interindividual variability (range, 2 to 25). In an associated cross-sectional study in transgender men who had undergone sexual reassignment surgery and had been using testosterone for an average of 9.9 years (N=50), the median PG score was 24 with a range of 6 to 34. Moderate to severe alopecia was reported in 31%. Neither the FG score nor alopecia was positively correlated with duration or type of testosterone therapy in the cross-sectional group. Alopecia was correlated with age. In the prospective study group, all participants received testosterone undecanoate 1000 mg IM every 3 months. In the cross-sectional study group, testosterone was administered as testosterone esters 250 mg (not an FDA-approved product) IM every 2 or 3 weeks (n=35), testosterone undecanoate 1000 mg

IM every 12 weeks (n=7), or transdermal testosterone 50 mg/day (n=8); one participant used an oral and transdermal formulation together [56].

5) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and HAD-D scores in the hormonal-therapy group were not significantly affected by length of time on therapy or whether the patient had undergone any SR surgeries [8].

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* Total SADS score ranges from 0 to 28, with higher scores indicating greater social anxiety.

** Significant difference versus no-hormone-therapy group

^ HAD-A and HAD-D subscales each contain 7 items rated on a 4-point Likert scale. Total score of 0 to 7 is considered normal range (ie, without symptoms), 8 to 10 indicates possible symptoms, and 11 or higher indicates symptoms (probable presence of mood disorder) for the respective scale.

d) Pediatric:

1) Adolescent

a) In a cross-sectional study in transsexual patients attending a gender identity unit (age range, 15 to 61 years), those who had undergone hormonal sex-reassignment (SR) therapy (n=120; 70% male-to-female, 30% female-to-male) had significantly lower social distress, anxiety, and depression scores compared with those who had not undergone hormonal therapy (n=67; 43% male-to-female, 57% female-to-male). Assessments were completed using the Social Anxiety and Distress Scale (SADS; scale ranges from 0 to 28 with higher scores indicating greater social anxiety) and the Hospital Anxiety and Depression Scale (HADS; anxiety [-A] and depression [-D] subscales of 7 items each; 0 to 7 on either scale is normal, 8 to 10 suggests mood disorder, 11 or higher shows probable mood disorder). Results for the mean SADS, HAD-A, and HAD-D scores are shown in the table below. Symptoms or possible symptoms of anxiety (HAD-A scale) were present in significantly more treated versus untreated patients (61% vs 33%) and similarly, significantly more patients experienced symptoms or possible symptoms of depression (HAD-D scale) without treatment than with treatment (31% vs 8%). Therapy was administered as either testosterone esters depot 1000 mg IM every 10 to 14 weeks or testosterone transdermal gel 50 mg topically daily. The average duration of therapy was 4.7 years. Mean SADS, HAD-A, and

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Dose Adjustments

Adult Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

Hypogonadism, Male

1) FDA Dosage, Striant(R)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [17].

b) Usual dose: One 30-mg buccal system applied to the gum approximately every 12 hours, applying to opposite sides of the mouth with each dose; monitor testosterone levels at 4 to 12 weeks after initiation, and discontinue if levels are consistently outside normal range [23]

c) Dosing notes: If the system fails to adhere or falls off within 8 hours of application, a new system may be applied and continued for a total of 12 hours from the placement of the first system; however, if it is within 8 hours of the next scheduled dose, apply the new system for 12 hours and then continue with the next dose. Remove system prior to oral care and apply a new system after [23].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Striant(R) testosterone buccal system is not indicated for use in women [23].

Nasal route

Hypogonadism, Male

1) FDA Dosage, Natesto(TM)

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [16].

b) Usual dose: 1 actuation per nostril (2 pump actuations, 11 mg) intranasally 3 times a day (morning, afternoon, and evening, 6 to 8 hours apart) at the same time each day for a total daily dose of 33 mg; after 1 month check testosterone levels periodically [22]

c) If total testosterone level usually below 300 nanograms/dL, consider alternative therapy [22].

d) If total testosterone level generally greater than 1050 nanograms/dL, discontinue treatment with testosterone nasal gel [22].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Natesto(TM) testosterone nasal gel is not indicated for use in women [22].
There is insufficient evidence of long-term safety (ie, cardiovascular and prostate cancer risks) for Natesto(TM) testosterone gel treatment in geriatric patients [22].
The safety and efficacy of Natesto(TM) testosterone gel treatment have not been established in patients with a BMI greater than 35 kg/m(2) [22].

Topical application

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [5][15][1][3][2][18].

2) FDA Dosage, Axiron(R)

a) Initial dose: 60 mg (1 pump or twist actuation of 30 mg to each axilla) applied once daily at the same time each morning to clean, dry, intact skin of the axilla; do not apply to any other parts of the body; obtain serum testosterone concentration at least 14 days after initiation; draw 2 to 8 hours after application [20]

b) Dose titration: decrease or increase dose by 30-mg increments based on serum testosterone concentration from a single blood draw 2 to 8 hours after application and at least 14 days after starting treatment or following dose adjustment, according to the following recommendation [20][20]:

Serum testosterone concentration below 300 nanogram/deciliter (ng/dL): Increase daily dose from 60 to 90 mg or from 90 mg to 120 mg

Serum testosterone concentration exceeds 1050 ng/dL: Decrease daily dose from 60 mg to 30 mg, or discontinue therapy if at the lowest daily dose of 30 mg

3) FDA Dosage, AndroGel(R) 1%

a) Initial dosage: 50 mg topically once daily (4 pump actuations, or 5 g of gel) preferably in the morning to clean, dry, intact skin on shoulders and upper arms and/or abdomen [5]

b) Dose titration: May increase once-daily dose to 75 mg (6 pump actuations, or 7.5 g of gel) and further to 100 mg (8 pump actuations, or 10 g of gel) if testosterone concentration below normal physiologic level [5]

c) Discontinue use if serum testosterone concentrations consistently exceed the normal range at a daily dose of 50 mg [5]

4) FDA Dosage, AndroGel(R) 1.62%

a) Initial dosage: 40.5 mg (2 pump actuations or 2.5 g of gel) applied topically once daily in the morning to clean, dry, intact skin of the shoulders and upper arms; measure predose morning serum testosterone concentration at approximately 14 and 28 days [15]

b) Dosage titration: Decrease or increase dose to minimum of 20.25 mg/day (1 pump actuation or 1.25 g of gel) up to 81 mg/day (4 pump actuations, or 5 g of gel), based on predose morning serum testosterone concentration drawn approximately 14 and 28 days after starting treatment or following dose adjustment, according to the following recommendation [15]:

Pre-Dose Morning Total Serum Testosterone Concentration	Dose Titration
Greater than 750 ng/dL	Decrease daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Equal to or greater than 350 and equal to or less than 750 ng/dL	No change: continue current dose
Less than 350 ng/dL	Increase daily dose by 20.25 mg (1 pump actuation or 1.25 g of gel)
Key: ng = nanograms	

c) The application site and dose of AndroGel(R) 1.62% are not interchangeable with other topical testosterone products [15]

5) FDA Dosage, Fortesta(TM)

a) Initial dose: 40 mg (4 pump actuations) applied once daily to clean, dry, intact skin of the front and inner thighs in the morning; measure serum testosterone level at approximately 14 and 35 days, draw 2 hours post-application [21]

b) Dose titration: decrease or increase dose to a minimum of 10 mg/day or maximum of 70 mg/day, based on serum testosterone concentrations, drawn 2 hours after application at approximately 14 days and 35 days after treatment initiation or following dose adjustments, according to the following recommendation [21]:

Total Serum Testosterone Concentrations 2 hours Post Fortesta(TM) Application	Dose Titration

Equal to or greater than 2500 ng/dL	Decrease daily dose by 20 mg (2 pump actuations)
Equal to or greater than 1250 and less than 2500 ng/dL	Decrease daily dose by 10 mg (1 pump actuation)
Equal to or greater than 500 and less than 1250 ng/dL	No change: continue current dose
Less than 500 ng/dL	Increase daily dose by 10 mg (1 pump actuation)
Key: ng = nanograms	

c) The application site and dose of Fortesta(TM) are not interchangeable with other topical testosterone products [21].

6) FDA Dosage, Testim(R) 1% Gel

a) Initial dose: one 5 g tube applied once daily (preferably in morning) to clean, dry, intact skin on the shoulder and/or upper arms; measure morning testosterone level 2 weeks after initiation [24].

b) Dose titration: increase dose to 10 g/day (2 tubes) if serum testosterone concentration is below the normal physiologic range or if desired clinical response is not observed [24]

7) FDA Dosage, Vogelxo(TM)

a) Initial dose: 50 mg (1 tube or packet or 4 pump actuations) applied topically to clean, dry, intact skin of shoulders or upper arms once daily; measure morning predose testosterone level after approximately 14 days [25]

b) Dose titration: may increase to 100 mg (2 tubes or packets or 8 pump actuations) once daily if morning predose testosterone level remains below normal (ie, 300 to 1000 nanograms/dL) [25]

c) Maximum dose: 100 mg/day [25]

8) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (1.6% gel): 50 to 100 mg applied topically once daily. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used). Avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

AndroGel(R), 1%, Androgel(R) 1.62%, Natesto(TM), Striant(R), Testim(R), and Vogelxo(TM) topical testosterone gel products are not indicated for use in women [25][22][49][27][24][23]

Transdermal route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage (patch): 2.5 to 7.5 mg/day. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions (guideline dosage) [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage, Androderm(R) 2 mg/day and 4 mg/day System

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [14].

b) Initial dose: One 4 mg/day transdermal system (not two 2 mg/day systems) applied every 24 hours at night; measure early morning serum testosterone level 2 weeks later [19]

c) Dose titration: Increase dose to 6 mg daily at night (one 4 mg/day plus one 2 mg/day system) or decrease dose to 2 mg daily at night (one 2 mg/day system) if early morning serum testosterone level drawn 2 weeks after starting therapy is outside the target range (400 to 930 nanograms/dL) [19].

2) FDA Dosage, Switching from Androderm(R) 2.5 mg/day, 5 mg/day, and 7.5 mg/day System to Androderm(R) 2 mg/day, 4 mg/day, and 6 mg/day System

At next scheduled dose, make switch according to following recommendation [19]:

patients currently on the 2.5 mg/day system may switch to the 2 mg/day system [19]
patients currently on the 5 mg/day system may switch to the 4 mg/day system [19]
patients currently on the 7.5 mg/day system may switch to the 6 mg/day system [19]

Two weeks after switching therapy, measure an early morning serum testosterone level [19]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks. Maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks. Base dosage (initial, maintenance, and adjustments) on patient response and presence of adverse reactions [82].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg IM every 2 weeks [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Usual dosage: 50 to 400 mg IM every 2 to 4 weeks as replacement therapy; dose based on diagnosis, response to treatment, and presence of adverse effects. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Metastatic breast cancer, Female

1) Usual dosage (women): 200 to 400 mg IM every 2 to 4 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Dosage: 100 to 200 mg subQ every 2 weeks or 50% of the dose subQ once weekly [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Prior to initiation: Confirm the diagnosis of hypogonadism with serum testosterone concentration below the normal range when measured in the morning on at least 2 separate days [74].

b) Initial dosage: 75 mg subQ in the abdominal region once a week [74]

c) Dosage titration: Measure total testosterone trough concentration (Ctrough) 7 days after the most recent dose after 6 weeks of dosing, following 6 weeks after dose adjustment, and periodically while on treatment. If Ctrough is 650 nanograms (ng)/dL or higher, decrease the dose by 25 mg. If Ctrough is less than 350 ng/dL, increase the dose by 25 mg. If Ctrough is 350 to less than 650 ng/dL, maintain the same dose [74].

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage

a) Initial dosage: 1000 mg IM at 0 and 6 weeks and then every 12 weeks to maintain testosterone levels in the normal male range (usually 320 to 1000 nanograms/dL, but dependent on assay used); avoid sustained supraphysiologic levels to reduce risk of adverse reactions [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [58].

b) Usual dosage: 750 mg IM, and then 750 mg IM 4 weeks later, and then 750 mg IM every 10 weeks thereafter [59]

2) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

3) Off-label Dosage

a) Off-Label Dosage: 1000 mg IM, and then 1000 mg IM at week 6, and then 1000 mg IM every 12 weeks [60]

Oral route

Hypogonadism, Male

1) Tlando(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [53].

b) Dosage: 225 mg (2 capsules) orally twice daily in the morning and evening with food; do not adjust dosage [53].

c) Measure serum testosterone following 3 to 4 weeks of treatment and periodically thereafter; draw level 8 to 9 hours after the morning dose [53].

d) Continue treatment if serum testosterone is 300 to 1080 ng/dL, otherwise discontinue treatment [53].

2) Jatenzo(R) - FDA Dosage

a) Confirm diagnosis by measuring serum testosterone concentrations in the morning on at least 2 separate days [57].

b) Initial dosage: 237 mg twice daily in the morning and evening with food [57]

c) Adjust dose based on serum testosterone concentrations measured 6 hours after the morning dose in plain tubes, clotted at room temperature for 30 minutes prior to centrifugation. Wait seven days after starting treatment or adjusting the dose before checking the serum testosterone concentration. Thereafter, periodically monitor serum testosterone concentrations 6 hours after the morning dose. Administer the same dose in the morning and evening according to the following table [57]:

Testosterone Concentration in Serum From Plain Tube Drawn 6 hours After Morning Dose	Current dose (mg, twice daily)	New dose (mg, twice daily)
Less than 425 nanograms/dL	158	198
	198	237
	237	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	396 (two 198 mg capsules)
425 to 970 nanograms/dL	No dose change	
More than 970 nanograms/dL	396 (two 198 mg capsules)	316 (two 158 mg capsules)
	316 (two 158 mg capsules)	237
	237	198
	198	158
	158	Discontinue therapy

d) Maximum dosage: 396 mg (two 198 mg capsules) twice daily [57]

3) Guideline Dosage

a) Dosage titration: Adjust dosage to achieve a total testosterone level of 450 to 600 nanograms/dL; consider discontinuation of therapy 3 to 6 months after initiation if target testosterone level is obtained, but signs or symptoms do not improve [26]

Dosage in Renal Failure

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Hepatic Insufficiency

A) Testosterone Enanthate

1) No specific recommendations are available [76]

Dosage in Other Disease States

A) Testosterone Enanthate

1) In patients who develop edema with or without congestive heart failure, discontinue testosterone enanthate and restart at a lower dose [73].

Pediatric Dosage

Normal Dosage

Important Note

Testosterone

Topical testosterone products are not interchangeable as they have different strengths, doses, and application instructions that may result in different systemic exposure [1][2][3][4][5].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Cypionate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Enanthate

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone Undecanoate

Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53].

Beers Criteria: Use caution or avoid use as potentially inappropriate in older adults [6].

Testosterone

Buccal mucosa route

a) The safety and effectiveness of Striant(R) testosterone buccal system have not been established in males younger than 18 years [23].

Nasal route

a) The safety and efficacy of Natesto(TM) testosterone gel have not been established in patients younger than 18 years [22].

Topical application route

Female-to-male transsexual - Gender dysphoria

1) Off-label Dosage, Adolescent

a) Dosage (gel): 50 mg applied topically once daily [8]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

The safety and efficacy of AndroGel(R) 1%, AndroGel(R) 1.62%, Axiron(R), Fortesta(TM), Testim(R) 1%, and Vogelxo(TM) have not been established in males younger than 18 years [20][25][27][24][49][21]. Acceleration of bone age and premature closure of epiphyses may occur with improper use [21].

Transdermal route

a) Safety and efficacy of testosterone transdermal system have not been established in males younger than 18 years. Acceleration of bone age and premature closure of epiphyses may occur with improper use [19].

Testosterone Cypionate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Primary hypogonadism, Male

1) Usual dosage (12 years or older): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Base dosage (initial, maintenance, and adjustments) on patient response, presence of adverse reactions, age, and skeletal age. Some regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses [82].

Testosterone cypionate is not interchangeable with testosterone propionate because of differences in the duration of action [82].

Testosterone Enanthate

Intramuscular route

Delayed puberty, Male

1) Usual dosage (adolescent males): 50 to 200 mg IM every 2 to 4 weeks for a limited duration, such as 4 to 6 months. Some dosage regimens include low initial doses and gradual increases with progressing puberty and may or may not include decreased maintenance doses. Other regimens include higher initial doses for the induction of puberty followed by lower maintenance doses. Although various dosing regimens may be used, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses in addition to patient response and adverse effects [73].

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hypogonadism, Male

1) Usual dosage (adolescent males): 50 to 400 mg IM every 2 to 4 weeks as replacement therapy. Although various dosing regimens may be used to induce pubertal changes in hypogonadal males, the patient's chronological and skeletal age should be considered when determining initial and maintenance doses. Doses above 400 mg per month are generally not required and injections are usually not administered more than every 2 weeks [73].

Subcutaneous route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) subQ every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg subQ every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Testosterone Undecanoate

Intramuscular route

Female-to-male transsexual - Gender dysphoria

1) Guideline Dosage, Adolescents

a) Induction of male puberty: 25 mg/m(2) IM every 2 weeks; increase dose by 25 mg/m(2) every 6 months up to 100 mg/m(2) every 2 weeks. Alternatively may administer half of the dose once weekly or double the dose every 4 weeks [7]

b) Postpubertal transgender male: 75 mg IM every 2 weeks for 6 months then increase to 125 mg every 2 weeks; dose can be increased more rapidly than every 6 months [7]

c) Maintenance: Adjust dosage to mimic physiological testosterone levels [7]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years [59].

Oral route

a) General Dosage Information

1) The safety and effectiveness of testosterone undecanoate have not been established in pediatric patients younger than 18 years. Improper use may result in acceleration of bone age and premature closure of epiphyses [53][57].

Administration

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist

actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27][49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1

30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due

to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal

around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Comparative Efficacy

Acetylcarnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate 160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but

remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Chlorotrianisene

Engorgement of breasts

a) SUMMARY: Chlorotrianisene is less effective than the combination of testosterone enanthate plus estradiol valerate in the treatment of postpartum breast engorgement.
b) In a double-blind study of lactation suppression in clinic patients, testosterone enanthate with estradiol valerate (Deladumone OB) 2 milliliters IM immediately prior to delivery was compared to chlorotrianisene 72 mg orally every 12 hours for 4 doses. At day 4, Deladumone OB(R) patients experienced significantly less breast tenderness and lactation than did patients receiving chlorotrianisene. Both drugs were significantly more effective than placebo [212].
c) In a study of 484 puerperal patients who did not wish to breast feed, testosterone enanthate with estradiol valerate was more effective than chlorotrianisene for inhibition of lactation and relief of breast engorgement and discomfort [213].

Chorionic Gonadotropin

Male hypogonadotropic hypogonadism

a) Weekly 5000 unit chorionic gonadotropin injections (n=16) were compared with monthly 250 milligram long-acting testosterone injections (n=22) in male hypogonadotropic hypogonadism patients [216]. Both treatments produced comparable virilizing effects measured as progression through Tanner stages. Chorionic gonadotropin, however, produced increases in testicular volume to near-normal, which did not occur with testosterone. This additional benefit of chorionic gonadotropin may enhance later induction of fertility when such treatment is undertaken.

Cyproterone

Contraception, Male

a) In a small study all men who received testosterone and cyproterone became azoospermic compared to 3 of 5 men receiving testosterone only. Fifteen men were randomized to receive cyproterone 50 mg orally twice daily plus testosterone enanthate 100 mg intramuscularly (IM) weekly; cyproterone 25 mg orally twice daily plus testosterone 100 mg IM weekly; or testosterone 100 mg IM weekly alone for 16 weeks. Patients in the cyproterone 100 mg, cyproterone 50 mg, and testosterone only groups achieved azoospermia at mean times of 6.8, 8.4, and 14 weeks, respectively. After treatment baseline sperm counts were achieved in all men. Lipoprotein profiles nor liver function tests were detected in any patient. No significant differences in sexual behavior were reported among the three groups [215].

Estrogen

Disorder of bone development

a) In a case report concerning a 31-year old hypogonadal male with aromatase deficiency, 50 micrograms of estradiol, given transdermally twice weekly for 9 months, was able to affect epiphyseal closure and improvement in bone pain. Prior treatment with testosterone enanthate, 250 milligrams intramuscularly every ten days for six months had not achieved these results. The baseline bone age of 14.8 years did not change with testosterone enanthate, but increased to more than 16 years after 9 months of estradiol therapy. Further research is required to confirm these results [211].

Fluoxymesterone

Anemia

a) A randomized clinical trial was conducted to compare the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis [210]. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg orally daily, oxymetholone 1 mg/kg orally daily, or nandrolone decanoate 3 mg/kg intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen.

Nandrolone

Anemia

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram of body weight intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 mg/kg of body weight orally daily, oxymetholone 1 mg/kg of body weight orally daily, or nandrolone decanoate 3 mg/kg of body weight intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had a 5% increase in hematocrit following the administration of either injectable androgen [217].

Oxymetholone

Anemia secondary to renal failure

a) A randomized clinical trial compared the erythropoietic effects of several androgens in 143 patients (103 males, 40 females) with anemia who were receiving maintenance hemodialysis. The patients received either testosterone enanthate 4 milligrams/kilogram intramuscularly weekly (the female patients did not receive testosterone), fluoxymesterone 0.4 milligram/kilogram orally daily, oxymetholone 1 milligram/kilogram orally daily, or nandrolone decanoate 3 milligrams/kilogram intramuscularly weekly. Control periods of at least 2 months were followed by treatment periods consisting of one of the androgens for 6 months followed by another control period; three courses utilizing a different drug each time were administered. Seventy-seven, 56, and 35 patients completed the first, second, and third treatment periods, respectively. The 2 agents administered by injection, which included testosterone, were judged superior to the orally administered agents in terms of patient response and mean rise in hematocrit. Approximately 50% of the patients had an increase of at least 5 percentage points in hematocrit following the administration of either injectable androgen [218].

Propionyl-L-Carnitine

Aging, Male

a) Carnitines and testosterone both improved sexual dysfunction, depressed mood, and fatigue associated with male aging. However, testosterone treatment caused prostate enlargement, which carnitine treatment did not. In a randomized, placebo- controlled trial, men over age 60 with symptoms of decreased libido and erectile quality, depressed mood and intellectual concentration ability, irritability, fatigue, and serum testosterone lower than 6 picograms/milliliter were randomized to receive testosterone undecanoate

160 milligrams/day (mg/d) (n=40), propionyl-L-carnitine 2 grams/day (g/d) plus acetyl-L-carnitine 2 g/d (n=45), or placebo (n=45) for 6 months. At 6 months, peak systolic velocity, resistive index of the right cavernosal artery, and nocturnal penile tumescence were increased in both the testosterone group and the carnitines group and unchanged in the placebo group. Erectile function, sexual desire, and sexual satisfaction increased at 3 or 6 months or both in both active treatment groups. Carnitine scores were significantly better than testosterone scores with respect to erectile function at 3 months (p less than 0.05) and 6 month (p less than 0.01), orgasm at 6 months (p less than 0.01), and sexual well-being at 6 months (p less than 0.01). Other physiological scores were not different for the 2 groups. Both active treatments lowered the Hamilton Depression and Melancholia Scale scores, but carnitines more so (p less than 0.01, carnitines vs testosterone). Carnitines and testosterone equally decreased fatigue scale scores. Prostate volume increased with testosterone treatment from 15 cubic centimeters at baseline to 25 cubic centimeters at 6 months. Prostate volume was unchanged by carnitine or placebo treatment. In the testosterone group, prostate volume had decreased (to 18 cubic centimeters) by 6 months after termination of therapy but remained elevated above baseline. All other parameters reverted to baseline levels by 6 months after termination of therapy [214].

Stanozolol

1) Efficacy

a) Oral stanozolol 6 mg/day produced more undesirable lipoprotein effects than intramuscular testosterone 200 mg once weekly in male weight lifters in a 6-week, crossover study [219]. Stanozolol reduced HDL-cholesterol and the HDL-2 subfraction by 33% and 71%, respectively; however, the HDL-cholesterol concentration was decreased by only 9% with testosterone, with the decrease being in the HDL-3 subfraction. Apolipoprotein A-1 levels were reduced by 8% and 40% with testosterone and stanozolol, respectively. LDL-cholesterol concentrations decreased 16% with testosterone, but increased by 29% with stanozolol. An increase in the postheparin hepatic triglyceride lipase activity of 123% was observed with stanozolol, however, increases with testosterone (25%) were not significant. Intramuscular testosterone is preferable to oral stanazolol for clinical indications requiring prolonged androgen or anabolic steroids.

Place In Therapy

A) Testosterone

1) Transdermal, Topical, Buccal, Intranasal

a) Testosterone preparations are indicated for primary hypogonadism (congenital or acquired) due to testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. Typically, low serum testosterone concentrations and high gonadotropin (FSH, LH) concentrations are present. Additionally, it is indicated for hypogonadotropic hypogonadism (congenital or acquired) due to idiopathic gonadotropin or luteinizing hormone releasing hormone (LHRH) deficiency or pituitary-hypothalmic injury from tumors, trauma or radiation. Typically, low serum testosterone concentrations and low to normal gonadotropin (FSH, LH) concentrations are present [22][23][85][84].

b) Testosterone preparations are also indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone including congenital or acquired primary hypogonadism and congenital or acquired hypogonadotropic hypogonadism [22][23][28][84].

B) Testosterone Cypionate

Testosterone cypionate is indicated for replacement therapy in adults and pediatric patients age 12 and older for conditions associated with a deficiency or absence of endogenous testosterone, such as:

Primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy [83]
Hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing

hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [83]

1) Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater the younger the child. Assessment of bone age in the wrist and hand is recommended every 6 months [83].

C) Testosterone Enanthate

1) Delayed Puberty

a) Testosterone enanthate injection is indicated to stimulate puberty in select male patients with delayed puberty, for a limited duration of treatment such as 4 to 6 months. Cautious use of androgens in the pediatric population is necessitated by the likelihood of adverse effects on bone maturation. The risk of a compromised final mature height is greater in the younger child. Assessment of bone age in the wrist and hand every 6 months is recommended [73].

2) Male Hypogonadotropic hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in congenital or acquired hypogonadotropic hypogonadism, such as gonadotropin or luteinizing hormone–releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation [74][75]. Testosterone enanthate IM injection is also indicated in adolescent males. Concurrent treatment with appropriate adrenal cortical and thyroid hormone replacement therapy are of primary importance, however. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

3) Male Primary Hypogonadism

a) Testosterone enanthate injection is indicated in adult men for replacement therapy in primary congenital or acquired hypogonadism, such as testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchidectomy [74][75], Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals[74]. Testosterone enanthate IM injection is also indicated in adolescent males. Replacement therapy needed prior to puberty will be needed during adolescence for secondary sexual characteristic development. Replacement therapy needed following puberty will require prolonged duration of therapy to maintain sexual characteristics [73].

4) Metastatic Mammary Cancer in Women

a) IM testosterone enanthate is indicated for palliation of inoperable metastatic (skeletal) mammary cancer in women who are 1 to 5 years postmenopausal, when a goal of therapy includes ablation of the ovaries. Testosterone enanthate injection has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and have a hormone-responsive tumor [73].

D) Testosterone Undecanoate

1) Testosterone undecanoate IM and oral capsules are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone. These include primary hypogonadism (congenital or acquired): testicular failure from conditions such as cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals (men with these conditions have low serum testosterone concentrations and gonadotropins above the normal range) and hypogonadotropic hypogonadism (congenital or acquired): idiopathic gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation (men with these conditions have low serum testosterone concentrations and gonadotropins in the normal or low range) [53][57][59]. Testosterone undecanoate oral capsules are available in different oral formulations that are not interchangeable [53]. Testosterone undecanoate IM should only be used in patients who require testosterone replacement therapy and in whom the benefits of the product outweigh the serious risks of pulmonary oil microembolism and anaphylaxis [59]. Safety and efficacy of testosterone undecanoate have not been established in males younger than 18 years old [57][59].

2) A mean 24-hour serum testosterone level within normal range (300 to 1080 nanograms/dL) was achieved in 80% of patients receiving testosterone undecanoate capsules (Tlando(R)) 225 mg twice daily with food for 24 days (N=95); no dosage adjustments were permitted. Majority of those not achieving a eugonadal range had a BMI of 30 kg/m(2) or greater [61].

3) Mean plasma total testosterone over 24 hours was within the normal eugonadal range in 87% of patients in a 4-month study of adult hypogonadal males who received testosterone undecanoate capsules [57].

4) In an 84-week study of hypogonadal adult male patients with low serum testosterone, 94% of patients maintained an average testosterone concentration within the normal range following the third injection of testosterone undecanoate IM [59].

MEDICATION SAFETY

Contraindications

A) Testosterone

1) Breast cancer, male [25][22][23][84][28][21][85][86][87][88]

2) Females who are pregnant, may become pregnant, or who are breastfeeding; known teratogen; exposure of female fetus or nursing infant to testosterone residue may result in varying degrees of virilization [25][22][23][84][28][21][85][86][87][88]

3) Hypersensitivity to testosterone or any component of the product [86][87][88]

4) Prostate cancer, known or suspected [25][22][23][84][28][21][85][86][87][88]

5) Use in women [84][86]

B) Testosterone Cypionate

1) Breast cancer, male [82]

2) Cardiac, hepatic, or renal disease, serious [82]

3) Women who are pregnant or may become pregnant [82]

4) Hypersensitivity to testosterone cypionate [82]

5) Prostate cancer, known or suspected [82]

C) Testosterone Enanthate

1) Breast cancer in males [74][75][73]

2) Females who are pregnant or may become pregnant; known teratogen [74][75][73]

3) Hypersensitivity to testosterone enanthate or any component of the product, including sesame oil [74][75][73]

4) Known or suspected prostate cancer [74][75][73]

5) Men with hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [74].

D) Testosterone Undecanoate

1) Breast carcinoma [57][59]

2) Hypersensitivity to testosterone undecanoate or any component of the product (eg, refined castor oil, benzyl benzoate) [57][59]

3) Pregnancy, nursing, or women of childbearing potential; may cause fetal harm and serious adverse reactions in nursing infants, such as virilization [57][92]

4) Known or suspected prostate carcinoma [57][59]

5) Hypogonadal conditions, such as age-related hypogonadism, that are not associated with structural or genetic etiologies [57]

Precautions

A) Testosterone

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

4) Cardiovascular: Edema, with or without congestive heart failure, may occur in patients with preexisting cardiac, renal or hepatic disease [25][22][23][84][28][21][85][86][88][87]; discontinuation and diuretic therapy may be required [25][22][23].

5) Dermatologic: Use of magnetic resonance imaging has caused skin burns at application site due to the presence of aluminum in the patch [84].

6) Endocrine and metabolic: Increased risk of hypercalcemia and associated hypercalciuria in cancer patients; monitoring recommended [25][22][23][84][28][21][85][87][88]

7) Endocrine and metabolic: Dyslipidemia may occur; monitoring recommended [25][22][23]; dosage adjustment or discontinuation may be warranted [84][28][21][87][85].

8) Endocrine and metabolic: Decreased levels of thyroxine-binding globulins, resulting in decreased total T4 serum levels and increased resin uptake of T3 and T4, may occur [90].

9) Flammability: Alcohol-based formulations are flammable until dry [25][28][21][85][86][87].

10) Gastrointestinal: Gum-related adverse reactions, including severe gum irritation, have been reported and may warrant dental consultation; monitoring recommended [23].

11) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [17][2][1][14][16][5][15][3][18].

12) Hematologic: Polycythemia may occur; monitoring recommended [25][22] and dose adjustment may be warranted [25][23][84][28][21][85][86][88][87].

13) Hepatic: Serious hepatic adverse effects, including cholestatic jaundice, liver cancer, and peliosis hepatitis have been reported with prolonged use of high doses of orally active androgens [25][22][23][84][28][21][85][86][88][87]; discontinue use until cause is determined [25][22][23].

14) Musculoskeletal: Osteolysis may be stimulated by periods of immobilization and can result in hypercalcemia [88].

15) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [17][2][1][14][16][5][15][3][18].

16) Reproductive: Secondary exposure in children and women may result in virilization, inappropriate changes in genital size, and other serious adverse effects [25][28][21][85][86][87][91]; discontinue use until cause of virilization is determined [25].

17) Reproductive: Increased risk of worsening benign prostatic hyperplasia [25][22][23][84][28][21][85][86]; monitoring recommended [25][22][23][84][28][21][85]

18) Reproductive: Increased risk of prostate cancer with androgen use; monitoring recommended [25][22][23][84][28][21][85][86][87]

19) Reproductive: Gynecomastia, possibly persistent, may occur [25][22][23][84][28][21][85][86][88][87].

20) Reproductive: Suppression of spermatogenesis may occur with large doses [25][22][23].

21) Reproductive: Avoid use in men who are trying to conceive [26]

22) Respiratory: Nasal adverse reactions (ie, nasopharyngitis, rhinorrhea, epistaxis) have been reported and may require further evaluation or discontinuation [22].

23) Respiratory: Use is not recommended in patients with mucosal inflammatory disorders, sinus disease, or a history of nasal disorders, nasal or sinus surgery, nasal fracture (within last 6 months), or nasal fracture resulting in deviation of the anterior nasal septum [22].

24) Respiratory: Increased risk of sleep apnea in patients with obesity or chronic lung diseases [25][22][23][84][28][21][85][86][87]

B) Testosterone Cypionate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [89].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Possible increased risk of major adverse cardiovascular events (eg, cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) have been reported with testosterone therapy in men [82]

5) Cardiovascular: Preexisting cardiac disease; edema may occur, with or without congestive heart failure [82]

6) Endocrine and metabolic: Gynecomastia may occur [82]

7) Endocrine and metabolic: Hypercalcemia may occur in immobilized patients; discontinue if occurs [82]

8) Hematologic: Thromboembolic events (eg, DVT and pulmonary embolism) have been reported with testosterone therapy; discontinue use if suspected [82]

9) Hepatic: Increased risk of hepatic adenomas, hepatocellular carcinoma, or peliosis hepatitis with prolonged use at high doses [82]

10) Hepatic: Preexisting hepatic disease; edema may occur, with or without congestive heart failure [82]

11) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

12) Renal: Preexisting renal disease; edema may occur, with or without congestive heart failure [82]

13) Reproductive: Delayed puberty in healthy male children; use may accelerate bone maturation and result in compromised adult stature; monitoring recommended [82]

14) Reproductive: Priapism or excessive sexual stimulation may occur; interrupt use and reduce the dosage if restarting therapy [82]

15) Reproductive: Oligospermia may occur with prolonged or excessive use; interrupt use and reduce the dosage if restarting therapy [82]

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Benign prostatic hypertrophy; increased risk of acute urethral obstruction; interrupt use and reduce the dosage if restarting therapy [82]

18) Special populations: Athletic performance enhancement; use not recommended [82]

19) Special populations: Contains benzyl alcohol, which may cause "gasping syndrome" and death in pediatric patients, with an increased risk in premature and low-birth weight infants [82]

20) Special populations: Elderly patients may be at increased risk of developing prostatic hypertrophy or prostatic carcinoma [82]

C) Testosterone Enanthate

1) Beers Criteria: Avoid unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious cardiovascular and psychiatric adverse reactions; if suspected, measure serum testosterone [74].

3) Cardiovascular: Possible increased risk of heart attack, stroke, or death has been reported [75] [93]; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

4) Cardiovascular: Edema, with or without congestive heart failure, may occur, especially in patients with preexisting cardiac, hepatic, or renal disease; discontinuation may be necessary [74] and/or

lower restarting dose used [75][73]

5) Endocrine and metabolic: Hypercalcemia may occur in patients with breast cancer or who are immobilized; discontinue use if occurs [75][73]

6) Endocrine and metabolic: Hypercalcemia, and associated hypercalciuria, may occur in cancer patients at risk; monitoring recommended [74]

7) Endocrine and metabolic: Altered serum cholesterol concentrations may occur, and caution should be used, especially in patients with history of myocardial infarction or coronary artery disease; monitoring recommended [75][73]

8) Endocrine and metabolic: Changes in serum lipid profile may occur; monitoring recommended and discontinuation of therapy may required [74]

9) Endocrine and metabolic: Thyroxine-binding globulin concentrations may be decreased [74]

10) Hematologic: Venous thromboembolic events, including DVT, have been reported with testosterone therapy; discontinue use if suspected [74][75]

11) Hematologic: Increases in hematocrit reflective of increases in red blood cell mass may occur; monitoring recommended and discontinuation may be required [74]

12) Hepatic: Prolonged use of high doses has been associated with serious hepatic adverse effects (peliosis hepatitis, hepatic neoplasms, cholestatic hepatitis, and jaundice); discontinue therapy if hepatic dysfunction occurs [74]

13) Hepatic: Life threatening or fatal peliosis hepatitis or hepatic neoplasms (eg, hepatocellular carcinoma) may occur with prolonged use at high doses[74][75][73]

14) Hepatic: Cholestatic hepatitis accompanied by jaundice may occur; discontinue use [75][73]

15) Hepatic: Liver function test abnormalities may occur; discontinue use [75][73]

16) Musculoskeletal: Use cautiously in healthy males with delayed puberty, as effects on bone maturation may occur; monitoring recommended and dosage adjustment may be necessary [75] [73]

17) Musculoskeletal: Use caution in pediatric patients, as bone maturation may be accelerated, resulting in compromised adult stature; monitoring recommended [75][73]

18) Neurologic: Possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [93]

19) Psychiatric: Depression and suicidal ideation and behavior, including completed suicide, have been reported; monitoring recommended [74]

20) Reproductive: Elderly patients; increased risk for prostatic hypertrophy or prostatic carcinoma [75][73]

21) Reproductive: Gynecomastia may occur and can possibly persist in those being treated for hypogonadism [74][75][73]

22) Reproductive: Use cautiously in female patients, as virilization may occur; monitoring recommended and discontinue use if suspected [75][73]

23) Reproductive: Worsening of benign prostatic hyperplasia may occur in patients with condition; monitoring recommended [74]

24) Reproductive: Increased risk of prostate cancer; evaluate for prostate cancer prior to and during therapy [74]

25) Reproductive: Spermatogenesis may be suppressed and result in adverse effects on semen parameters including sperm count [74]

26) Reproductive: Avoid use in men who are trying to conceive [26]

27) Respiratory: Venous thromboembolic events, including pulmonary embolism, have been reported; discontinue use if suspected [74][75]

28) Respiratory: Sleep apnea may occur, especially in patients with risk factors such as obesity or chronic lung disease [74]

D) Testosterone Undecanoate

1) Beers Criteria: Avoid use unless indicated for symptomatic hypogonadism due to potential for cardiac toxicities. Contraindicated in men with prostate cancer [6].

2) Abuse: Abuse, usually at higher than prescribed doses and usually in conjunction with other anabolic androgenic steroids, has been reported and may result in serious safety risks (eg, heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity, infertility); if suspected, measure serum testosterone [57][89].

3) Cardiovascular: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

4) Cardiovascular: Edema with or without congestive heart failure may occur in patients with cardiac, hepatic, or renal disease; discontinuation may be necessary [57][92].

5) Endocrine and metabolic: Lipid abnormalities may occur; discontinuation may be necessary [57][92]; monitoring recommended [57].

6) Endocrine and metabolic: Cancer patients at risk for hypercalcemia or hypercalciuria; monitoring recommended [57][92]

7) Hematologic: Hematocrit and red blood cell mass increases may occur and increase risk for thromboembolism; monitoring recommended and interrupt or discontinue if necessary [57][92].

8) Hematologic: Venous thromboembolic events, including DVT and pulmonary embolism, have been reported; monitoring recommended; discontinue use if suspected [57][63].

9) Hepatic: Serious hepatic adverse effects (eg, peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, jaundice) have been reported with prolonged use of high doses of other androgens (eg, oral methyltestosterone); discontinue use if suspected [57][92].

10) Neurologic: A possible increased risk of heart attack, stroke, or death has been reported; testosterone therapy should only be used in male patients with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests [57][63].

11) Psychiatric: Depression and suicidal ideation have been reported [57]

12) Reproductive: Prostate cancer may occur; monitoring recommended [57][92].

13) Reproductive: Worsening of signs and symptoms of benign prostatic hyperplasia (BPH) may occur in patients with BPH; monitoring recommended [57][92].

14) Reproductive: Virilizing effects may occur in women (unapproved use) [57][92].

15) Reproductive: Spermatogenesis suppression, resulting in adverse effects on sperm count, may occur with large doses of androgens [57][92].

16) Reproductive: Avoid use in men who are trying to conceive [26]

17) Reproductive: Gynecomastia may occur in patients treated for hypogonadism [57][92].

18) Respiratory: Sleep apnea may occur; increased risk with obesity or chronic lung disease [57][92].

Adverse Effects

Cardiovascular Effects

Testosterone

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [17][2][1][14][16][5][15][3][18].

Disease of cardiovascular system, acute

a) General Information

1) Risk of acute cardiovascular events may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 26% increased risk of composite acute cardiovascular (CV) events (myocardial infarction, unstable angina, stroke) compared with transdermal

gels when assessed over a 1-year followup period. There was no significant difference in the risk of acute CV events between the transdermal gel or patch [105].

Edema

a) General Information

1) Androgens may promote sodium and water retention [23][25][22]

2) Edema, with or without congestive heart failure, may be serious complication in patients with cardiac, renal, or hepatic disease [23][25][22][99][86][100][88][87][94]

b) Prevention and Management

1) Discontinuation and diuretic therapy may be required if edema occurs [23][25][22][86][100][88][87][94]

c) Adult Postmarketing

1) Edema has been reported [87]

Hypertension

a) Incidence: Up to 3% [28][87][99][100]

b) Prevention and Management

1) Clinicians should monitor development of hypertension in elderly patients are at increased risk for cardiovascular disease [106].

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): Less than 1% [100]

2) Replacement therapy (topical route): 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): 0% to 3% [87][28]

4) Replacement therapy (topical route): At least 2 of 155 patients [99]

Increased blood oxygen pressure

a) Incidence: 3% or less [25][22][99][86]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Less than 3% [22]

2) Replacement therapy (topical route): Less than 1% [99]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

Myocardial infarction

a) General Information

1) Myocardial infarction has been reported with use of anabolic steroids [101][102].

2) May increase risk of major adverse cardiovascular events, such as myocardial infarction [17][2][1][14][16][5][15][3][18].

3) An increased risk of serious cardiovascular effects has been reported in men treated with testosterone therapy [103][104].

4) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Low serum testosterone levels: 2-fold increased risk of acute nonfatal myocardial infarction within 90 days among men 65 years or older [104].

3) Low serum testosterone levels: 2- to 3-fold increased risk of heart attack within the 90 days in men younger than 65 years with preexisting heart disease [104]

4) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 30% increased risk of myocardial infarction (MI) compared with transdermal gels when assessed over a 1-year followup period. Risk of MI was slightly increased with use of patch versus gel, but there was no significant difference in overall risk of acute cardiovascular events (ie, MI, unstable angina, stroke) between the 2 transdermal forms [105].

c) Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

Unstable angina

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with a 21% increased risk of unstable angina compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of unstable angina between the transdermal gel or patch [105].

Vasodilatation

a) Incidence: Less than 1% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Testosterone Cypionate

Myocardial infarction

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

Testosterone Enanthate

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [75].

Hypertension

a) Incidence: 2.3% to 12.7% [74]

b) General Information

1) In clinical trials, systolic blood pressure increased by an average of 4 mmHg during the first 12 weeks of treatment, and by an average of 4 mmHg from baseline following 1 year of treatment [74].

2) Ten percent of patients required initiation or adjustment of antihypertensive medications [74].

3) Increases in blood pressure may increase risk for major adverse cardiovascular events, especially in patients with established cardiovascular disease. In some patients the blood pressure elevation may be too small to detect but may still lead to increased cardiovascular risk [74].

c) Prevention and Management

1) Prior to initiation, consider baseline cardiovascular risk and ensure blood pressure is adequately controlled [74].

2) Initiation or adjustment of antihypertensive medication may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 12.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [75].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [75]

Peripheral edema

a) Incidence: 2.7% [74]

b) General Information

1) Edema, with or without congestive heart failure, may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease [74].

2) Androgens may promote sodium and water retention [74].

c) Prevention and Management

1) Diuretic therapy may be necessary [74].

2) Drug discontinuation may be required [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Angina pectoris

a) Postmarketing

1) Has been reported [58]

Death, Cardiovascular

a) General Information

1) May increase risk of major adverse cardiovascular events, such as cardiovascular death [53][58].

b) Postmarketing

1) Has been reported [58]

Edema

a) Incidence: Greater than 2% [57]

b) General Information

1) May promote sodium and water retention [53][57][58]

2) May be a serious complication in patients with preexisting renal, cardiac, or hepatic disease [53][57][58]

c) Prevention and Management

1) Discontinuation and diuretic therapy may be required [53][57][58]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Peripheral edema, greater than 2% with testosterone undecanoate (Study N=569) [57]

Hypertension

a) Incidence: Greater than 2% to 5.1% [53][57][58]

b) General Information

1) In clinical trials after 4 months of treatment, systolic blood pressure increased by an average of 4.9 mmHg and 2.8 mmHg [57], and 4.3 mmHg and 4.8 mmHg [53], as measured by ambulatory blood pressure monitoring and blood pressure cuff, respectively; and average blood pressure had not plateaued by trial termination [57].

2) Led to initiation of antihypertensive medication or intensification of preexisting antihypertensives medications in 7% of patients in clinical trials over 4 months [57].

3) Increases risk for major adverse cardiovascular events (MACE), with greatest risk in patients with established cardiovascular disease or risk factors for cardiovascular disease [53][57].

4) In some patients, increase in blood pressure may be too small to detect, but may still increase the risk for MACE [53][57].

5) Increases in blood pressure were larger in patients with a history of hypertension [57].

c) Management

1) Treat new-onset or exacerbations of preexisting hypertension [53][57].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 5.1% with testosterone undecanoate (Study N=138); lead to treatment discontinuation in 1.4% [53]

2) Testosterone replacement (Jatenzo(R), oral route): 3.6% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): At least 3% [58]

Myocardial infarction

a) General Information

1) May increase risk of major adverse cardiovascular events, such as myocardial infarction [53][58].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dermatologic Effects

Testosterone

Acne

a) Incidence: Up to 8% [25][28][87][100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route) Less than 1% [100]

2) Replacement therapy (topical route): Less than 1% [25]

3) Replacement therapy (topical route): 1% to 8% (incidence increases with increasing dose) [87]

4) Replacement therapy (topical route): 2% or less [28]

5) Replacement therapy (topical route): 3.1% [87]

6) Replacement therapy (topical route): At least 2 out of 155 patients [99]

c) Adult Case Reports

1) Acne fulminans on face and shoulders developed in a 21-year-old man following self-administration of testosterone or other anabolic steroids for 4 weeks [112].

Alopecia

a) Incidence: Up to 1% [87]
b) General Information

1) Hair loss has been reported with anabolic steroid use [102].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Up to 1% [87].

Application site erythema

a) Incidence: 5% to 7% [99][100]
b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (topical route): 5% to 7% [99]

2) Replacement therapy (transdermal route): 7% [100]

Application site irritation

a) Incidence: Up to 8% [28][99]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 0.9% [28]

2) Replacement therapy (topical route): 7% to 8% [99]

Application site reaction

a) Incidence: 2% to 16.1% [110][25]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 16.1% with testosterone gel (N=149) [110]

2) Replacement therapy (topical route): 2% to 4% vs 3% with placebo [25]

Burning pain

a) Incidence: 3% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 3% [100]

Contact dermatitis

a) Incidence: 2.1% to 4% [28][100]
b) General Information

1) Nonscrotal systems produced contact allergy and more topical irritation than scrotal systems in one study [111].

c) Adult Clinical Trials

1) Replacement therapy (topical route): 2.1% vs 0% with placebo [28].

2) Replacement therapy (transdermal route): 4% [100].

Erythema, Generalized

a) Adult Clinical Trials

1) Replacement therapy (topical route): At least 2 out of 155 patients [99]

Flushing

a) Adult Clinical Trials

1) Replacement therapy (topical route): Hot flushes, 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Injection site pain, Intramuscular injection

a) General Information

1) Inflammation and pain at the site of IM injection has been reported [88][94].

Pruritus

a) Incidence: 37% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 37% [100]

2) Replacement therapy (topical route): Pruritus, 1.9% [87]

Psoriasis

a) Adult Case Reports

1) Exacerbation of psoriasis was precipitated by an estradiol 50 mg/testosterone 100 mg implant in a 47-year-old woman [113].

Rash

a) Incidence: 2% [100]

b) Prevention and Management

1) Applying a small amount of 0.1% triamcinolone acetonide cream to the skin under the central drug reservoir of the Androderm(R) system has been shown to reduce the incidence and severity of skin irritation, and does not significantly alter transdermal absorption of testosterone from the system (Wilson et al, 1998).

2) Ointment formulations should not be used for pretreatment, however, as they may significantly reduce testosterone absorption (Wilson et al, 1998).

c) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Scab of skin, Nasal

a) Incidence: 3.8% to 5.8% [22]

b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 5.8% [22]

Skin eschar

a) Adult Case Reports

1) A 78-year-old man who received testosterone 5 mg transdermal patches for hypogonadism experienced occasional irritation and subsequent eschar formation at the application site [114].

Testosterone Cypionate

Acne

a) Acne may occur in patients receiving testosterone cypionate [83].

Alopecia

a) Male pattern baldness may occur in patients receiving testosterone cypionate [83].

Hirsutism

a) Hirsutism may occur in patients receiving testosterone cypionate [83].

Injection site inflammation

a) Inflammation at the injection site may occur in patients receiving testosterone cypionate [83].

Injection site pain

a) Pain at the injection site may occur in patients receiving testosterone cypionate [83].

Seborrheic dermatitis

a) Seborrhea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Acne

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Alopecia

a) General Information

1) Male pattern baldness has been reported following administration of testosterone enanthate [73].

Erythema at injection site

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Hirsutism

a) General Information

1) Hirsutism has been reported following administration of testosterone enanthate [73].

Injection site bruising

a) Incidence: 3.8% to 6.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 6.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Injection site hemorrhage

a) Incidence: 3.3% to 6% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 6% with testosterone enanthate (n=133) [74]

Injection site inflammation

a) General Information

1) Inflammation at the injection site has been reported following administration of testosterone enanthate [73].

Injection site pain

a) General Information

1) Pain at the injection site has been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Acne

a) Incidence: 5.2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 5.2% with testosterone undecanoate (Study N=153) [59]

Erythema at injection site

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hyperhidrosis

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Injection site pain

a) Incidence: 4.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Endocrine/Metabolic Effects

Testosterone

Decreased body growth

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Gynecomastia

a) Incidence: 1% to 3% [25][86][87]
b) General Information

1) May occur with testosterone therapy for hypogonadism [23][25][22][100][94][88]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

c) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

d) Adult Clinical Trials

1) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

2) Replacement therapy (topical route): 1% to 3% [87]

Hypercalcemia

a) General Information

1) Increased risk among those with cancer [23][25][22] and immobilized patients [88][94].

b) Prevention and Management

1) Regularly monitor at-risk patients [23][25][22]

2) Discontinue if condition occurs [88][94]

Hyperthyroidism

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Hypokalemia

a) Adult Clinical Trials

1) Replacement therapy (topical route): Abnormal laboratory tests including hypokalemia, less than 1% [87]

Increased glucose level

a) General Information

1) Insulin sensitivity or glycemic control may change in patients treated with androgens [25][87].

2) In diabetic patients, the metabolic effects of androgens may decrease blood glucose and, therefore, insulin requirements [25][87].

b) Adult Clinical Trials

1) Replacement therapy (topical route): Increased blood glucose in at least 2 of 155 patients [85]

2) Replacement therapy (topical route): Abnormal laboratory tests, including elevated glucose levels in less than 1% [87]

Lipids abnormal

a) Incidence: Up to 2% [28]

b) General Information

1) The serum lipid profile may change[23], including lipid abnormalities, such as LDL-C elevations and severe HDL-C reductions [102].

c) Prevention and Management

1) Monitor lipid profiles periodically, especially after treatment initiation [23][25] [22] and with dosage increases [25].

2) Discontinuation may be required with changes in serum lipid profile [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Hyperlipidemia, up to 2% [28]

2) Replacement therapy (topical route): Changes in serum lipid levels (ie, hyperlipidemia, elevated triglycerides, and decreased HDL), less than 1% [87]

Thyroxine transport defect

a) General Information

1) Androgens may decrease thyroxine-binding globulin concentrations [25][22] [23]; however, there has been no clinical evidence of thyroid dysfunction with androgen use [23].

Testosterone Cypionate

Gynecomastia

a) General Information

1) Gynecomastia may occur in patients receiving testosterone cypionate [83].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Testosterone Enanthate

Hypercalcemia

a) General Information

1) Hypercalcemia has been reported following administration of testosterone enanthate. If hypercalcemia occurs, therapy should be discontinued [73].

b) Prevention

1) Use caution in cancer patients at risk for hypercalcemia [74]

Hypernatremia

a) General Information

1) Sodium and water retention has been reported following administration of testosterone enanthate. In patients with preexisting cardiac, renal, or hepatic disease, there is an increased risk of edema with or without congestive heart failure [73].

Increased cholesterol esters

a) General Information

1) Increased serum cholesterol has been reported following administration of testosterone enanthate [73].

b) Management

1) Adjustment of lipid lowering therapy or discontinuation of testosterone therapy may be necessary [74]

Increased testosterone level

a) Incidence: 2.7% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Testosterone Undecanoate

Decreased HDL level

a) Incidence: 3% [57]

b) Management

1) Adjustment of lipid lowering drugs may be necessary [57].

2) Discontinuation may be necessary [57].

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 3% with testosterone undecanoate (Study N=166) [57]

Diabetes mellitus

a) Postmarketing

1) Diabetes mellitus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Disorder of lipid metabolism

a) General Information

1) Changes in serum lipid profile may occur [53][57].

b) Management

1) Adjustment of lipid lowering drugs may be necessary [53][57].

2) Discontinuation may be necessary [53][57].

Gynecomastia

a) General Information

1) May develop and persist in patients being treated for hypogonadism [53][57][59]

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

c) Postmarketing

1) Gynecomastia was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Hyperprolactinemia

a) Incidence: 6.3% [53]
b) General Information

1) The mean increase from baseline in serum prolactin was 7 nanograms/mL in a 24-day study (Study N=93) [53]

c) Management

1) If serum prolactin remains elevated, discontinue [53]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): 6.3% with testosterone undecanoate (Study N=93) [53]

Increased estradiol level

a) Incidence: 2.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Weight increased

a) Incidence: 1.3% to 2.1% [53][59]
b) General Information

1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]

c) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

2) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Gastrointestinal Effects

Testosterone

Decrease in appetite

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

Diarrhea

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 3% to 4% [85]

Gastrointestinal hemorrhage

a) Incidence: 2% [100]
b) Adult Clinical Trials

1) Replacement therapy (transdermal route): 2% [100]

Lip swelling

a) Postmarketing

1) Has been reported during postmarketing use [23].

Nausea

a) General Information

1) May occur with injectable, topical, and intranasal forms [22][87][88][94]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): 1 patient [22]

c) Adult Postmarketing

1) Nausea has been reported [87]

Oral irritation

a) Incidence: 9.2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days [108]
2) Tenderness generally resolved in 1 to 14 days [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum or mouth irritation, 9.2% [108]

Sore gums

a) Incidence: 3.1% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): Gum pain and tenderness: 3.1% [108]

Stomatitis

a) Postmarketing
1) Has been reported during postmarketing use [23]

Swollen gums

a) Incidence: 2% [108]
b) General Information
1) Irritation generally resolved in 1 to 8 days, and tenderness generally resolved in 1 to 14 days for the buccal system [108]
c) Adult Clinical Trials
1) Replacement therapy (buccal route): 2% [108]
d) Postmarketing
1) Gingival swelling has been reported during postmarketing use [23].

Taste sense altered

a) Incidence: 1% to 4.1% [25][22]
b) General Information
1) Cause of treatment discontinuation with intranasal form [22]
c) Adult Clinical Trials
1) Replacement therapy (topical route): Taste disorder, 1% vs 0% with placebo [25]
2) Replacement therapy (intranasal route): Dysgeusia, less than 3%, with treatment discontinuation in 1 patient [22]
3) Replacement therapy (buccal route): Bitter taste or taste perversion, 2% to 4.1% [108]
d) Postmarketing
1) Dysgeusia has been reported during postmarketing use [23].

Ulcer of mouth

a) Postmarketing
1) Has been reported during postmarketing use [23]

Vomiting

a) Incidence: 3% to 4% [85]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 3% to 4% [85]

Xerostomia

a) Postmarketing
1) Dry mouth has been reported during postmarketing use [23].

Testosterone Cypionate

Nausea

a) Nausea may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Abdominal pain

a) Incidence: 2% [74]
b) Adult Clinical Trials
1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Nausea

a) Incidence: 2.3% [74]
b) General Information
1) Nausea has been reported following administration of testosterone enanthate [73].
c) Adult Clinical Trials
1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Diarrhea

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Gastric ulcer with hemorrhage

a) General Information
1) Led to discontinuation in 1.1% of patients in a clinical trial (Study N=95) [53]

Indigestion

a) Incidence: Greater than 2% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Nausea

a) Incidence: Greater than 2% to 2.4% [57]
b) Adult Clinical Trials
1) Testosterone replacement (oral route): 2.4% with testosterone undecanoate (Study N=166) [57]
2) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Hematologic Effects

Testosterone

Deep venous thrombosis

a) General Information
1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]
b) Prevention and Management
1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [17][2][1][14][16][5][15][3][18]
2) Evaluate for pulmonary embolism in patients with acute shortness of breath [17][2][1][14][16][5][15][3][18]
3) Discontinue if condition suspected and initiate workup and management [17][2][1][14][16][5][15][3][18]
c) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of

treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported [17][2][1][14][16][5][15][3][18]

Erythrocytosis

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

2) Polycythemia has been reported with injectable testosterone [94][88].

b) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51]

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): Hematocrit increase, four subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%. No hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): Hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): Hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

d) Adult Case Reports

1) Two cases of IM testosterone-induced polycythemia were reported to have been reversed by switching to transdermal testosterone [95].

2) A report of secondary polycythemia characterized by increases in RBC, hemoglobin, hematocrit, and red cell volume with decreases in serum B12 levels and erythropoietin was documented following the use of transdermal testosterone patches (10 mg androstanolone daily) in a 73-year-old man [96].

Hematocrit - PCV - high

a) Incidence: 4% to 7% [85]

b) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85][23].

c) Prevention and Management

1) Assess hematocrit level at baseline and repeat 3 to 6 months after treatment initiation [25][51][85] and annually thereafter [25][22][51][23].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose reduction or interruption may be required if condition occurs [25][22][51][85]; therapy may resume when hematocrit decreases to an acceptable level [25][23].

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): hematocrit increase, 4 subjects developed hematocrit levels above 55% from baseline levels of 48% to 51%; no hematocrit levels exceeded 58% [22]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

3) Replacement therapy (topical route): hematocrit increase, 4% to 7% [85]

4) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

e) Postmarketing

1) Red blood cell increase has been reported in postmarketing use [23].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy have been reported [94][88].

Increased hemoglobin

a) Adult Clinical Trials

1) Replacement therapy (topical route): hematocrit or hemoglobin increase, 2.1% vs 0% with placebo [28]

2) Replacement therapy (topical route): hematocrit or hemoglobin increase, 1% to 2% vs 0% with placebo [25][86]

b) Adult Case Reports

1) Replacement therapy (topical route): Hemoglobin increases were reported in at least 2 men with 120 days of treatment [85].

Venous thromboembolism

a) General Information

1) Polycythemia (increases in RBC mass) may increase risk of thromboembolic events [25][22][51][85]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate for DVT if lower-limb warmth, pain, erythema, or edema develop [25] [22]

2) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]

3) Discontinue if thromboembolic event suspected and initiate workup and management [25][22]

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported with testosterone products [25][22]

Testosterone Cypionate

Deep venous thrombosis

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Erythrocytosis

a) General Information

1) Polycythemia may occur in patients receiving testosterone cypionate [83].

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

b) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy may occur with testosterone cypionate [83].

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Erythrocytosis

a) Incidence: 1.8% to 2% [74]

b) General Information

1) Polycythemia has been reported following administration of testosterone enanthate [73].

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Ensure hematocrit is not elevated prior to initiating therapy [74].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Interruption or discontinuation of therapy may be necessary [74].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 1.8% with testosterone enanthate in pooled studies (n=283) [74]

Hematocrit - PCV - high

a) Incidence: 8.3% to 14% [74]

b) General Information

1) In clinical studies; treated resulted in mean hemotocrit increases of 3.8 +/- 3.4% at 6 months and 5.4+/- 3.4% at 1 year [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Management

1) Intervention is required if hematocrit is 54% or greater during treatment, such as dose reduction or temporary discontinuation [26].

d) Adult Clinical Trials

1) Hypogonadism (subQ route): Hematocrit increased, 14% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): Hematocrit increased, 8.3% with testosterone enanthate (n=133) [74]

3) Hypogonadism (subQ route): Hematocrit increased to 55% or greater, 4.2% with testosterone enanthate in pooled studies (n=283) [74]

Hemorrhage

a) General Information

1) Suppression of clotting factors II, V, VII and X, and bleeding in patients receiving concomitant anticoagulant therapy has been reported with testosterone enanthate [73].

Increased hemoglobin

a) General Information

1) In clinical studies, mean hemoglobin increases of 1 +/- 1.1 g/dL at 6 months and 1.1 +/- 1.4 g/dL at 1 year were reported [74]

2) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following

IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

3) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

Increased white blood cell count

a) General Information

1) Mild but significant increases in mean WBC, RBC, hematocrit, and hemoglobin concentrations in 33 male subjects (aged 21 to 39 years) were reported following IM testosterone enanthate 200 mg every 3 weeks or 4 weeks for 24 weeks. Negligible changes occurred in mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration. Although significant increases occurred in blood parameters in these individuals, clinical manifestations were not apparent [121].

Thromboembolic disorder

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Testosterone Undecanoate

Deep venous thrombosis

a) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT [53][57][58].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215) -control (n=909,530) population-based study; a trend of decreased

risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][58].

Erythrocytosis

a) Incidence: Greater than 2% [57]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Monitor hematocrit levels at baseline and during therapy [92].

2) Intervention is required if hematocrit is 54% or greater during treatment [26].

3) Dose interruption or discontinuation may be necessary [53][92]

d) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

e) Postmarketing

1) Polycythemia was reported during postmarketing surveillance [92]

Hematocrit - PCV - high

a) Incidence: 1.3% to 4.8% [53][57][92]
b) General Information

1) Hematocrit elevations, which reflect increased red blood cell mass, may increase the risk of thromboembolic events [53][92][92]

2) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Prevention and Management

1) Intervention is required if hematocrit is 54% or greater during treatment [26].

2) Increases in hematocrit, reflective of increases in red blood cell mass, may necessitate lowering of the dose or permanent discontinuation of therapy [53][57][92].

d) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 4.3% with testosterone undecanoate (Study N=138) [53]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166) [57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

4) Hypogonadism (IM route): 1.3% [92]

Increased hemoglobin

a) Incidence: 2% [92]
b) General Information

1) Risk of treatment-induced increases in hemoglobin and hematocrit is greatest with injectable testosterone [26]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 2% [92]

Venous thromboembolism

a) General Information

1) Transgender

a) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with

reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Prevention and Management

1) Evaluate patients who experience symptoms of pain, edema, warmth, and erythema in the lower extremity for DVT and those who present with shortness of breath for pulmonary embolism [53][57].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57].

c) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

d) Postmarketing

1) There have been postmarketing reports of venous thromboembolic events, including DVT and pulmonary embolism, in patients using testosterone replacement [53][57].

Hepatic Effects

Testosterone

Cholestatic jaundice syndrome

a) General Information

1) Cholestatic hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88]

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

c) Pediatric Case Reports

1) Fanconi anemia: Multiple hepatic tumors with cholestasis and peliosis hepatitis were reported in a 13-year-old boy following several years of androgen and corticosteroid therapy, including testosterone propionate 20 mg/day [109].

Jaundice

a) General Information

1) Jaundice may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23].

b) Prevention and Management

1) Discontinue use immediately if jaundice occurs [23].

Liver carcinoma

a) General Information

1) Hepatocellular carcinoma has been reported rarely in patients receiving long-term oral therapy with androgens in high doses; androgen withdrawal did not lead to regression of the tumors in all cases[86][87][100][88][94].

Liver function tests abnormal

a) General Information

1) Alterations in liver function tests have occurred with testosterone therapy [94] [88].

b) Postmarketing

1) Abnormal liver function tests (eg, transaminases, elevated GGTP, and bilirubin) have been reported during postmarketing surveillance of testosterone gel [87].

Neoplasm of liver

a) General Information

1) Hepatic neoplasms may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue if condition occurs [23][25][22]

Peliosis hepatis

a) General Information

1) Life-threatening peliosis hepatitis may develop with prolonged use of high-dose of orally active 17-alpha-alkyl-androgens [23][25][22][86][87][100][94][88].

b) Prevention and Management

1) Discontinue use if condition occurs [25][22][23]

Testosterone Cypionate

Cholestatic jaundice syndrome

a) Cholestatic jaundice may occur in patients receiving testosterone cypionate [83].

Liver function tests abnormal

a) Altered liver function tests may occur in patients receiving testosterone cypionate [83].

Neoplasm of liver

a) Hepatocellular neoplasm may rarely occur in patients receiving testosterone cypionate [83].

Peliosis hepatis

a) Peliosis hepatis may rarely occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Hepatotoxicity

a) Adult Case Reports

1) A 26-year-old body builder developed toxic hepatitis with hepatocellular necrosis after self-administration of stanozolol 40 mg/day, IM testosterone enanthate 500 mg twice weekly, and oral methylandrostenediol 30 mg/day for 5 weeks. On admission to the hospital, the patient's AST and ALT levels were 5870 and 10,580 international units/L, respectively. The patient's bilirubin and alkaline phosphatase were also elevated. Liver biopsy showed toxic hepatic lesions. After supportive care and within 12 weeks of discontinuation of androgenic/anabolic steroids, clinical signs and laboratory findings improved substantially [122].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

2) Cholestatic jaundice has been reported following administration of testosterone enanthate [73].

3) Jaundice is reversible with drug therapy discontinuation [73].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74][73].

c) Adult Case Reports

1) A case of anabolic steroid-induced cholestasis was reported in a 29-year-old male bodybuilder. Following self-administered testosterone enanthate injections once weekly for 4 weeks, the patient developed pruritus and deep jaundice. These symptoms, along with weight loss, persisted for 2 months. After this time period, the patient received corticosteroids and complete resolution of jaundice occurred within 2 weeks [123].

Liver function tests abnormal

a) General Information

1) Altered liver function tests have been reported in patients receiving testosterone enanthate [73].

b) Management

1) If altered liver function tests occur, therapy should be discontinued and etiology determined [73].

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [74][108].

3) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Peliosis hepatis

a) General Information

1) Peliosis hepatitis has rarely been reported following administration of testosterone enanthate [73].

2) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects (peliosis hepatis, hepatic neoplasms, cholestatic hepatitis, and jaundice) [74].

3) May be life-threatening or fatal [74]

b) Management

1) Promptly discontinue use if signs or symptoms of hepatic dysfunction occur [74].

Testosterone Undecanoate

Cholestatic hepatitis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Hepatitis, Peliosis

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including peliosis hepatitis; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) May be life-threatening or fatal [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Jaundice

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including jaundice; testosterone undecanoate has not been reported to cause this adverse event [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Malignant neoplasm of liver

a) General Information

1) Prolonged use of high doses of orally active 17-alpha-alkyl androgens (eg, methyltestosterone) has been associated with serious hepatic adverse effects including hepatic neoplasms; testosterone undecanoate has not been reported to cause this adverse event [53][57].

2) Long-term therapy with IM testosterone enanthate has produced multiple hepatic adenomas [53][57].

b) Prevention and Management

1) Promptly discontinue use if suspected [53][57].

2) Advise patients to report any signs or symptoms of hepatic dysfunction [53][57].

Immunologic Effects

Testosterone

Hypersensitivity reaction

a) General Information

1) Allergic reaction (eg, hives, lip and tongue swelling) cause of treatment discontinuation with intranasal form [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Allergic reaction was cause of treatment discontinuation in 1 patient [22]

Testosterone Cypionate

Hypersensitivity reaction

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Non-allergic anaphylaxis

a) Hypersensitivity reactions, including anaphylactoid reactions, may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Non-allergic anaphylaxis

a) General Information

1) Anaphylactoid reactions have rarely been reported following administration of testosterone enanthate [73].

Testosterone Undecanoate

Anaphylaxis

a) General Information

1) Anaphylaxis may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Anaphylaxis occurred in 2 hypogonadal men who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Episodes of anaphylaxis, including life-threatening reactions, were reported during postmarketing surveillance [59].

Hypersensitivity reaction

a) Postmarketing

1) Hypersensitivity was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Systemic lupus erythematosus

a) Postmarketing

1) Systemic lupus erythematosus was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Musculoskeletal Effects

Testosterone

Advanced bone age

a) General Information

1) May accelerate bone maturation and cause premature closure of epiphyses in pediatric patients [25][22][88]

2) Use in pediatric patients may reduce adult stature, with greatest impact among youngest children [88]

b) Pediatric Clinical Trials

1) Replacement therapy: Height stunting in adolescents has been reported with anabolic steroid use [102]

Myalgia

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): Cause of treatment discontinuation in combination with arthralgia, fever, chills, and petechiae in 1 patient [22]

Pain in limb

a) Incidence: 4.3% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Pain in extremity, 4.3% [22]

Testosterone Enanthate

Arthralgia

a) Incidence: 2% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Backache

a) Incidence: 3.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3% with testosterone enanthate (n=150) [74]

Increased creatine kinase level

a) Incidence: 3.3% to 3.8% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 3.3 with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3.8% with testosterone enanthate (n=133) [74]

Testosterone Undecanoate

Musculoskeletal pain

a) Incidence: 2.1% [53]
b) Adult Clinical Trials

1) Testosterone replacement (oral route): 2.1% with testosterone undecanoate (Study N=95) [53]

Neurologic Effects

Testosterone

Amnesia

a) Incidence: Less than 1% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [17][2][1][14][16][5][15][3][18].

2) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Adult Clinical Trials

1) Low serum testosterone levels: increased risk of myocardial infarction, stroke, and all-cause mortality, 29% during a median of 531 days after coronary angiography [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 21% increased risk of stroke compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of stroke between the transdermal gel or patch [105].

c) Adult Case Reports and Postmarketing

1) Has been reported [17][2][1][14][16][5][15][3][18]

2) A cerebrovascular accident involving the basal ganglia and internal capsule was reported in a 21-year-old man without other predisposing factors for thromboembolism [107]

Headache

a) Incidence: 1% to 6% [25][22][85][86][87][100][108]
b) General Information

1) One of the most common adverse reactions and cause of treatment withdrawal with intranasal form [22]

2) Has been reported with administration via injection, intranasal, or topical routes

[22][85][86][87][100][108]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3%, with treatment withdrawal in 1 patient [22]

2) Replacement therapy (topical route): 5% to 6% [85]

3) Replacement therapy (topical route): 1% vs 0% with placebo [25][86]

4) Replacement therapy (topical route): 0% to 4% [87]

5) Replacement therapy (transdermal route): 4% [100]

6) Replacement therapy (buccal route): 3.1% [108]

Insomnia

a) Incidence: Up to 2% [25][28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]

2) Replacement therapy (topical route): 2% or less [28].

Paresthesia

a) Incidence: Less than 1% [87][100]

b) General Information

1) Generalized paresthesias have been reported with oral testosterone and testosterone injections [94].

c) Adult Clinical Trials

1) Replacement therapy (topical route): Less than 1% [87]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Anxiety

a) General Information

1) Has occurred with some androgens [83]

Cerebrovascular accident

a) General Information

1) Has occurred with some androgens [82]

2) Increased risk of major adverse cardiovascular events reported in some, but not all, studies of testosterone replacement therapy in men [82]

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

Headache

a) General Information

1) Has occurred with some androgens [83]

Paresthesia

a) General Information

1) Has occurred with some androgens [83]

Testosterone Enanthate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [75].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [75]

Headache

a) Incidence: 5.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 5.3% with testosterone enanthate (n=150) [74]

Insomnia

a) Incidence: 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Paresthesia

a) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Testosterone Undecanoate

Cerebrovascular accident

a) General Information

1) May increase risk of major adverse cardiovascular events, such as stroke [53] [58].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [97].

b) Postmarketing

1) Has been reported [53][57][58]

Dizziness

a) General Information

1) Led to discontinuation in 1 patient in a clinical trial (Study N=138) [53]

Headache

a) Incidence: Greater than 2% to 4.8% [53][57]
b) Adult Clinical Trials

1) Testosterone replacement (Tlando(R), oral route): 2.1% with testosterone undecanoate (Study N=95) [57]

2) Testosterone replacement (Jatenzo(R), oral route): 4.8% with testosterone undecanoate (Study N=166); led to treatment discontinuation in 1.2% of patients[57]

3) Testosterone replacement (Jatenzo(R), oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Insomnia

a) Incidence: 2% [58]
b) General Information
1) Led to treatment discontinuation in 1 patient in a clinical trial (Study N=138) [53]
c) Adult Clinical Trials
1) Hypogonadism (IM route): 2% [58]

Transient ischemic attack
a) Postmarketing
1) Has been reported [58]

Psychiatric Effects

Testosterone

Anxiety
a) Incidence: Less than 1% [87]
b) General Information
1) Anxiety has been reported with injectable and buccal testosterone [108][88][94].
c) Adult Clinical Trials
1) Replacement therapy (topical route): At least 2 out of 155 patients [85]
2) Replacement therapy (topical route): Less than 1% [87]

Depression
a) Incidence: 3% [100]
b) General Information
1) Depression has been reported with injectable testosterone [88][94].
c) Adult Clinical Trials
1) Replacement therapy (transdermal route): 3% [100]
2) Replacement therapy (buccal route): 1 of 117 patients treated for at least 6 months [108]

Dream disorder
a) Incidence: 1.3% [110]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Abnormal dreams, 1.3% with testosterone gel (N=149) [110]

Hostile behavior
a) Incidence: Less than 1% [87]
b) Adult Clinical Trials
1) Replacement therapy (topical route): Hostility, less than 1% [87]

Mood swings
a) Incidence: Up to 1% [25]
b) Adult Clinical Trials
1) Replacement therapy (topical route): 0% to 1% vs 0% with placebo [25]
2) Replacement therapy (topical route): Emotional lability, 2.6% vs 0% with placebo [28]

Testosterone Cypionate

Depression
a) Depression may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Anxiety
a) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

b) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Depression

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Depression leading to discontinuation occurred in 2 patients in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

c) Adult Clinical Trials

1) Hypogonadism (IM route): has been reported [73].

Suicidal thoughts

a) General Information

1) Depression and suicidal ideation and behavior have been reported [74].

2) Suicide attempts (1 complete and 1 incomplete) were reported in pooled results from clinical studies (n=283) [74].

b) Management

1) Advise patients to seek medical attention for manifestations of suicidal ideation or behavior, new onset or worsening depression, anxiety, or other mood changes [74].

Testosterone Undecanoate

Aggressive behavior

a) Incidence: 1.3% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Depression

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Irritability

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Mood swings

a) Incidence: 2% [59]

b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Suicidal thoughts

a) General Information

1) Has been reported [57]

b) Prevention and Management

1) Advise patients to seek medical attention for new onset or worsening of depression, suicidal ideation or behavior, anxiety, or other mood changes [57].

Renal Effects

Testosterone

Increased frequency of urination

a) Incidence: Up to 2% [28]
b) Increased frequency of urination

1) Replacement therapy (topical route): 2% or less [28]

Testosterone Enanthate

Hematuria

a) Incidence: 2% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

Urinary tract infectious disease

a) Incidence: 2.7% to 3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reproductive Effects

Testosterone

Atrophy of testis

a) Adult Clinical Trials

1) Replacement therapy (intranasal route): Testicular atrophy in 1 patient [22]

b) Adult Postmarketing

1) Reported during postmarketing surveillance of testosterone gel [87]

Azoospermia disorder

a) General Information

1) Azoospermia may occur with exogenous androgen administration [22]

Benign prostatic hyperplasia

a) Incidence: Up to 2% [28]
b) General Information

1) Patients with benign hyperplasia are at an increased risk of exacerbation with androgen treatment [23][25][22][51][22].

2) Geriatric patients are at greater risk for benign prostatic hyperplasia [22] and prostatic hypertrophy [86].

c) Prevention and Management

1) Monitor for worsening signs and symptoms [23][25][22][51].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Up to 2% [28]

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Drug-induced virilization

a) General Information

1) Virilization in children who were secondarily exposed to testosterone gel has been reported [25][85][87]. [87].

2) Reported signs and symptoms have included enlargement of the penis or clitoris, premature development of pubic hair, increased erections and libido, aggressive behavior, and advanced bone age [87].

3) Upon removal of the testosterone gel exposure, signs and symptoms regressed in a majority or cases. However, in a few cases, enlarged genitalia did not fully return to age-appropriate normal size, and bone age remained modestly greater than chronological age [87].

4) In some cases, direct contact with the application site of testosterone gel was reported, and in at least one case, exposure was suspected to be secondary to exposure to the testosterone gel user's shirt, towels, and/or sheets [87].

5) Amenorrhea, menstrual irregularities, the inhibition of gonadotropin secretion, and virilization are the most common side effects of androgen therapy in women [88].

Large prostate

a) Incidence: 11.7% [87]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 11.7% [87]

Oligozoospermia

a) General Information

1) Oligospermia may occur with high-dose androgen treatment [25][22] for prolonged periods [94][88].

2) Large doses of androgens may suppress spermatogenesis and adversely affect semen, including decreased sperm count [23].

b) Adult Postmarketing

1) Oligospermia has been reported [87].

Penile erection, Spontaneous

a) Incidence: 1% [90]
b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% with testosterone 50 mg (n=103) and 0% with testosterone 100 mg (n=149) vs 0% with placebo (n=99) [90]

Priapism

a) Pediatric Case Reports and Postmarketing

1) A case of priapism was reported in a 15-year-old boy following the administration of an IM injection of Triolandren(R), a combination of testosterone esters [116].

2) Priapism has been reported during postmarketing surveillance [87].

Prostate cancer

a) Incidence: Up to 1.2% [51][100]
b) General Information

1) Androgen treatment increases risk for prostate cancer [23][25][22][51].

2) Geriatric patients are at increased risk for prostatic carcinoma [86].

3) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement

therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

c) Prevention and Management

1) Contraindicated in patients with prostate cancer [23][25][22]

2) Evaluate patients at baseline [23], within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22].

d) Adult Clinical Trials

1) Replacement therapy (topical route): Prostatic carcinoma, 1.2% [51]

2) Replacement therapy (transdermal route): Prostatic carcinoma, less than 1% [100]

e) Adult Postmarketing

1) Replacement therapy: Two cases of prostatic adenocarcinoma and one case of chronic impotence occurred in 3 men during testosterone treatment [118]

2) Impotence (IM route): Adenocarcinoma developed in a 58-year-old man treated with testosterone 180 mg every 2 weeks [119]

Raised prostate specific antigen

a) Incidence: 1% to 11.1% [22][28][85]

b) General Information

1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]

c) Prevention and Management

1) Evaluate for prostate cancer at baseline, within 3 to 6 months of treatment initiation, and thereafter per screening guidelines [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 5.1% to 5.8%, with mean serum PSA level increases of 0.1 to 0.2 ng/mL; and treatment discontinuation in 1 patient [22]

2) Replacement therapy (topical route): PSA level increase, 11.1% (mean 0.14 nanograms/mL) vs 0% (mean 0.12 ng/mL) with placebo [28]

3) Replacement therapy (topical route): PSA levels increased by a significant 21.9% (between 0.19 to 0.61 nanograms/dL) from baseline in treatment-inexperienced men with baseline testosterone levels of less than 250 ng/mL; nonsignificant elevations in PSA levels occurred in men with baseline testosterone levels of 250 ng/dL or more. PSA levels significantly decreased in both groups over 12 months of treatment [120].

4) Replacement therapy (topical route): 1% to 4% [85]

5) Replacement therapy (topical route): Serum PSA levels increased by 18%, with a significant 0.26 ng/mL increase during the initial 6 months of treatment and an overall mean change from baseline of 0.11 ng/mL over 3 years. Prostate cancer was detected in 2 patients [87].

Reduced libido

a) Incidence: Up to 2% [28]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 2% or less [28]

2) Replacement therapy (transdermal route): Less than 1% [100]

Testosterone Cypionate

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative

invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) Excessive frequency and duration of penile erections may occur in patients receiving testosterone cypionate [83].

Increased libido

a) Increased libido may occur in patients receiving testosterone cypionate [83].

Oligozoospermia

a) Oligospermia may occur in patients receiving high doses of testosterone cypionate [83].

Prostate cancer

a) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

Reduced libido

a) Decreased libido may occur in patients receiving testosterone cypionate [83].

Testosterone Enanthate

Amenorrhea

a) General Information

1) Amenorrhea has commonly been reported in female patients following administration of testosterone enanthate [73].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Excessive erection

a) General Information

1) Excessive frequency and duration of penile erections has been reported following administration of testosterone enanthate [73].

Gynecomastia

a) General Information

1) Gynecomastia has been reported [74][73].

2) Symptoms may include breast pain, breast tenderness or nipple tenderness [26]

b) Management

1) If symptoms occur, a period of monitoring based on clinical judgment should be considered as breast symptoms sometimes abate [26].

Increased libido

a) General Information

1) Increased libido has been reported following administration of testosterone enanthate [73].

Oligozoospermia

a) General Information

1) Oligospermia and spermatogenesis has been reported following administration of testosterone enanthate at high doses [74][73].

Priapism

a) Adult Case Reports

1) A case of testosterone-induced priapism was documented in a 23-year-old man with hypergonadotropic hypogonadism. The patient received 250 mg testosterone enanthate IM every 14 days. Upon the fourth injection, a dose of 500 mg was administered at the patient's request. Severe priapism developed 12 hours later, which lasted until the patient presented in the emergency room 36 hours later. Complete detumescence was achieved 17 hours after a corporeal glandular shunt was performed. Two months postoperatively, the patient continued with biweekly testosterone injections at a dose of 250 mg without further incidence of priapism. These data suggest that priapism was related to a high dose of testosterone and that testosterone-induced priapism may be dose-dependent [125].

2) Severe priapism in a 20-year-old man following IM injections of testosterone enanthate 250 mg every 2 weeks has been reported. Three days after the third injection, the patient developed a painful erection that was not accompanied by sexual stimulation. Subsequent conservative therapy failed to reverse the priapism and the patient had to undergo 2 surgical procedures to achieve detumescence [126].

Prostate cancer

a) General Information

1) Patients treated with androgens may be at increased risk for prostate cancer [74].

b) Prevention

1) Evaluate for prostate cancer prior to beginning thearpy [74].

c) Adult Clinical Trials

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs matched control patients without prostate cancer (n=1378) who received testosterone replacement therapy between 2009 and 2012; the risk did not increased when analyzed by form (gel vs other forms) or timing/duration of therapy [117].

d) Adult Case Report

1) A case of prostate cancer was reported in a patient with Klinefelter syndrome who had undergone long-term testosterone replacement therapy since childhood. Intramuscular testosterone enanthate every 1 to 2 weeks was initiated at age 16 and continued for 35 years. The patient's initial prostate-specific antigen (PSA) level at age 49 was 3.6 ng/dL. The following year, his PSA level rose to 5.4 ng/dL and 6 months later, the PSA level reached 12.2 ng/dL. The rise in PSA was accompanied by a slight increase in irritative voiding symptoms and adenocarcinoma was confirmed. Radical prostatectomy was performed and the patient recovered well from surgery. Androgen replacement therapy was not reintroduced until the patient remained recurrence-free for a minimum of 1 year following surgery [127].

Prostatitis

a) Incidence: 2.7% to 3% [74]

b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Raised prostate specific antigen

a) Incidence: 3% to 12% [74]

b) General Information

1) Defined as a increase from baseline of at least 1.4 nanogram (ng)/mL, or greater than 4 ng/mL [74]

2) Led to discontinuation in 4.6% of patients in clinical studies [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 12% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 3% with testosterone enanthate (n=133) [74]

Reduced libido

a) General Information

1) Decreased libido has been reported following administration of testosterone enanthate [73].

Virilization

a) General Information

1) Virilization, including inhibition of gonadotropin secretion, deepening of the voice, and enlargement of the clitoris has commonly been reported in female patients following administration of testosterone enanthate. If administered during pregnancy, virilization of the external genitalia may occur in female fetuses [73].

Testosterone Undecanoate

Benign prostatic hyperplasia

a) General Information

1) Patients treated with androgens are at an increased risk for worsening of signs and symptoms of benign prostatic hyperplasia (BPH) [53][57].

b) Prevention

1) Monitor for worsening signs or symptoms of BPH [53][57]

c) Postmarketing

1) BPH was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Breast cancer

a) Adult Case Reports

1) A 58-year-old female-to-male transsexual patient with a 25-year history of testosterone therapy was found to have breast cancer upon consultation for bilateral mastectomy. The patient had a hysterectomy previously. Preoperative mammography revealed mammary gland involution that was confirmed by ultrasonography, which showed an irregular structure in the in the left breast with a maximum diameter of 7 mm. Upon bilateral mastectomy, histology showed estrogen-receptor positive, progesterone-receptor negative, HER2 negative invasive ductal carcinoma .The mastectomy performed on the left side included axillary lymph node dissection, and the patient received chemotherapy. A recurrence developed about 2 years later, and the patient underwent re-excision, radiotherapy, and tamoxifen therapy; the patient has been in remission since that time [115].

Disorder of ejaculation

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Disorder of prostate, Induration

a) Incidence: 1.3% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Hypogonadism

a) Incidence: 2.6% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2.6% with testosterone undecanoate (Study N=153) [59]

Large prostate

a) Adult Clinical Trials

1) Testosterone replacement (oral route): Greater than 2% with testosterone undecanoate (Study N=569) [57]

Prostate cancer

a) Incidence: 1.3% [59]
b) General Information

1) No significant difference was found in prostate cancer risk in a case control study comparing patients with prostate cancer (n=284) vs controls (n=1378) who received testosterone replacement therapy; the risk did not increased when analyzed by form (gel vs other forms) or timing or duration of therapy [117].

c) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

d) Incidence: 1.3% [59]
e) General Information

1) Patients treated with androgens are at an increased risk for prostate cancer [53][57].

f) Adult Clinical Trials

1) Hypogonadism (IM route): 1.3% with testosterone undecanoate (Study N=153) [59]

Raised prostate specific antigen

a) Incidence: 4.6% [59]
b) General Information

1) Mean increase in prostate specific antigen (PSA) in a clinical trial was 0.2 nanograms (ng)/mL from baseline with testosterone undecanoate (n=161); increases in serum PSA from baseline of at least 1.4 ng/mL or PSA greater than 4 ng/mL occurred in 1.9% of patients [57]

c) Adult Clinical Trials

1) Hypogonadism (IM route): 4.6% with testosterone undecanoate (Study N=153) [59]

Respiratory Effects

Testosterone

Bleeding from nose

a) Incidence: 3.8% to 6.5% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

2) Symptoms usually mild to moderate [22]

c) Prevention and Management

1) Consider further evaluation or possible withdrawal if condition occurs [22]

d) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 6.5% [22]

Bronchitis

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Cough

a) Incidence: Less than 3% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): Less than 3% [22]

Discomfort, Nasal

a) Incidence: 3.8% to 5.9% [22]
b) General Information
1) One of the most common adverse reactions and cause of treatment discontinuation with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Nasal discomfort, 3.8% to 5.9%, with treatment withdrawal in 1 subject [22]

Excoriation of skin, Nasal

a) Adult Clinical Trials
1) Replacement therapy (intranasal route): 1 patient [22]

Nasal congestion

a) Incidence: Up to 3.9% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 3.9% [22]

Nasal discharge

a) Incidence: 3.8% to 7.8% [22]
b) General Information
1) Rhinorrhea was of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): Rhinorrhea, 3.8% to 7.8% [22]

Nasal mucosa dry

a) Incidence: Up to 4.2% [22]
b) Adult Clinical Trials
1) Replacement therapy (intranasal route): More than 2% to 4.2% [22]

Nasopharyngitis

a) Incidence: 3.8% to 8.7% [22]
b) General Information
1) One of the most common adverse reactions with intranasal form [22]
2) Symptoms usually mild to moderate [22]
c) Prevention and Management
1) Consider further evaluation or possible withdrawal if condition occurs [22]
d) Adult Clinical Trials
1) Replacement therapy (intranasal route): 3.8% to 8.7% [22]

Pulmonary embolism

a) Prevention and Management
1) Evaluate for pulmonary embolism (PE) if acute dyspnea develops [25][22]
2) Discontinue if condition suspected and initiate workup and treatment [25][22]
b) Adult Clinical Trials
1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case

(n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Adult Postmarketing

1) Venous thromboembolism, including DVT and PE, has been reported in postmarketing surveillance [25][22]

Sense of smell altered

a) Incidence: 5.8% [22]
b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Parosmia, 5.8% [22]

Sinusitis

a) Incidence: 3.8% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% [22]

Sleep apnea

a) General Information

1) Testosterone may contribute to sleep apnea onset, particularly in at-risk (eg, obesity or chronic lung disease) hypogonadal men [23][25][22][85][86][87].

Upper respiratory infection

a) Incidence: 3.8% to 4.3% [22]
b) General Information

1) One of the most common adverse reactions with intranasal form [22]

c) Adult Clinical Trials

1) Replacement therapy (intranasal route): 3.8% to 4.3% [22]

Testosterone Cypionate

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

Testosterone Enanthate

Cough

a) Incidence: 2.7% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2.7% with testosterone enanthate (n=150) [74]

Pulmonary embolism

a) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis) a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

b) Prevention and Management

1) Evaluate patients with pain, edema, warmth, or erythema in the lower extremity for DVT and those with acute shortness of breath for pulmonary embolism [74].

2) Discontinue use if suspected and initiate appropriate work up and management [74].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing use in patients using testosterone products [74].

Sleep apnea

a) Incidence: 2% [74]

b) General Information

1) Treatment with testosterone products may potentiate sleep apnea [74].

2) Increased likelihood in at risk patients (eg, obesity, chronic lung disease) [74]

c) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

d) Adult Case Reports

1) After receiving intramuscular testosterone enanthate weekly for a period of 10 months as an experimental contraceptive agent, and human chorionic gonadotropin (5000 international units) intramuscularly for 3 months, a 36-year-old moderately obese man began to experience difficulty in sleeping, daytime somnolence, and mood depression. His medical history and physical examination were unremarkable; routine hematologic and blood-chemistry studies were normal. In addition, he had received cimetidine (300 mg 3 times daily) for reflux esophagitis, and amoxapine (150 mg daily) for depression. Upper airway examination had revealed no source of obstruction; however, pulmonary function tests revealed a reduced functional residual capacity consistent with obesity as well as a mild obstructive defect. Sleep studies, testosterone levels, discontinuance of testosterone, and repeat rechallenge confirmed an association with exacerbations of clinical symptoms and testosterone administration. In comparison with normal apnea index values (less than 5 episodes of apnea lasting for more than 10 seconds per hour of sleep), his values increased to 26 and 40 following testosterone administration. Discontinuation of the drug resulted in normalization of most laboratory values (apneic index, total sleep time, free testosterone, hypoxic and hypercapnic ventilatory response, oxygen consumption) within 5 weeks. Complete reversal was achieved after 6 months [124].

Testosterone Undecanoate

Pulmonary embolism

a) Prevention and Management

1) Evaluate patients who present with shortness of breath for pulmonary embolism [53][57][92].

2) Discontinue use and initiate appropriate workup and management if suspected [53][57][58].

b) Adult Clinical Trials

1) Testosterone treatment (multiple routes): VTE (pulmonary embolism and deep vein thrombosis), a significant 63% increased risk during the first 6 months of treatment with testosterone as compared to no testosterone therapy in a case (n=19,215)-control (n=909,530) population-based study; a trend of decreased risk was noted with prolonged (greater than 6 months) or recent (2-year testosterone-free period) testosterone use [98].

c) Postmarketing

1) Venous thromboembolic events, including DVT and pulmonary embolism, have been reported during postmarketing experience [53][57][92].

Pulmonary embolism, Oil microembolism

a) General Information

1) Symptoms such as coughing, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness, and syncope occurred during or immediately after the injection [59].

2) Although the majority of reactions lasted a few minutes and responded to supportive care, some lasted several hours and required emergency intervention and/or hospitalization [59].

3) POME reactions may occur after the first dose or with any injection during the course of therapy [59].

b) Adult Clinical Trials

1) Pulmonary oil microembolism (POME) occurred in 8 hypogonadal men (9 total events) who received IM testosterone undecanoate during 18 clinical trials (n=3556) [59].

c) Postmarketing

1) Serious POME reactions were also reported with testosterone undecanoate 1000 mg IM during postmarketing surveillance [59].

Sleep apnea

a) General Information

1) Treatment of hypogonadal men with testosterone may potentiate sleep apnea in some patients, especially those with risk factors (eg, obesity, chronic lung disease) [53][57][59].

b) Postmarketing

1) Sleep apnea syndrome was reported with IM testosterone undecanoate during postmarketing surveillance [59].

Upper respiratory infection

a) Incidence: 3.6% [53]

b) Adult Clinical Trials

1) Testosterone replacement (oral route): 3.6% with testosterone undecanoate (Study N=138) [53]

Other

Testosterone

Death

a) General Information

1) Risk may be increased following initiation of IM injection versus the transdermal gel [105].

b) Adult Clinical Trials

1) Low serum testosterone levels (unspecified route): increased risk of myocardial infarction, stroke, and all-cause mortality, 29% [103]

2) Unspecified indication (all routes): Initiation of IM testosterone injections was associated with 34% more deaths compared with transdermal gels when assessed over a 1-year followup period. There was no significant difference in the risk of death between the transdermal gel or patch [105].

Pain of breast

a) Incidence: 1% to 3% [87]

b) Adult Clinical Trials

1) Replacement therapy (topical route): 1% to 3% [87]

Persistent pain following procedure

a) Incidence: 4.3% [22]

b) Adult Clinical Trials

1) Replacement therapy (intranasal route): Procedural pain, 4.3% [22]

Testosterone Cypionate

Drug abuse

a) The dependence on a combination of anabolic and androgenic steroids including testosterone cypionate was reported in a 24-year-old, noncompetitive male weight lifter. The patient met the DSM-III-R criteria for psychoactive substance dependence, and appeared depressed with some anxiety. Mild psychomotor retardation was present, and prior to medical examination the patient reported suicidal tendencies [128].

Testosterone Enanthate

Fatigue

a) Incidence: 2% to 2.3% [74]
b) Adult Clinical Trials

1) Hypogonadism (subQ route): 2% with testosterone enanthate (n=150) [74]

2) Hypogonadism (subQ route): 2.3% with testosterone enanthate (n=133) [74]

Neoplasm of liver

a) General Information

1) Hepatocellular neoplasms have rarely been reported following administration of testosterone enanthate [73].

2) Long-term therapy with testosterone enanthate, which elevates blood levels for prolonged periods, has produced multiple hepatic adenomas [108].

Testosterone Undecanoate

Fatigue

a) Incidence: 2% [59]
b) Adult Clinical Trials

1) Hypogonadism (IM route): 2% with testosterone undecanoate (Study N=153) [59]

Black Box Warning

1) Testosterone

a) Topical (Gel/Jelly)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to testosterone gel.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [15][5][18][3][2].

b) Topical (Solution)

Secondary Exposure to Testosterone

Virilization has been reported in children who were secondarily exposed to topical testosterone products.
Children should avoid contact with unwashed or unclothed application sites in men using testosterone topical solution.
Healthcare providers should advise patients to strictly adhere to recommended instructions for use [1].

2) Testosterone Enanthate

a) Subcutaneous (Solution)

1) Warning: Blood Pressure Increases

Testosterone enanthate can cause blood pressure (BP) increases that can increase the risk for major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.

Before initiating testosterone enanthate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.

Starting approximately 6 weeks after initiating therapy, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone enanthate.

Re-evaluate whether the benefits of testosterone enanthate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.

Due to this risk, use testosterone enanthate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [74].

3) Testosterone Undecanoate

a) Intramuscular (Solution)

Serious Pulmonary Oil Microembolism (POME) Reactions and Anaphylaxis

Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose.
Following each injection of testosterone undecanoate, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis.
Because of the risks of serious POME reactions and anaphylaxis, testosterone undecanoate is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the Aveed(R) REMS Program [58].

b) Oral (Capsule)

Warning: Blood Pressure Increases

Testosterone undecanoate can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death, with greater risk for MACE in patients with cardiovascular risk factors or established cardiovascular disease.
Before initiating testosterone undecanoate, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled.
Starting approximately 3 weeks after initiating therapy or changing the dose, periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension in patients on testosterone undecanoate.
Re-evaluate whether the benefits of testosterone undecanoate outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease while on treatment.
Due to this risk, use testosterone undecanoate only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies [57].

REMS

No results available

Drug Interactions (single)

Drug-Drug Combinations

Alclometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Amcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Anisindione

1) Interaction Effect: increased risk of bleeding
2) Summary: A number of case reports have demonstrated that coadministration of oral anticoagulants and 17-alkylated androgens (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) has resulted in a prolonged prothrombin time and hemorrhages[134][135][136][137][138]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may result in bleeding in patients receiving concomitant anticoagulant therapy [139].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of anabolic steroids and anisindione should be avoided when possible. If the drugs must be used together, frequent monitoring of the anticoagulant response must be maintained.
7) Probable Mechanism: unknown
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance dicumarol's anticoagulant activity perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [129][130][131][132][133].

Beclomethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Betamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].

3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Budesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Bupropion

1) Interaction Effect: lowering of the seizure threshold
2) Summary: Concomitant administration of buPROPion and agents that lower seizure threshold, such as systemic steroids, should be undertaken with caution. In addition to using small initial doses and gradual dose increases, follow the dosing regimen recommendation according to each product labeling as xaximum daily dose varies by product formulation and indication[157][158][159][160][161].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: The concurrent administration of buPROPion and systemic steroids should be used with caution. Maximum daily dose varies by product formulation and indication: 1) When coadministration of buPROPion immediate-release (Wellbutrin(R)) is required, do not exceed the total daily dose of 450 mg. Minimize the risk of seizure by giving the daily dose three times daily, and limit each single dose to 150 mg or less[157]. 2) When coadministered with buPROPion extended-release tablets (Wellbutrin XL(R)), do not exceed the total daily dose of 450 mg [158]. 3) Coadministration of sustained-release buPROPion (Wellbutrin SR(R)) should not exceed the total daily maximum of 400 mg, and should be given twice daily. Each single dose should not be higher than 200 mg to minimize high peak concentration of buPROPion [159]. 4) When administration of buPROPion extended-release or sustained-release buPROPion (Zyban(R)) is indicated for smoking cessation, the total daily dose should not exceed more than 300 mg. Give the daily dose twice daily, and limit each single dose to 150 mg or less [160][161]. Furthermore, consider using small initial doses and gradual dose increases.
7) Probable Mechanism: unknown

Ciclesonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clobetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Clocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Corticotropin

1) Interaction Effect: increased risk of edema
2) Summary: Coadministration of testosterone with corticotropin (ACTH) may enhance the formation of edema, especially in the susceptible patient with a history of cardiac or hepatic dysfunction[156].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Testosterone and corticotropin should be co-administered with caution, especially in patients with cardiac or hepatic disease.
7) Probable Mechanism: unknown

Cortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified

5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Cyclosporine

1) Interaction Effect: an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias)
2) Summary: Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity[153][154][155].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If clinically possible, avoid this combination. If these two drugs are given concomitantly, monitor circulating cycloSPORINE levels and adjust cycloSPORINE dosage as necessary; also, monitor patients for increased cycloSPORINE toxicity (renal dysfunction, neurotoxicity).
7) Probable Mechanism: decreased cycloSPORINE metabolism
8) Literature Reports

a) Concomitant administration of cycloSPORINE and anabolic steroids may result in increased cycloSPORINE blood levels and toxicity. This effect has been observed in 2 case studies with methyltestosterone and in 1 case study with danazol [150][151][152].

Dehydroepiandrosterone

1) Interaction Effect: increased risk of adverse androgenic and hepatic effects
2) Summary: Patients electing to take both dehydroepiandrosterone (DHEA) and testosterone are at increased risk for androgenic side effects. Data are conflicting on the extent that DHEA increases the testosterone-epitestosterone (T/E) ratio[174][175]. The effect appears to be dose-dependent, and at doses commonly used by body-builders (e.g. 1000 milligrams), androgenic effects are likely. Concomitant use is not advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of dehydroepiandrosterone (DHEA) and testosterone. DHEA may increase testosterone levels, increasing the incidence of adverse androgenic adverse effects such as oligospermia (in men), gynecomastia, prostatic hypertrophy (especially in elderly males), and virilization in women (deepening voice, hirsutism, acne, clitoromegaly, and menstrual irregularities). Libido may increase or decrease. Adverse hepatic effects may also occur (peliosis hepatitis, hepatic neoplasms).
7) Probable Mechanism: additive androgenic effect, since dehydroepiandrosterone appears to act as a pro-drug for testosterone
8) Literature Reports

a) Dehydroepiandrosterone (DHEA) increased the testosterone-epitestosterone (T/E) ratio in an uncontrolled study of 4 human volunteers. Two over the counter DHEA preparations were used in this study. Nature's Pride "DHEA 50 mg+" (product A) contained DHEA 50 milligrams (mg), suma 25 mg, Korean ginseng 25 mg, muira pauma 25 mg, shitake mushroom concentration 15 mg, and green tea extract 5 mg. The second product, YourLife DHEA (product B), contained DHEA 25 mg as the only active ingredient listed on the label. Neither product contained testosterone as detected by gas chromatography-mass spectrometry (GC-MS) analyses. All subjects (except subject 4) took the product once daily for 4 days at breakfast. Subject 1 (age 47) took both preparations at 3 dosage levels at different times over a 6 month period: product A 50 mg/day, product A 100 mg/day, and product B 150 mg/day for 4 days. Subjects 2 (age 61) and 3 (age 28) took product B 50 mg/day and 100 mg/day, respectively. Subject 4 (age 27) took product A 100 mg/day for 2 days. A 24-hour urine was collected on day 3 and spot urine samples were taken in the morning and evening of day 4. Subject 1 at DHEA doses of 50 mg/day, 100 mg/day, and 150 mg/day had T/E ratios of 8.1, 11.4, and 14.4, respectively, compared to a pre-dose ratio of 2.4. Pre-dose T/E ratios for subjects 2 and 3 were 1.3 and 1.7, respectively, and T/E ratios were 1.6 and 3.9, respectively after DHEA. Subject 4 had a pre-dose T/E ratio of 0.8 and a T/E ratio of 1.1 following DHEA. Ratios exceeding 6:1 are used by several organizations including the United States Military and the International Olympic Committee (IOC) as an indication

that additional tests are warranted to rule out use of exogenous physiological steroids. Manipulation of the steroid endocrine system to improve athletic performance has led some DHEA supplement providers on the internet to recommend up to 1000 mg/day [171].

b) Differences in baseline mean T/E ratios and dehydroepiandrosterone (DHEA) treatment mean ratios were not significant in 7 healthy subjects. Mean baseline T/E ratio was 0.67 (range: 0.1 to 1.2). DHEA 50 mg was taken each morning for 30 days with urinary samples collected before and two to three hours after ingestion with no voiding before collection. Individual variation was prevalent. The greatest individual variation from baseline to treatment mean T/E ratio was 1.20 to 2.11. The greatest difference from baseline mean to peak treatment mean T/E ratio was 1.2 to 3.7. A single dose of DHEA 250 mg resulted in a 40% increase in the T/E ratio relative to the pre-dose value (peak T/E ratio equal to 1.2). DHEA at this dose had a minimal effect on urine T/E ratios and would not be expected to result in a positive screen for testosterone abuse as the T/E ratio must exceed 6:1 [172].

c) Two female volunteers demonstrated three to four fold increases in plasma testosterone levels following dehydroepiandrosterone (DHEA) 100 mg administration. In subject 1, the pre-DHEA testosterone level was 0.07 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL ninety minutes after DHEA administration. In subject 2, the pre-DHEA testosterone level was 0.08 mcg/100 mL compared to a maximum level of 0.28 mcg/100 mL sixty minutes after DHEA administration. This demonstrates that in vivo conversion of DHEA to testosterone occurs in women as well as men [173].

Desonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Desoximetasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dexamethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase

fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dicumarol

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of dicumarol and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of dicoumarol and testosterone is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol. The anabolic steroids enhance anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

Diflorasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Diflucortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Difluprednate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may

increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Dong Quai

1) Interaction Effect: increased androgenic and/or adverse effects of testosterone
2) Summary: Dong quai (Angelica dahurica) extract significantly inhibited the metabolism of testosterone in vitro[177]. The effect of dong quai on the metabolism of nifedipine in humans is unknown, as the dose used in the animal study (1 gram/kilogram) is higher than that usually used in humans. Theoretically, if dong quai similarly affects the pharmacokinetics of testosterone in humans, increased levels of testosterone may occur which may result in greater androgenic effect. It is suspected that dong quai may affect other drugs metabolized by CYP2C11, CYP3A, and CYP1A enzymes. Caution is advised.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Monitor for increased androgenic effects of testosterone (such as acne, hirsutism, behavior changes) in patients taking testosterone and dong quai concomitantly.
7) Probable Mechanism: inhibition of hepatic cytochrome P450 enzyme metabolism of testosterone
8) Literature Reports

a) Angelica dahurica (dong quai) extract 1 gram/kilogram orally significantly inhibited 2-alpha-hydroxylase, 16-alpha-hydroxylase, and 6-beta-hydroxylase activity in rat liver microsomes. 2-alpha-hydroxylase activity was inhibited from one to 24 hours after dong quai administration (p less than 0.01), with 17.2 percent to 68.7 percent of its activity remaining. 16-alpha-hydroxylase activity was inhibited from 1 to 6 hours after dong quai administration (p less than 0.01), with 28.5 percent to 39.8 percent of its activity remaining. 6-beta-hydroxylase activity was inhibited 6 hours after dong quai administration (p less than 0.05), with 70 percent of its activity remaining. Cytochrome P450 (CYP) 2C11 mediates 2-alpha- and 16-alpha-hydroxylase activity, while CYP3A and CYP1A mediate 6-beta-hydroxylase activity [176].

Flucloronide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fludrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flumethasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Flunisolide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortin

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluocortolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluorometholone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Fluticasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Glimepiride

1) Interaction Effect: increased blood glucose lowering effect and increased risk of hypoglycemia
2) Summary: Exercise caution when coadministering glimepiride and androgens as this may increase the risk of hypoglycemia. If concomitant use is required, monitor more

closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of glimepiride and androgens may increase the risk of hypoglycemia. If concomitant use is required, monitor more closely for hypoglycemia. Upon discontinuation of androgens, monitor the patient for worsening of glycemic control[149].
7) Probable Mechanism: unknown

Halcinonide

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Hydrocortisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Insulin

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Aspart, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in

changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Bovine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Degludec

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Detemir

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glargine, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Glulisine

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Insulin Lispro, Recombinant

1) Interaction Effect: increased risk of hypoglycemia (CNS depression, seizures)
2) Summary: Use caution when coadministering insulin and testosterone as this may result in changes in insulin sensitivity or glycemic control. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of insulin and testosterone may result in changes in insulin sensitivity or glycemic control and should be undertaken with caution. Decreases in blood glucose may occur in patients with diabetes and may necessitate a reduction in insulin dosage[59].
7) Probable Mechanism: unknown

Licorice

1) Interaction Effect: decreased testosterone effectiveness
2) Summary: Licorice significantly reduced endogenous testosterone levels in healthy men and in women with polycystic ovary disease[166][167]. This may occur in clinically significant levels and may adversely affect testosterone supplementation. Licorice may inhibit conversion of androstenedione to testosterone through inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase [166][168][169]. Indirect evidence suggests that licorice may also stimulate aromatase activity and thereby increase the estradiol to testosterone ratio [170][169][167].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Avoid concomitant use of licorice and testosterone. Patients reporting decreased libido or other sexual dysfunction for which testosterone supplementation is being considered should be questioned regarding licorice use and advised to discontinue licorice.
7) Probable Mechanism: inhibition of 17-beta-hydroxysteroid dehydrogenase and 17,20-lyase which catalyze the conversion of androstenedione to testosterone; increased estradiol synthesis though aromatase stimulation
8) Literature Reports

a) Licorice decreased testosterone levels in 7 healthy men (age 22 to 24 years). Subjects received licorice 7 grams daily, administered as a commercial tablet preparation (Saila, Bologna, Italy), each containing 0.5 grams of glycyrrhizic acid as confirmed by gas chromatography-mass spectrometry. Baseline testosterone levels were 740 nanograms/deciliter (ng/dL), decreasing to 414 ng/dL by day 4 (p less than 0.001), and remained significantly decreased on day 7 at 484 ng/dL (p less than 0.001). Four days after licorice discontinuation, testosterone increased to 704 ng/dL. This demonstrates that licorice inhibits 17-beta-hydroxysteroid dehydrogenase conversion of androstenedione to testosterone. A comparable increase in 17-hydroxyprogesterone occurred by day 7 with no increase in androstenedione, indicating inhibition of 17,20-lyase, which catalyzes conversion of 17-hydroxyprogesterone to androstenedione. The authors conclude that since this amount of licorice is eaten by many people, that men with decreased libido or other sexual dysfunction should be questioned regarding licorice use [164].

b) An herbal combination of peony root and licorice root reduced serum testosterone levels in 34 infertile Japanese women with polycystic ovary disease. Women received 7.5 grams of the combination for 24 weeks. At 4 weeks, serum testosterone and free testosterone levels were significantly decreased by 56.3% and 59.3%, respectively. The mean testosterone level at 4 weeks was 85.3 ng/dL compared with the baseline level of 137.1 ng/dL (p less than 0.001). At 12 and 24 weeks, mean testosterone levels remained significantly lower than pretreatment levels (p less than 0.001 and p less than 0.01, respectively). Serum testosterone levels were significantly lower after 12 weeks in patients who became pregnant after treatment versus those who did not (p less than 0.05). The estrogen to testosterone ratio increased significantly after 4 weeks (p less than 0.05). After 24 weeks, the luteinizing hormone to follicle stimulating hormone ratio was significantly reduced for the first time (p less than 0.001) [165].

Loteprednol

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Methylprednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Mometasone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Oxyphenbutazone

1) Interaction Effect: elevated serum levels of oxyphenbutazone
2) Summary: Coadministration of oxyphenbutazone and androgens may result in elevated serum levels of oxyphenbutazone[148].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical

6) Clinical Management: Clinicians should be aware that concomitant use of testosterone and oxyphenbutazone may result in elevated serum levels of oxyphenbutazone.
7) Probable Mechanism: unknown

Paclitaxel

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel and CYP2C8 inhibitors such as testosterone[162].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Paclitaxel Protein-Bound

1) Interaction Effect: increased paclitaxel exposure resulting in increased risk of paclitaxel toxicity
2) Summary: Testosterone, a known inhibitor of the isoenzyme CYP2C8, inhibits the metabolism of paclitaxel to its primary metabolite 6-alpha-hydroxypaclitaxel, in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo in the presence of a CYP2C8 inhibitor. Caution should be exercised with the concomitant use of paclitaxel protein-bound and CYP2C8 inhibitors such as testosterone[163].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor patients for increased adverse effects due to paclitaxel toxicity including bone marrow suppression, myalgia/arthralgia, nausea/vomiting, and mucositis. Dose adjustment for either medication may be required.
7) Probable Mechanism: inhibition of CYP2C8-mediated paclitaxel metabolism by testosterone

Phenprocoumon

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of phenprocoumon and testosterone may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients receiving concomitant anticoagulant therapy [88]. If coadministration of phenprocoumon and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when androgen treatment is initiated or discontinued [140] [88].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144] [145].

Prednicarbate

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Prednisone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Rimexolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Triamcinolone

1) Interaction Effect: increased risk of edema
2) Summary: Use caution when coadministering testosterone and this drug as this may increase fluid retention and increase the risk of edema. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those

with cardiac, renal, or hepatic disease[23].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of testosterone and this drug may increase fluid retention and increase the risk of edema and should be undertaken with caution. If concomitant use of testosterone and a corticosteroid is required, monitor patients carefully, especially those with cardiac, renal, or hepatic disease[23].
7) Probable Mechanism: unknown

Warfarin

1) Interaction Effect: an increased risk of bleeding
2) Summary: Concomitant use of testosterone and warfarin may result in an increased risk of bleeding. A number of case reports have demonstrated prolonged prothrombin time and hemorrhages with coadministration of oral anticoagulants and 17-alkylated androgens[141][142][146][144][147]. Testosterone has been reported to suppress the clotting factors II, V, VII, and X, which may lead to bleeding in patients on concomitant anticoagulant therapy [88]. If coadministration of testosterone and warfarin is deemed necessary, make INR determinations and increase prothrombin time monitoring, particularly when treatment with testosterone is initiated or discontinued [140][88].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: If the concomitant use of oral anticoagulants and testosterone is required, make INR determinations and increase monitoring of prothrombin time, particularly at androgen treatment initiation and discontinuation[140][88].
7) Probable Mechanism: modification of coagulation factor, hepatic synthesis, and competitive inhibition of plasma protein binding by testosterone
8) Literature Reports

a) Anabolic steroids have been well documented to cause important interactions with dicumarol, another anticoagulant. Anabolic steroids enhance the anticoagulant activity of dicumarol perhaps through reductions in clotting factor formation and increased clotting factor degradation. The 17-alpha-alkylated steroids (fluoxymesterone, oxandrolone, oxymetholone, methyltestosterone, methandrostenolone, stanozolol) appear to be more likely to induce this reaction than the non-substituted steroids [141][142][143][144][145].

b) Significant enhancement of the anticoagulant effects of warfarin was described in a 69-year-old woman following application of a vaginal ointment of testosterone propionate [141]. The mechanism of interaction is unclear.

IV Compatibility (single)

No results available

Pregnancy & Lactation

A) Teratogenicity/Effects in Pregnancy

1) Micromedex Pregnancy Rating: Contraindicated

a) Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Yes

3) Clinical Management

a) Testosterone is not indicated for use in women and should not be used in women [85][108][181][182]. Testosterone is contraindicated during pregnancy [57][74]. Advise patient of possible consequences to the fetus if pregnancy occurs during use[28], including masculinization of the

external genitalia of the female fetus. Pregnant women or those who may become pregnant should be aware of potential transfer of testosterone by men being treated with this drug [183][88].

4) Literature Reports

a) Based on animal findings and its mechanism of action, testosterone is teratogenic and can cause fetal harm when given to a pregnant woman [57][74][28][85].

b) Exposure of a female fetus to testosterone may result in varying degrees of virilization [57][74][22][85]. At least 16 cases have been reported of female offspring with virilization of genitalia after their mothers were treated with either testosterone or methyltestosterone during pregnancy [178][179]. In addition, clitoromegaly with or without labioscrotal fusion were reported in these cases. In one follow-up case, female endocrine function was normal with secondary sexual development occurring at puberty, and the internal female sex organs were also normal [180].

c) Suppressed spermatogenesis via feedback inhibition of the hypothalamic-pituitary-testicular axis may occur with treatment using large doses of exogenous androgens, including testosterone. Decreased fertility has been noted in some men receiving testosterone replacement therapy, and may be irreversible [57][74].

d) In animal developmental studies, structural impairments in male (ie, increased testicular weight, larger seminal tubular lumen diameter, and higher frequency of occluded tubule lumen) and female (ie, increased ano-genital distance, phallus development, empty scrotum, no external vagina, intrauterine growth retardation, reduced ovarian reserve, and increased ovarian follicular recruitment) offspring were observed when pregnant animals received IM testosterone during organogenesis at doses that were comparable to doses used for testosterone replacement therapy. In addition, increased pituitary weight was observed in both male and female offspring, as well as hormonal and behavioral changes. At testosterone doses that were about twice the doses used for testosterone replacement therapy, hypertension was observed in pregnant female rats and in their offspring [57][74].

B) Breastfeeding

1) World Health Organization Rating: Avoid breastfeeding.

2) Micromedex Lactation Rating: Infant risk has been demonstrated.

a) Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding.

3) Clinical Management

a) Testosterone is not indicated for use in women [57][74]. Testosterone is contraindicated in nursing women [108][182][88][181].

4) Literature Reports

a) It is not known how much testosterone transfers into human milk [85][28]. However, testosterone has been concentrated in the breast tissue of women with breast cancer [185].

5) Drug Levels in Breastmilk

a) Active Metabolites

1) dihydrotestosterone [200][205]

Monitoring

A) Testosterone

1) Therapeutic

a) Laboratory Parameters

1) Buccal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [17]

b) Monitor morning serum testosterone 4 to 12 weeks after initiating therapy to assess therapeutic response [23].

c) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Nasal Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [16]

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; intranasal formulations should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to assess therapeutic response [22].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

3) Topical Gel

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [5][15][3][2][18].

b) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; topical gels should be measured between two to four weeks after initiation [26].

c) Monitor serum testosterone levels periodically during therapy to ensure proper dosing [25] and assess therapeutic response [51][4].

d) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

4) Topical Solution

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [1].

b) Monitor serum testosterone levels within 2 to 8 hours and at least 14 days after initiating therapy (or dose adjustment) to assess therapeutic response [85].

c) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

5) Transdermal

a) Measure serum testosterone in the morning on at least 2 separate occasions and ensure that levels are below the normal range prior to treatment initiation [14].

b) Two weeks after therapy initiation, following system application the previous evening, evaluate the early morning serum testosterone level to assess therapeutic response [84].

c) Two weeks after switching from the 2.5, 5, and 7.5 mg/day systems to the 2, 4, and 6 mg/day systems, following system application the previous evening, assess the early morning serum testosterone level [84].

d) Once therapeutic levels have been achieved, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Assess serum prostate specific antigen (PSA) periodically during therapy (buccal, nasal gel, topical gel) [25][22][23][51][4]. For topical solution and transdermal system, evaluate PSA levels prior to initiating therapy, every 3 to 6 months during therapy, and in accordance with prostate cancer screening practices thereafter [84][85].

2) Monitor hematocrit levels [25] prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [22][23][51][4][84][85]. It is recommended that periodic monitoring of hematocrit levels should be standard practice in testosterone replacement therapy, especially in older men, due to reports linking topical testosterone with the development of polycythemia [96].

3) For topical solution, topical gel, and transdermal testosterone system, monitor hemoglobin levels prior to initiation of therapy, at 3 to 6 months after initiation, and annually thereafter [51] [4][84][85].

4) Periodically monitor liver function tests [51][4][84][85].

5) Periodically monitor lipid concentrations [25][22][23][51][4][84][85], particularly after initiation of therapy [22].

6) Regularly monitor serum calcium levels in cancer patients who have an increased risk of hypercalcemia and associated hypercalciuria [25][22][23][51][4][84][85].

b) Physical Findings

1) Evaluate for prostate cancer prior to and during therapy [25][23][51][4]. In patients receiving nasal gel or transdermal testosterone treatment, evaluate for prostate cancer prior to initiating treatment, 3 to 6 months following therapy initiation, and then in accordance with prostate cancer screening practices [22][84].

2) Monitor patient for signs and symptoms of worsening benign prostatic hyperplasia [25][22][23], especially in geriatric patients [22][51][4][84][85].

B) Testosterone Cypionate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [82].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone cypionate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

2) Toxic

a) Laboratory Parameters

1) Monitor hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during long-term therapy [82][83].

b) Physical Findings

1) Monitor bone maturation and assess the bone age of the wrist and hand every 6 months in pediatric males with delayed puberty [82][83].

C) Testosterone Enanthate

1) Therapeutic

a) Laboratory Parameters

1) Improvement in serum testosterone levels may be indicative of efficacy in hypogonadal males.

2) Measure serum testosterone and confirm hypogonadism diagnosis prior to treatment initiation [74][75].

3) Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved; testosterone enanthate should be measured no earlier than three to four cycles [26].

4) Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Ablation of the ovaries may indicate efficacy in women with advancing inoperable metastatic mammary cancer [75].

2) Toxic

a) Laboratory Parameters

1) Xyosted(TM)

a) Monitor hematocrit before initiating therapy and every 3 months during therapy [74].

b) Monitor PSA before initiating therapy and periodically during treatment [74].

c) Monitor lipid concentrations periodically, particularly after starting testosterone therapy [74].

d) Monitor calcium concentrations regularly in cancer patients at risk of hypercalcemia [74].

2) Delatestryl(R)

a) Monitor serum hematocrit and hemoglobin levels at baseline [26] and periodically for polycythemia during high-dose androgen therapy [75].

b) Periodically monitor lipid concentrations, particularly in patients with a history of myocardial infarction or coronary artery disease [75].

c) Monitor serum and urine calcium levels frequently in women with disseminated breast cancer [75].

b) Physical Findings

1) Xyosted(TM)

a) Assess blood pressure before initiating therapy, approximately 6 weeks after initiation, and periodically thereafter [74].

b) Monitor patients with benign prostatic hyperplasia (BPH) for worsening signs and symptoms [74]

2) Delatestryl(R)

a) Close clinical monitoring is necessary in women treated for metastatic breast carcinoma because androgen therapy occasionally appears to accelerate the disease [75].

b) Observe female patients for signs of virilization including deepening of the voice, hirsutism, acne, clitoromegaly, or menstrual irregularities [75].

c) In prepubertal males treated for delayed puberty, obtain an x-ray of the wrist and hand every 6 months to monitor bone age, the rate of bone maturation, and the effect of the drug on epiphyseal closure [75].

D) Testosterone Undecanoate

1) Therapeutic

a) Laboratory Parameters

1) Measure serum testosterone in the morning on at least 2 separate days before therapy initiation to confirm hypogonadism [57]. Following initiation in men, measure a total testosterone level after an appropriate interval to ensure target testosterone levels have been achieved. IM testosterone undecanoate should be tested halfway between the first two 10-week injections [26]. For oral capsules, measure serum testosterone concentrations 6 hours after the morning dose. Wait 7 days after treatment initiation or dose adjustment before checking the serum testosterone concentration [57]. Once therapeutic levels have been achieved in men, measure serum testosterone levels every 6 to 12 months to ensure maintenance of target levels [26].

b) Physical Findings

1) Improvement in serum testosterone levels may be indicative of efficacy.

2) Re-evaluate whether benefits outweigh potential risks in patients who develop cardiovascular risk factors or cardiovascular disease during treatment [57].

2) Toxic

a) Laboratory Parameters

1) Monitor hemoglobin at baseline [26] and periodically during treatment [58].

2) Monitor prostatic specific antigen (PSA) periodically during treatment [57].

3) Monitor serum lipid profile periodically during treatment [57][58], particularly after starting testosterone therapy [57].

4) (Jatenzo(R)) Evaluate hematocrit prior to treatment and every 3 months during use [57]

5) (Aveed(R)) Evaluate hematocrit prior to treatment, 3 to 6 months after initiation of treatment, and annually thereafter [58].

6) Regularly monitor serum calcium concentrations in cancer patients at risk for hypercalcemia [57][58].

7) If testosterone abuse is suspected, check testosterone concentrations to ensure they are within normal limits [57].

b) Physical Findings

1) Observe patients for signs of anaphylaxis or serious pulmonary oil microembolism reactions (ie, urge to cough, dyspnea, tightening of the throat, chest pain, dizziness, or syncope) for 30 minutes after each injection [58].

2) Monitor patients with benign prostatic hyperplasia for exacerbation or worsening signs or symptoms [57][58].

3) Evaluate for prostate cancer prior to and during treatment [57][58].

4) Consider baseline cardiovascular risk prior to therapy [57].

5) Assure blood pressure is adequately controlled prior to therapy and periodically monitor for new-onset hypertension or exacerbations of pre-existing hypertension starting approximately 3 weeks after initiation of therapy [57].

6) Evaluate patients for signs or symptoms consistent with DVT or pulmonary embolism [57].

Do Not Confuse

No results available

MECHANISM OF ACTION

Mechanism of Action

A) Testosterone

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [22][28][85].

B) Testosterone Cypionate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [83].

C) Testosterone Enanthate

1) Mechanism of Action

a) Testosterone is an endogenous androgen. Androgens are responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics. Testosterone is involved in the growth and maturation of the prostate, seminal vesicles, penis, and scrotum; development of male hair distribution (eg, beard, pubic, chest and axillary hair); laryngeal enlargement, vocal cord thickening, and alterations in body musculature and fat distribution [74] [73].

D) Testosterone Undecanoate

1) Mechanism of Action

a) Metabolites of testosterone undecanoate, testosterone and dihydrotestosterone (DHT), modulate the normal growth and development of male sex organs (eg, prostate, seminal vesicles, penis and scrotum) and maintain male secondary sex characteristics such as facial, pubic, chest, and axillary hair, laryngeal enlargement, vocal chord thickening, and body musculature and fat distribution alterations [53][59].

PHARMACOKINETICS

Pharmacokinetics

Onset and Duration

A) Onset

1) Testosterone

a) Peak Response

1) Hypogonadism, transdermal: 3 to 24 months [186].

a) Full effect of transdermal testosterone 3 to 9 milligrams/day on bone mineral density was achieved at 24 months while full effects on lean muscle mass, erythropoiesis, prostate volume, energy, and sexual function occurred within 3 to 6 months [186].

2) Testosterone Undecanoate

a) Peak Response

1) Hypogonadism, IM: 7 days [59]

a) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response of orally administered testosterone undecanoate [53].

B) Duration

1) Testosterone

a) Multiple Dose

1) Hypogonadism: 2 to 10 days (topical) [28][187][85]; 24 hours (transdermal) [84]

a) Following the last application of AndroGel(R) 1.62%, serum testosterone levels return to pretreatment levels within 48 to 72 hours [28].

b) By the fifth day after last application of AndroGel(R), serum testosterone levels return to pretreatment levels [187].

c) Testosterone serum concentrations returned to pretreatment levels 7 to 10 days following discontinuation of testosterone topical solution (administered until steady state was achieved) [85].

d) Testosterone serum concentrations returned to pretreatment levels 24 hours following the removal of the testosterone patch [84].

2) Testosterone Undecanoate

a) Single Dose

1) Hypogonadism, IM: 10 weeks [59]

a) Testosterone undecanoate 750 mg IM produces a steady state serum total testosterone level in the normal range (300 to 1000 nanograms/dL) for 10 weeks [59].

2) Hypogonadism, oral: Cannot be characterized [53]

a) There is insufficient data to characterize an exposure-response relationship or time course of pharmacodynamic response or orally administered testosterone undecanoate [53].

Drug Concentration Levels

A) Testosterone

1) Therapeutic Drug Concentration

a) Hypogonadism, Intranasal, Topical, and Transdermal: 300 to 1050 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [85]

1) Following intranasal administration of testosterone gel 33 mg/day, the circulating testosterone concentrations achieved in men with hypogonadism are similar to those observed in healthy men (ie, 300 to 1050 nanogram/dL) [22].

2) Following axillary administration, testosterone topical solution delivers approximately normal physiologic circulating testosterone ranges (300 to 1050 nanograms/dL) as seen in healthy men [85].

3) Following application of testosterone 1.62% topical gel, approximately normal physiologic circulating testosterone ranges (300 to 1000 nanograms/dL) are achieved [28].

4) Transdermal testosterone delivers a continuous daily dose of testosterone resulting in normal physiologic concentrations of testosterone (300 to 1030 nanograms/dL) in healthy adult men [84].

2) Peak Concentration

a) Sublingual (solution), single-dose: 3.79 nanograms (ng)/mL (0.25 mg); 5.31 ng/mL (0.5 mg); 6.73 ng/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded total testosterone mean Cmax values of 3.79 nanogram (ng)/mL (% coefficient variation (CV), 39.9), 5.31 ng/mL (%CV, 37.8), and 6.73 ng/mL (%CV, 39.6), respectively. Mean free testosterone Cmax levels following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.021 ng/mL (%CV, 39.7), 0.032 ng/mL (%CV, 37.6), and 0.043 ng/mL (%CV, 45.7), respectively. The difference in Cmax was statistically different between all 3 doses for both total and free testosterone measurements (p less than 0.0001) [189].

b) Topical (solution), multiple-dose, hypogonadal men (30 mg to 120 mg): within normal range [85]

1) In a multicenter, open-label, efficacy study, hypogonadal men (n=155; median age, 53 years; range, 19 to 78 years) received testosterone topical solution 60 mg daily to the axilla for 15 days, then maintenance or titration upward or downward on day 45 and day 90 to 30-, 60-, 90-, or 120 mg based on serum testosterone concentration measured on day 15 and day 60, respectively. The table below describes the mean testosterone Cmax (normal serum testosterone range, 300 to 1050 nanograms/dL) in patients who completed the 120 day treatment (n=135) [85]:

Day	Testosterone topical solution dose				
	30 mg	60 mg	90 mg	120 mg	Overall (n=135)
	Cmax nanograms/dL				
Day 15		744 +/- 502 (n=135)			744 +/- 502
Day 60	491 (n=1)	898 +/- 664 (n=105)	646 +/- 382 (n=29)		840 +/- 620
Day 120	779 +/- 416 (n=3)	839 +/- 436 (n=97)	664 +/- 336 (n=25)	658 +/- 353 (n=10)	792 +/- 417
KEY: mg = milligrams; dL = deciliter.					

2) Following axillary administration of testosterone topical solution 30-, 60-, or 90-mg daily, steady-state concentrations were achieved in approximately 14 days. The mean steady-state dihydrotestosterone (DHT, active metabolite)-to-testosterone ratio remained within normal limits during treatment, ranging from 0.17 to 0.26 across all doses on days 15, 60, and 120 [85].

c) Topical (gel), multiple-dose, effect of sunscreen or moisturizing lotion (40.5 mg): 13% to 17% increase [28]

1) Application of sunscreen or moisturizing lotion increased exposure to testosterone in a randomized, 3-way crossover study of hypogonadal men (n=18). Subjects applied testosterone 1.62% gel 40.5 mg topically to the upper arms/shoulders followed in 1 hour by

sunscreen (SPF 50), moisturizing lotion, or nothing, for 7 days. The testosterone Cmax increased 13% and 17% when sunscreen and moisturizing lotion, respectively, were applied, compared with the control phase [28].

d) Transdermal, single-dose: 925 nanograms (ng)/dL (two 2.5 mg/day patches); 905 ng/dL (single 5 mg/day patch)[84]

1) In a study of 20 hypogonadal patients, average Cmax concentrations over 24 hours were 925 +/- 340 nanograms (ng)/dL, following the application of two 2.5 mg/day patches and 905 +/- 254 ng/dL following the application of a single 5 mg/day patch [84].

e) Transfer to Non-treated Women

1) Topical (solution), single-dose, transferred testosterone to nontreated subjects, 60 mg: 17% to 297% increase [85]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women revealed a 17% increase in testosterone Cmax in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 17% increase in testosterone Cmax in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 297% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

2) Topical (gel), single-dose, transferred testosterone to nontreated subjects, 81 mg: 11% to 267% increase [28]

a) A clinical study of potential transfer of testosterone from treated men to nontreated women increased testosterone Cmax 11% in the nontreated females. Using a 1.62% testosterone gel formulation, men (n=12) received testosterone 81 mg topically to the shoulders and upper arms, then covered the area with a T-shirt. Two hours after application, women rubbed their hands, arms, and shoulders to the application site of the men for 15 minutes. The women were monitored for 24 hours after the transfer procedure. The transfer procedure led to an 11% increase in testosterone Cmax in the women compared with baseline. Another study in 8 men who received a 1.62% testosterone formulation topically revealed a 267% increase in testosterone Cmax following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [28].

3) Time to Peak Concentration

a) Buccal system: 0.4 to 12 hours [192][193][194].

1) The mean peak serum testosterone level of 26.7 nanomoles/liter (nmol/liter) was reached 4.8 hours after administration of 30 milligram buccal testosterone given twice daily in 12 testosterone-deficient men with a mean age of 44.4 years. Steady state was achieved within the first 24 hours of treatment and was maintained in the normal range with a mean of 19.3 nmol/liter [192].

2) The mean maximum serum total testosterone concentrations (Cmax) are reached within 10 to 12 hours. The Cmax ranges from 910 to 970 nanograms/deciliter [193].

3) Serum concentrations of testosterone reach steady state levels after the second dose of testosterone buccal system. The mean average serum total testosterone concentrations at steady state in clinical studies ranged from 520 to 550 nanograms/deciliter [193].

4) In 6 healthy, postmenopausal women, maximum testosterone concentrations were achieved 0.6 hour after the first transbuccal dose of testosterone 2 milligrams and 0.4 hour after 2 weeks of treatment (steady state). Maximum hormone concentrations were 35.4 and 34.9 nanomole/liter, respectively [194].

b) Intranasal, gel: 40 minutes [22]

1) The Tmax is approximately 40 minutes following intranasal testosterone gel administration [22].

c) Oral, capsules: 6 hours [188].

1) To avoid the problem of endogenous levels and fluctuations of testosterone and dihydrotestosterone, 45 women were enrolled in a randomized, open-label pharmacokinetic study of oral testosterone undecanoate. Two doses each of 20, 40 and 80 milligrams (mg) were given every 12 hours to 45 healthy women without childbearing potential. Maximum

serum concentrations of testosterone after the first dose (Cmax1) of oral testosterone undecanoate 20, 40, and 80 mg were 1.82, 3.86, and 7.68 nanograms/mL, respectively. The time to each was 6, 6, and 5.5 hours, respectively. The maximum serum concentrations of testosterone after the second dose (Cmax2) at 20, 40, and 80 mg were 1.56, 2.65, and 5.20 nanograms/mL, respectively. Time to each was 5.98, 5.97, and 5.97 hours, respectively.

d) Subcutaneous, pellet: 63 days [195].

e) Sublingual (solution): 14.3 to 15.6 minutes [189]

1) In 16 premenopausal women, mean Tmax values after SL testosterone doses of 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.4 minutes), 15.1 minutes (+/- 5.5 minutes), and 14.3 minutes (+/- 5.3 minutes), respectively. Free testosterone mean Tmax values following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 15.6 minutes (+/- 5.1 minutes), 14.4 minutes (+/- 5.5 minutes), and 12.8 minutes (+/- 6.3 minutes), respectively. The differences between doses were not statistically different for total or free testosterone [189].

f) Transdermal: 2 to 6 hours, Testoderm(R) [196][191]; 4 to 12 hours, Androderm(R) [84]

1) With Testoderm(R) application, the serum testosterone concentration rises to a maximum at 2 to 4 hours [196].

2) With daily Androderm(R) application a continuous daily dose of testosterone is absorbed over 24 hours with a median Tmax of 8 hours (4 to 12 hours); corresponding Cmax is 905 to 925 nanograms (ng)/dL [84].

3) Absorption of transdermal testosterone was improved when a heat-generating 5 milligram (mg) patch was utilized. Over a 12-hour study period, the heat-generating patch reached a mean maximum serum testosterone concentration of 939 nanograms/dL at 4 hours compared to a standard 5 mg patch which achieved a maximum concentration of 635 nanograms/dL at 6 hours [191].

g) Topical gel: 4 hours [187].

1) An increase in serum testosterone was seen in all patients within 30 minutes after administration of 10 grams of testosterone 1% gel. Normal range testosterone levels (298 to 1043 nanograms/dL) were seen in 8 of 9 patients within 4 hours after initial application. Steady-state concentrations are reached on day 2 or 3. The average steady-state serum concentrations on day 30 in patients using 5 and 10 grams daily were 566 +/- 262 nanograms/dL and 792 +/- 294 nanograms/dL, respectively [187].

4) Steady State

a) Intranasal gel, multiple-dose, 33 mg/day: 421 nanogram/dL [22]

1) The average daily testosterone level was 421 +/- 116 nanogram/dL following administration of intranasal testosterone gel 33 mg/day (11 mg 3 times daily) for 90 days in hypogonadal men (N=69) [22].

b) Intranasal gel, multiple-dose, patients with allergic rhinitis, 11 mg: 21% to 24% decrease [22]

1) Patients with allergic rhinitis who received intranasal testosterone 11 mg 3 times daily for 3 doses had total serum testosterone levels that were 21% to 24% lower during a symptomatic phase than during an asymptomatic phase (N=18) [22].

c) Transdermal, single dose: 424 nanograms (ng)/dL (single 2.5 mg/day patch); 584 ng/dL (two 2.5 mg/day patches); 766 ng/dL (three 2.5 mg/day patches)[84]

1) In a study of 12 hypogonadal men with an average baseline serum testosterone concentration of 76 nanograms (ng)/dL, average morning testosterone concentrations were 424 nanograms (ng)/dL, 584 ng/dL, and 766 ng/dL at steady state following the nightly application of 1, 2, or 3 (2.5 mg/day) transdermal testosterone patches, respectively. Equivalent serum testosterone concentrations were observed following the application of two 2.5 mg/day patches compared with the application of one 5 mg/day patch in a study of 20 hypogonadal patients. Average steady state concentrations were 613 +/- 169 ng/dL following the application of two 2.5 mg/day patches and 621 +/- 176 ng/dL following the application of a single 5 mg/day patch [84].

5) Area Under the Curve

a) Oral (capsules): 10 to 76 nanograms x hours/milliliters [188].

1) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The areas under the curve (AUC) from 0 to 12 hours for the 20, 40, and 80 mg dose were 10.3, 18.8, and 35.6 nanograms x hour/mL, respectively. The AUCs from 0 to the sampling time of the last measurable concentration after administration of the second dose were 25.8, 40.1, and 76.0 nanograms x hour/mL, respectively [188].

b) Sublingual (solution), single-dose: 194 nanograms (ng) x min/mL (0.25 mg); 266 ng x min/mL (0.5 mg); 337 ng x min/mL (0.75 mg) [189]

1) In 16 premenopausal women, single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg yielded baseline corrected total testosterone mean AUCs of 194 nanogram (ng) x min/mL (% coefficient variation (CV), 37.2), 266 ng x min/mL (%CV, 37.6), and 337 ng x min/mL (%CV, 34.7), respectively. Free testosterone AUCs following single SL doses of testosterone 0.25 mg, 0.5 mg, and 0.75 mg were 0.95 ng x min/mL (%CV, 51.8), 1.51 ng x min/mL (%CV, 40.2), and 1.87 ng x min/mL (%CV, 47.8), respectively There was a statistically significant difference in AUC between the 3 doses for both total and free testosterone measurements (p less than 0.0001), and the increase in AUC was dose-dependent [189].

c) Topical (gel), single-dose (50 mg): 4499 to 5865 nanograms x hours/deciliter [190].

1) The area under the curve of plasma testosterone concentration versus time achieved by a single dose of topical testosterone 50 milligram gel ranged from 4499.1 to 5864.5 nanograms x hour/deciliter [190].

d) Transdermal: 6273 to 8402 nanograms x hour/dL [191].

1) The AUC of testosterone was 6273 to 8402 nanograms x hour/dL following transdermal administration. There is no accumulation of testosterone during continuous treatment [191].

2) Increased Systemic Exposure With a Heat-Generating Patch

a) The area under the curve of plasma testosterone concentration versus time achieved by a heat-generating patch was 8402 nanograms x hour/dL versus a standard 5 mg patch which achieved a value of 6273 nanograms x hour/dL [191].

3) Systemic Exposure After Showering

a) In a two-way crossover study of 16 hypogonadal males, showering 3 hours after the application of a single 4 mg/day transdermal testosterone patch did not increase the systemic exposure of testosterone compared with not showering [84].

e) Topical (solution), single-dose, transfer to nontreated subjects (60 mg): 13% to 131% increased exposure [85]

1) A clinical study of potential transfer of testosterone from treated men to nontreated women showed a 13% increase in testosterone AUC (0 to 24 hours) in the nontreated females. Using a 2% testosterone formulation, men (n=10) received testosterone 60 mg topically to each axilla and then covered the area with a T-shirt. Two hours after the application, women rubbed their forearms on the axilla of the men for 15 minutes. The women were monitored for 72 hours after the transfer procedure. The transfer procedure led to a 13% increase in testosterone AUC (0 to 24 hours) in the women compared with baseline. Another study in men who received a 1% testosterone formulation topically revealed a 131% increase in testosterone AUC (0 to 72 hours) following direct skin-to-skin transfer compared with indirect (T-shirt) transfer [85].

f) Topical (solution), single-dose, effect of showering/washing (30 mg): up to 35% decreased exposure [85]

1) The effect of showering/washing on testosterone exposure was examined in a parallel design clinical study of healthy, premenopausal women (n=12). Subjects received testosterone 30 mg topically to one axilla and either washed with soap and water 2 or 6 hours later (n=6) or did not wash (n=6). Blood samples collected over 72 hours from all subjects revealed up to a 35% decrease in testosterone AUC (0 to 72 hours) in subjects who washed compared with subjects who did not wash. Patients should not swim or wash the application site for 2 hours following administration [85].

g) Topical (solution), single-dose, effect of deodorant/antiperspirant (30 mg): up to 33% decreased exposure [85]

1) In a parallel-group, clinical study on the effects of deodorant/antiperspirant use with testosterone topical solution, the testosterone AUC decreased up to 33% when a single-dose

of testosterone 30 mg topical solution was applied to the axilla of healthy premenopausal women 2 minutes after application of deodorant/antiperspirant spray (n=6) or stick (n=6) or deodorant spray (n=6) compared with the control group (n=6) [85].

B) Testosterone Enanthate

1) Therapeutic Drug Concentration

a) SubQ: 300 to 1100 nanograms/dL (approximately normal physiologic circulating testosterone ranges) [74]

1) SubQ administration of testosterone enanthate results in approximately normal physiologic concentrations of testosterone (300 to 1100 nanograms/dL) in healthy men [74].

2) The mean average concentration (0 to 168 hours) of total testosterone was 553 +/- 127 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Peak Concentration

a) SubQ, multiple-dose: 790 nanograms/dL [74]

1) The mean Cmax of total testosterone was 790 +/- 215 nanograms/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

2) Following weekly administration, the mean Cmax of testosterone enanthate was 169 +/- 68 nanograms/dL at week 12 [74].

3) Time to Peak Concentration

a) IM: 24 hours [206][207]

1) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 hypogonadal subjects was 1233 +/- 484 nanograms/dL 24 hours after injection; this was an increase of 1138 nanograms/dL from a basal serum level of 95 +/- 10 nanograms/dL [206].

2) The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 200 mg in 7 eugonadal subjects was 1965 +/- 391 nanograms/dL 6 hours after injection; this was an increase of 1486 nanograms/dL from a basal serum level of 497 +/- 63 nanograms/dL. The mean peak testosterone serum concentration following the administration of intramuscular testosterone enanthate 100 mg in 7 eugonadal subjects was 1181 +/- 204.7 nanograms/dL 24 hours after injection; this was an increase of 669 nanograms/dL from a basal serum level of 521 +/- 51.2 nanograms/dL [206].

b) SubQ: 11.9 hours [74]

1) The Cmax of total testosterone occurred at a median Tmax of 11.9 hours post-dose (range, 5.8 to 168.7 hours) following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks. Steady state concentrations were achieved by week 6 [74].

4) Area Under the Curve

a) SubQ, multiple-dose: 92,955 nanograms x hr/dL [74]

1) The mean AUC(0 to 168 hours) of total testosterone was 92,955 +/- 21,385 nanograms x hr/dL following weekly subcutaneous injections of testosterone enanthate (75 mg initially, then adjusted if needed to 50 mg or 100 mg based on total testosterone trough concentrations after 6 weeks of treatment; N=137) for 12 weeks [74].

C) Testosterone Undecanoate

1) Therapeutic Drug Concentration

a) Oral Route

1) Hypogonadism, oral: 476 nanograms (ng)/dL [53]

a) The average serum testosterone concentrations over 24 hours following oral administration of 225 mg was 476 ng/dL [53].

2) Hypogonadism, oral: 403 nanograms (ng)/dL [57]

a) The average daily NaF-EDTA plasma testosterone concentration was 403 +/- 128 ng/dL at the end of treatment, where the normal eugonadal range in NaF-EDTA plasma was 252 to 907 ng/dL in this study. Hypogonadal males received testosterone capsules 158 to 395 mg orally twice daily for at least 105 days [57].

b) Intramuscular Route

1) Hypogonadism, IM: 300 to 1000 nanograms/dL (750 mg) [59]

a) Testosterone undecanoate 750 mg IM produces circulating testosterone levels consistent with normal concentrations in health men (300 to 1000 nanograms/dL) [59].

2) Peak Concentration

a) Oral route, multiple doses, 225 mg twice daily: 979 to 989 nanograms (ng)/dL[53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of 5 hours [53].

b) Oral route, multiple doses, 158 to 396 mg twice daily: 1008 nanograms (ng)/dL [57]

1) The mean Cmax was 1008 +/- 581 ng/dL in a study of hypogonadal males (N=151) receiving testosterone capsules 158 to 396 mg orally twice daily for at least 105 days [57].

c) IM, single dose: 90.9 nanograms/dL [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

3) Time to Peak Concentration

a) Oral Route

1) Testosterone

a) Oral route: 5 hours [53]

1) Mean Cmax serum testosterone concentrations following morning and evening doses were 979 ng/dL and 989 ng/dL, respectively, with an observed median Tmax of around 5 hours [53].

b) Intramuscular Route

1) Testosterone Undecanoate

a) IM: 4 days [59]

1) The mean testosterone undecanoate Cmax was 90.9 +/- 68.8 nanograms/dL, achieved 4 days after a testosterone undecanoate IM injection [59].

2) Testosterone

a) IM: 7 days [59]

1) Serum testosterone concentrations reach maximum levels after a median of 7 days (range, 4 to 42 days) following a testosterone undecanoate 750 IM injection and then levels slowly decline [59].

ADME

Absorption

A) Testosterone

1) Bioavailability

a) Oral: absorbed from the GI tract, oral mucosa, and skin; however, the oral route of administration is not used due to almost complete first-pass hepatic metabolism [197].

1) A significant and reproducible rise in serum testosterone was detected following the ingestion of testosterone crystals in 26 male subjects [198].

b) Subcutaneous: slow [195].

1) Following subcutaneous implantations using testosterone pellets, absorption has been reported to be complete by day 189. The daily release rate is 1.18 mg per 200 mg pellet [195].

c) Sublingual (solution): decreases with increasing doses [189]

1) In a study with 16 premenopausal women, the bioavailability decreased with increasing doses of SL testosterone. Since there was no IV standard, investigators used the lowest dose (0.25 mg) as a reference value of 100%. The bioavailability of 0.5 mg and 0.75 mg doses were calculated as 69% and 58%, respectively [189].

d) Transdermal: good [84]

1) Transdermal testosterone, administered as two 2.5 mg/day patches, resulted in an average testosterone absorption of 4 to 5 mg over 24 hours in 34 hypogonadal men when applied to the abdomen, back, thighs, or upper arms. When applied to the chest or shins the average absorption rate was 3 to 4 mg over 24 hours. Similar concentration profiles were observed for the abdomen, back, thigh, and upper arm application sites while more interindividual variability was observed when transdermal testosterone was applied to the either the chest or shins. The table below describes the mean testosterone concentration for various application sites over 24 hours following a single-dose application of two 2.5 mg/day patches [84].

Sample Time (hour)	Abdomen (nanograms/dL)	Back (nanograms/dL)	Thigh (nanograms/dL)	Upper Arm (nanograms/dL)
0	90 +/- 82	80 +/- 74	85 +/-76	81 +/- 69
3	286 +/- 201	429 +/- 252	271 +/- 201	308 +/- 226
6	476 +/- 236	608 +/- 250	489 +/- 254	468 +/- 245
9	570 +/- 234	613 +/- 214	592 +/- 251	534 +/- 204
12	575 +/- 244	588 +/- 233	594 +/- 247	527 +/- 199
24	352 +/- 164	403 +/- 174	367 +/- 161	332 +/- 124

e) Topical (gel): approximately 10% [199][187]

1) Approximately 10% of the applied testosterone gel dose is absorbed during a 24-hour period [199][187].

B) Testosterone Cypionate

1) Bioavailability

a) absorbed slowly [83]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [83].

C) Testosterone Enanthate

1) Bioavailability

a) Absorbed slowly [73]

1) Testosterone esters in oil administered IM are absorbed slowly from the lipid phase, which permits dosing every 2 to 4 weeks [73].

D) Testosterone Undecanoate

1) Effects of Food

a) Reduced exposure when administered without food [53]

1) Administration in fasting conditions reduced exposure (AUC) by approximately 38% when compared to administration with high-fat food [53].

b) Reduced exposure when administered with a lesser amount of food [57]

1) When testosterone oral capsules were administered with a 15 g fat breakfast, there was a 25% decrease in testosterone exposure compared with a 30 g breakfast [57].

Distribution

A) Distribution Sites

1) Testosterone

a) Protein Binding

1) Testosterone-estradiol binding globulin: 98% [200][201].

a) Testosterone is bound to specific testosterone-estradiol binding globulin. The remaining 2% of testosterone remains free in plasma, and the amount of free testosterone determines its half-life [193][200][201][187].

2) Sex hormone-binding globulin: 40% [22][84][28][85]

a) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [22][84][28][85].

2) Testosterone Cypionate

a) Protein Binding

1) 98% [83]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [83].

b) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [83].

3) Testosterone Enanthate

a) Protein Binding

1) Specific testosterone-estradiol binding globulin: 98% [73]

a) Testosterone is 98% bound to a specific testosterone-estradiol binding globulin [73].

b) Approximately 40% of testosterone is bound to sex hormone-binding globulin. Approximately 2% is free or unbound, and the remainder is bound to albumin and other proteins [74].

c) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma [73].

4) Testosterone Undecanoate

a) Protein Binding

1) Albumin, unknown amount; Sex hormone binding hormone, 40% [53][57][59]

a) Testosterone is mostly bound to sex binding hormone (40%) and albumin; 2% of testosterone is unbound and the rest is loosely bound to albumin and other proteins [53][57][59].

B) Distribution Kinetics

1) Volume of Distribution

a) 74.9 to 122.5 L/kg [202].

1) The Vd at steady state in 2 healthy subjects following a single intramuscular 25 mg injection of testosterone propionate was reported as 74.9 and 122.5 L/kg, respectively [202].

Metabolism

A) Metabolism Sites and Kinetics

1) Testosterone

a) Liver, extensive first-pass hepatic metabolism [28][200][201][85].

1) Testosterone administered orally is not recommended [197]. Testosterone is metabolized in the liver to various 17-ketosteroids via 2 different pathways. Glucuronic and sulfuric acid conjugates of testosterone are found in urine with approximately 6% of testosterone excreted unchanged in the feces [22][28][200][201].

2) Testosterone is primarily inactivated in the liver [22][28][85].

b) Liver, transbuccal delivery of testosterone circumvents first-pass metabolism [193].

2) Testosterone Cypionate

a) Liver: primary site [83]

1) Testosterone activity depends on reduction to dihydrotestosterone in responsive

tissues [83].

2) Inactivation of testosterone happens primarily in the liver [83].

3) Testosterone Enanthate

a) Liver: Primary site [74][73]

1) Testosterone enanthate is metabolized to testosterone by ester cleavage of the enanthate group. Testosterone is metabolized to various 17-ketosteroids via 2 different pathways [74].

2) Testosterone activity depends on reduction to dihydrotestosterone in responsive tissues [73].

3) Inactivation of testosterone happens primarily in the liver [74][73].

4) Testosterone Undecanoate

a) Serum esterases (testosterone undecanoate): Primary [53]

1) Testosterone undecanoate is metabolized to active testosterone via ester cleavage of the undecanoate group [53]

b) Liver: Primary (testosterone) [53]

1) Inactivation of testosterone (the active metabolite of testosterone undecanoate) occurs primarily in the liver [53].

B) Metabolites

1) Testosterone

a) Estradiol and dihydrotestosterone (DHT): active [22][84][28][85]

1) Estradiol and dihydrotestosterone (DHT) are the major active metabolites of testosterone [22][84][28][85][200][201][187]. DHT concentration was linearly related to testosterone concentration during treatment with testosterone topical solution via axillary administration [85].

2) The average DHT:T and E2:T ratios, respectively, were 1:10 and 1:200 during steady-state pharmacokinetic studies in hypogonadal men [84].

b) Testosterone glucuronic conjugate, activity unknown [200][201].

c) Testosterone sulfuric acid conjugate, activity unknown [200][201].

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [22][85][200][201][187].

d) Testosterone-19-d3, active [202]

1) Active metabolite of testosterone propionate [202]

2) Testosterone Enanthate

a) Dihydrotestosterone (major): Active [74]

1) Dihydrotestosterone (DHT) is a major active metabolite of testosterone [74].

2) Following weekly administration of testosterone enanthate, the mean DHT/testosterone ratio was within normal range (0.07) pre-dose of week 12 [74].

b) Estradiol (major): Active [74]

1) Estradiol is a major active metabolite of testosterone [74].

c) Testosterone glucuronic conjugate: [74][73] Unknown activity

d) Testosterone sulfuric acid conjugate: [74][73] Unknown activity

e) 17-ketosteroid metabolites of testosterone: Inactive [74][73]

1) In addition to testosterone glucuronic and sulfuric acid conjugates, 17-ketosteroid metabolites of testosterone are produced by 2 different metabolic pathways in the liver [74][73]

3) Testosterone Undecanoate

a) Testosterone: Active (major) [53][57][59]

1) Testosterone undecanoate is metabolized to testosterone by ester cleavage. Testosterone is metabolized to various 17-keto steroids through 2 different pathways to estradiol and dihydrotestosterone [53][57][59].

Excretion

A) Kidney

1) Testosterone

a) Renal Clearance (rate)

1) approximately 2 L/min [202].

a) Clearance in 2 healthy male subjects following a single 25 mg intramuscular injection of testosterone propionate was reported as 2317.4 and 1958.0 mL/min, respectively [202].

b) Renal Excretion (%)

1) 90% [22][84][88][200].

a) Following an intramuscular dose of testosterone, approximately 90% is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and testosterone metabolites [22][84][28][200][88][85].

2) Testosterone Cypionate

a) Renal Excretion (%)

1) 90% [83]

a) Approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [83].

3) Testosterone Enanthate

a) Renal Excretion (%)

1) 90%, changed [74][73]

a) Following IM administration, approximately 90% of a testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates of testosterone and it's metabolites [74][73].

4) Testosterone Undecanoate

a) 90%, as conjugated metabolites [53][59]

1) Approximately 90% of an IM testosterone dose is excreted in the urine as glucuronic and sulfuric acid conjugates or other metabolites [53][59].

B) Feces

1) Testosterone

a) 6% [22][84][28][200][88][85]

1) Approximately 6% of a IM testosterone dose is excreted in feces, mainly in the unconjugated form [22][84][28][200][88][85].

2) Testosterone Cypionate

a) 6% [83]

1) Approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [83].

3) Testosterone Enanthate

a) 6%, mostly unchanged [74][73]

1) Following IM administration, approximately 6% of a testosterone dose is excreted in the feces; the majority as the unconjugated form [74][73].

4) Testosterone Undecanoate

a) 6% [53][59]

1) Approximately 6% of an IM testosterone dose is excreted in the feces as unconjugated testosterone [53][59].

Elimination Half-life

A) Parent Compound

1) Testosterone

a) 5.7 hours, buccal [192]; 2 to 3 hours, oral [188]; 70.8 days, subQ implanted pellet[195]; 49.7 to 58.5 minutes, sublingual (solution) [189];10 to 100 minutes [22] [84][199][204][201][85]

1) The mean half life of total testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 49.8 +/- 16 minutes, 49.7 +/- 22.4 minutes, and 58.5 +/- 24.6 minutes, respectively. The calculated half-life of total testosterone was significantly different only between the 0.5 mg and 0.75 mg doses (p=0.0125). The mean half life of free testosterone following SL doses of 0.25 mg, 0.5 mg, and 0.75 mg in healthy premenopausal women (n=16) was 42.3 +/- 14.6 minutes, 55.7 +/- 27.5 minutes, and 51.1 +/- 26.4 minutes, respectively. There was no statistical difference in half-life of free testosterone between the 3 doses [189].

2) The half-life of testosterone is highly variable, ranging from 10 to 100 minutes [22] [84][28][199][204][201][85]

3) The elimination half-life of buccal testosterone 30 milligrams given twice daily for 7 days to 12 testosterone-deficient men was 5.7 hours [192].

4) Two doses each of testosterone undecanoate 20, 40, and 80 milligrams were give 12 hours apart to 45 healthy women without childbearing potential. The baseline-corrected elimination half-lives for each dose were 2.35, 2.43, and 2.58 hours, respectively [188].

5) The terminal elimination half-life for subcutaneously implanted testosterone pellets is reported to be 70.8 days. Men with larger body mass apparently have a lower half-life [195].

2) Testosterone Cypionate

a) 10 to 100 minutes [83]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [83].

2) The amount of free testosterone (non-protein-bound) determines its half-life. The half-life of testosterone depends upon the route of administration and which testosterone ester is used; the half-life for intramuscularly administered testosterone cypionate is approximately 8 days [200].

3) Testosterone Enanthate

a) 10 to 100 minutes [73]

1) The half-life of testosterone depends on the amount of free testosterone, which is dependent of the amount of sex-hormone binding globulin in the plasma. The half-life of testosterone is variable, and can range from 10 to 100 minutes [73].

B) Metabolites

1) Testosterone Undecanoate

a) Testosterone

1) 10 to 100 minutes [53][59]

a) There is considerable variation in the half-life of testosterone, with reports ranging from 10 to 100 minutes [53][59].

PATIENT EDUCATION

Medication Counseling

No results available

Patient Handouts

A) Testosterone (Absorbed through the skin)
Testosterone

Treats low testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches or apply them more often than your doctor tells you to.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Wash your hands with soap and water before and after applying a patch.
Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVER CUT the wrapper or the patch with scissors. Do not use any patch that has been cut by accident.
The patient instructions will show the body areas where you can wear the patch. When putting on each new patch, choose a different place within these areas. Do not put the new patch on the same place you wore the last one. Be sure to remove the old patch before applying a new one.
Apply the patch to clean, dry skin with very little hair, on your back, abdomen, upper arms, or thighs. Apply the patch at about the same time every night.
Do not put the patch over burns, cuts, or irritated skin. Do not put the patch on oily or sweaty skin or on a spot that might put extra pressure on it (such as over a joint).
Bathing or swimming should not affect the patch. However, wait at least 3 hours after you apply the patch before you wash the skin area or shower or swim. Heavy exercise and sweating may cause the patch to fall off.
If the patch becomes loose, smooth it down and press it back onto your skin. If the patch comes off before 12 o'clock noon, put on a new patch, and then replace the new patch at your regular time. If the patch comes off after noon, just wait and put on a new patch at your next regular time.
Do not tape the patch to your skin.
Missed dose: If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next patch, wait until then to apply a new patch and skip the one you missed. Do not apply extra patches to make up for a missed dose.
Store the patches at room temperature in a closed container, away from heat, moisture, and direct light.
Fold the used patch in half with the sticky sides together. Throw any used patch away so that children or pets cannot get to it. You will also need to throw away old patches after the expiration date has passed.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Corticosteroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, cancer, diabetes, an enlarged prostate, heart disease, lung disease, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased numbers of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increase risk of heart attack or stroke
Lower sperm count (with large doses)

The skin patch contains aluminum, which may cause skin burns if you have an MRI (magnetic resonance imaging) scan. You must remove the patch before an MRI.
This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread to your arms, jaw, back, or neck, trouble breathing, coughing up blood, unusual sweating, faintness
Chest pain, trouble breathing, or coughing up blood
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Pain, redness, or swelling in your arm or leg
Severe skin blisters, redness, swelling, or burning where the patch is applied
Swelling in your hands, ankles, or feet
Unusual bleeding or bruising

If you notice these less serious side effects, talk with your doctor:

Mild skin soreness, redness, itching, or irritation where the patch was applied
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
B) Testosterone (Between cheek and gum)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Patch

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine looks like a tablet, but it sticks to your gum like a patch. To use the patch:

Put the flat side of the patch on your fingertip. Place the patch against your gum and to the left or right of your front teeth. Gently push it up as high as it will go. Then press on the patch from the outside of your lip for at least 30 seconds. The patch should stick to your gum.
Do not chew or swallow the patch.
Each time you put in a new patch, put it on the opposite side from where you put the last one.
Keep the patch in your mouth all the time, unless you are changing patches. Check to make sure

the patch is still in place after you eat or drink, use mouthwash, or brush your teeth.
To remove a patch, use your finger to gently loosen it. Then slide it down over your teeth and take it out.
Use this medicine 2 times a day, once in the morning and once in the evening (about 12 hours apart), unless your doctor tells you differently.

Missed dose: If the patch falls off within the first 8 hours, take it out and put in a new one. Put in the next patch at the regular time. If the patch falls off after more than 8 hours, take it out and put in a new one. This will count as your next dose, and the patch can stay in place for 12 hours.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, sleep apnea, a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

Gum pain, tenderness, or swelling
More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Testosterone (By injection)

Testosterone

Treats low or no testosterone levels. Also treats breast cancer in women and delayed puberty in male teenagers.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. You should not receive it if you had an allergic reaction to testosterone, benzyl benzoate, refined castor oil, or sesame oil. A man should not receive this medicine if he has breast cancer, prostate cancer, or age-related hypogonadism. A woman should not receive this medicine if she is pregnant or breastfeeding.

How to Use This Medicine:
Injectable
Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into a muscle in the buttocks. Xyosted™ is given as a shot under your skin in the stomach area.
A nurse or other health provider will give you this medicine.
Xyosted™:
You may be taught how to give your medicine at home. Make sure you understand all instructions before giving yourself an injection. Do not use more medicine or use it more often than your doctor tells you to.
You will be shown the body areas where this shot can be given. Use a different body area each time you give yourself a shot. Keep track of where you give each shot to make sure you rotate body areas.
Check the liquid in the prefilled syringe or autoinjector. It should be colorless to slightly yellow. Do not use the medicine if the liquid is cloudy, discolored, or has particles in it.
Use a new needle and syringe each time you inject your medicine.

This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Call your doctor or pharmacist for instructions.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:
Oxyphenbutazone
Blood thinner (including warfarin)
Insulin or oral diabetes medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:
It is not safe to take this medicine during pregnancy. It could harm an unborn baby. Tell your doctor right away if you become pregnant.
Tell your doctor if you have kidney disease, liver disease, lung disease, diabetes, an enlarged prostate, blood vessel or heart disease, heart failure, high cholesterol, lung disease, obesity, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:
High blood pressure
Serious lung reaction called pulmonary oil embolism (may be life-threatening)
Increased risk of prostate cancer
Increased number of red blood cells
Blood clot in your leg or lung
Slow growth in children
Increased risk of heart attack or stroke

Liver problems
Changes in mood or behavior

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, dizziness, tightening of your throat, unusual sweating
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Acne, hoarse voice, facial hair growth (women)
Changes in menstrual periods
More erections than usual or erections that last a long time
Pain, redness, or swelling where the shot was given
Swollen breasts (men)

If you notice other side effects that you think are caused by this medicine, tell your doctor.
D) Testosterone (By mouth)
Testosterone Undecanoate

Treats low or no testosterone levels.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone. Male patients who have breast cancer, prostate cancer, or age-related hypogonadism should not use this medicine. This medicine is not for use in women, especially if pregnant or breastfeeding.

How to Use This Medicine:
Capsule

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
It is best to take this medicine with food or milk.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Blood thinner (including warfarin)
Pain or cold medicine
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have liver disease, kidney disease, heart or blood vessel disease, blood disease, lung disease, diabetes, an enlarged prostate, heart failure, obesity, sleep apnea, high cholesterol, thyroid problems, or a history of heart attack or stroke.
This medicine may cause the following problems:

High blood pressure
Increased number of red blood cells
Increased risk of prostate cancer
Blood clot in your leg or lung
Increased risk of heart attack or stroke
Liver problems
Changes in mood or behavior, including thoughts of suicide

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
This medicine may lower your sperm count (with large doses). Talk with your doctor before using this medicine if you plan to have children. Some men who use this medicine have become infertile (unable to have children).
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Bone or muscle pain
Change in how much or how often you urinate, trouble urinating
Chest pain, cough, trouble breathing, tightening of your throat, unusual sweating, bluish-colored skin
Confusion, constipation, dry mouth, weight loss
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Dizziness, lightheadedness, or fainting
Numbness or weakness in your arm or leg, or on one side of your body, pain in your lower leg, sudden or severe headache, problems with vision, speech, or walking
Rapid weight gain, swelling in your hands, ankles, or feet
Unusual mood or behavior, thoughts of killing oneself
Unusual bleeding, bruising, or weakness

If you notice these less serious side effects, talk with your doctor:

Enlarged, swollen, or painful breasts in men
More erections than usual or erections that last a long time
Runny or stuffy nose, sore throat

If you notice other side effects that you think are caused by this medicine, tell your doctor.

E) Testosterone (Into the nose)

Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:

This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:

Gel/Jelly

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
This medicine is for use only in the nose. Do not get any of it in your eyes or on your skin. If it does get on these areas, rinse it off right away.
To use:

Prime the pump the first time you use this medicine. To do this, hold the pump upside down over a sink, and slowly press the pump 10 times. Rinse the sink with warm water. Wipe the tip with a clean, dry tissue. The medicine is now ready to use.
If you get the medicine on your hands, wash them with warm water and soap.
Gently blow your nose to clear the nostrils.
Insert the tip of the pump into your left nostril and gently tilt it so that it touches the side of your nose. This will make sure the medicine is applied properly.
Slowly press the pump until it stops. Remove the tip from your nose.
Repeat these steps to apply the medicine into your right nostril.
After you use the pump, wipe the tip with a clean, dry tissue and put the cap back on.
Press your nostrils together just below the bridge of your nose and lightly rub them together.
Do not blow your nose or sniff for 1 hour after you use this medicine.

Missed dose: Take a dose as soon as you remember. If it is almost time for your next dose, wait until then and take a regular dose. Do not take extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light. Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin
Other medicine that you use in your nose (including oxymetazoline)
Blood thinner (including warfarin)
Steroid (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, diabetes, an enlarged prostate, heart disease, high cholesterol, lung disease, sleep apnea, or a history of heart attack or stroke. Also tell your doctor if you have any nose or sinus problems, including allergies or history of nose or sinus surgery or a broken nose.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count

This medicine is not indicated for use in women and should never be used by a pregnant woman.
This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
VOLUME 3 OF 10 (Tabs 175-25 – 175-26)

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TAB 175-25 (continued)

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Change in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, legs, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Runny or stuffy nose, sneezing, nosebleeds, or discomfort, scabbing, or dryness of your nose
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
F) Testosterone (On the skin)
Testosterone

Treats low testosterone levels. Testosterone is a male hormone.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to testosterone, or if you have breast cancer or prostate cancer.

How to Use This Medicine:
Gel/Jelly, Kit, Liquid

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you.
This medicine should come with a Medication Guide. Ask your pharmacist for a copy if you do not have one.
Apply this medicine at the same time every day in the morning, unless your doctor tells you differently.
Apply the medicine to clean, dry, intact skin. Do not apply to skin that has a cut, scrape, or other injury.
Follow the manufacturer's directions on how to prime the pump before you use it the first time. Do not use the medicine that comes out during priming. Rinse it down the drain.
Gel:

Apply the gel only to your shoulders, upper arms, or thighs. Do not apply this medicine to your scrotum or penis.
Allow the gel to dry before you cover the area with clothing. Wait for at least 2 to 5 hours after you apply this medicine before you shower or swim.

Children and women should avoid contact with the unwashed or unclothed area where the testosterone gel has been applied. If another person accidentally gets this medicine on his or her skin, wash the area with soap and water right away.
Solution:

This medicine comes in 2 forms: a pump actuated metered dose bottle and a twist actuated metered dose bottle.
Apply an antiperspirant or deodorant spray at least 2 minutes before you apply this medicine.
Use an applicator to apply the solution to clean and dry underarms. Do not apply this medicine to any other part of your body.
Wipe any medicine that drips or runs with an applicator. Do not rub the solution with your fingers or hand.
Rinse the applicator cup with water and pat it dry with a tissue. Put the cup and cap back onto the pump actuated metered dose bottle. Put the lid back on the twist actuated metered dose bottle.
Allow the solution to dry for at least 3 minutes before you cover the area with clothing. Do not shower or swim for at least 2 hours.

Wash your hands with soap and warm water after you use this medicine.
If any medicine gets in your eyes, rinse them right away with water and call your doctor. Do not drink this medicine.
The medicine is flammable until it dries on the skin. Do not smoke or go near an open flame until the gel or solution has dried and you have covered the area with clothing.
Missed dose: Apply a dose as soon as you can. If it is almost time for your next dose, wait until then and apply a regular dose. Do not apply extra medicine to make up for a missed dose.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.
Keep the medicine in a safe place. Do not give it to anyone else, even if you have the same symptoms.
Throw away the empty pump, tube, or packet in a place where children and pets cannot reach it.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how testosterone works. Tell your doctor if you are using any of the following:

Insulin, oxyphenbutazone
Blood thinner (including warfarin)
Steroid medicine (including dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone)

Warnings While Using This Medicine:

Tell your doctor if you have kidney disease, liver disease, heart disease, lung disease, blood clotting problems, diabetes, an enlarged prostate, high cholesterol, sleep apnea, or a history of heart attack or stroke.
This medicine may cause the following problems:

Increased risk of prostate cancer
Blood clot in your leg or lung
Possible increased risk of heart attack or stroke
Lower sperm count
Liver problems

This medicine can be habit-forming. Do not use more than your prescribed dose. Call your doctor if you think your medicine is not working.
Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Changes in how much or how often you urinate, trouble urinating
Chest pain that may spread, trouble breathing, coughing up blood, unusual sweating, faintness
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Pain, redness, or swelling in your arm or leg
Swelling in your hands, ankles, or feet

If you notice these less serious side effects, talk with your doctor:

More erections than usual or erections that last a long time
Swollen breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.

TOXICOLOGY

Clinical Effects

No results available

Range of Toxicity

No results available

Treatment

No results available

ABOUT

How Supplied

No results available

Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Testosterone
Testosterone, Micronized
Testosterone Cyp
Testosterone Cypionate
Testosterone Decanoate
Testosterone Enanthate
Testosterone Isocaproate
Testosterone Phenylpropionate
Testosterone Propionate
Testosterone Propionate, Micronized
Testosterone Undecanoate

C) Orphan Drug Status

1) Testosterone

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

2) Testosterone Cypionate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

3) Testosterone Enanthate

a) This drug has one or more orphan drug designations, which may include approval or withdrawal of status; Access citation for FDA Orphan Drug Information [52]

D) Physicochemical Properties

1) Testosterone

a) Molecular Weight

1) 288.4 [85]; 288.42 [28]

2) Testosterone Cypionate

a) Molecular Weight

1) 412.61 [83]

b) Solubility

1) Testosterone cypionate is freely soluble in alcohol, chloroform, dioxane, ether, and vegetable oils, and is insoluble in water [83].

3) Testosterone Enanthate

a) Molecular Weight

1) 400.6 [73]

4) Testosterone Undecanoate

a) Molecular Weight

1) 456.7 [59]

Storage & Stability

A) Testosterone

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [50].

b) Buccal mucosa route

1) Administration

a) The rounded side of the buccal system surface should be placed against the gum and held firmly in place with a finger over the lip for 30 seconds to ensure adhesion [23].

b) If the buccal system falls off during the first 8 hours after application, replace with a new system that should be retained until a total of 12 hours have elapsed from placement of the first system; then continue usual dosing schedule. If the buccal system falls off 8 or more hours after application, apply a new buccal system that may be retained for 12 hours; then continue usual dosing schedule [23].

c) The buccal system should not be chewed or swallowed. Remove system prior to oral care and apply a new system after [23].

c) Nasal route

1) Preparation

a) Prime the pump prior to the first use by depressing the pump 10 times, discarding initial drug delivered. Wash off the gel with warm water then wipe tip with clean, dry tissue. If the product comes into contact with hands, wash hands with soap and water [22].

2) Administration

a) Completely depress the pump 1 time in each nostril; do not apply to any other part of the body. To administer, blow nose, uncap pump, and place the finger on the actuator. Then insert pump until the finger reaches the bottom of the nose. Apply gel to lateral nasal wall and remove pump once fully depressed, wiping the tip along the inside of the lateral nostril. Press on the nostrils just below the bridge of the nose and lightly massage the applied product. Do not blow nose or sniff for 1 hour [22].

d) Topical application route

1) Axiron(R)

a) If using antiperspirant or deodorant stick, roll-on, or spray, apply these 2 minutes prior to the application of testosterone topical solution as part of a normal, consistent, daily routine [20].

b) When using for the first time, prime the pump by depressing the pump-actuated or by twisting the dose dial 3 times; discard product dispensed directly into a basin, sink, or toilet and then wash the liquid away thoroughly [20].

c) Pump actuated: After priming, depress the pump completely only 1 time each time (1 pump actuation equals 30 mg) [20].

d) Pump actuated: Apply using the applicator provided. Position the nozzle over the applicator cup and depress the pump fully once. Do not fill the cup with more than 30 mg (1 pump actuation) [20].

e) Twist actuated: After priming, completely twist (180 degree turn) the dose dial 1 time (1 twist actuation equals 30 mg). The applicator should be filled with no more than 30 mg (1 twist actuation). Dosing that requires greater than 1 twist actuation must be applied in increments of 30 mg [20]

f) Keep the applicator upright. Place it up into the axilla and wipe steadily down and up into the axilla. If the solution drips or runs, wipe it back up with the applicator cup. Do not rub the solution into the skin with fingers or hand [20].

g) Apply each morning to clean, dry, intact skin of the axilla. Do not apply to any other parts of the body. Allow each application site to dry completely prior to the next application (for higher doses) or dressing [20].

h) 30 mg, 1 pump or twist actuation: Apply once to 1 axilla only (left or right) [20].

i) 60 mg, 2 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla [20].

j) 90 mg, 3 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left or right axilla [20].

k) 120 mg, 4 pump or twist actuations: Apply 1 actuation to the left axilla and 1 actuation to the right axilla. Wait for the product to dry and then apply once again 1 actuation to the left axilla and 1 actuation to the right axilla [20].

l) After use, rinse the applicator under room temperature, running water, and then pat dry with a tissue. Place the applicator and cap on the bottle for storage [20].

m) Wash hands thoroughly with soap and water after applying testosterone topical solution [20].

n) Cover the application site with clothing or dressing after the solution has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [20].

o) Wait at minimum 2 hours prior to washing the application site or swimming [20].

p) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [20].

2) AndroGel(R)

a) Prime the AndroGel(R) pump by depressing the actuator 3 times while canister is in upright position. Safely discard the gel dispensed from the first 3 actuations. Priming is only necessary before the first dose [27][49].

b) Apply to clean, dry, intact skin of shoulder or upper arm that will be covered by clothing. For the 40.5 mg (2.5-g packets), squeeze a portion of the gel from the packet into the palm of hand and apply to application sites (as this size packet needs to be split between the left and right shoulder) and repeat until entire contents have been applied. The gel may be delivered from the actuator into the palm of one hand, then applied to the intended site, or may be applied directly from the pump to the intended application site [24][27][49].

c) Apply AndroGel(R) 1.62%, to the shoulder or upper arm (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to any other part of the body, including abdomen or genitals. Wait a minimum of 2 hours prior to washing the application site or swimming [49].

d) AndroGel(R) 1%, apply to the shoulder and upper arm and/or abdomen (area of application should be limited to the area that will be covered by the patient's short sleeve t-shirt); do not apply to genitals. Avoid swimming or showering for at least 5 hours after application [51].

e) Patients should wash hands thoroughly with soap and water immediately after applying testosterone topical gel [27][49].

f) Cover the application site with clothing or dressing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [27][49].

g) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [27][49].

h) Children and women should avoid contact with unwashed or unclothed application site [27] [49].

i) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [27][49].

j) Application recommendations for AndroGel(R) 1.62% for pump or packets are in the table below [15]:

AndroGel(R) 1.62%						
Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Upper Arm and Shoulder		Total Packets *	Gel Applications per Upper Arm and Shoulder *	
		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2		Upper Arm and Shoulder #1	Upper Arm and Shoulder #2
20.25 mg	1	1	0	One 1.25-g packet	One 1.25-g packet	0
40.5 mg	2	1	1	One 2.5-g packet	Half the contents of one 2.5-g packet	Half the contents of one 2.5-g packet
60.75 mg	3	2	1	One 1.25-g AND one 2.5-g packet	One 2.5-g packet	One 1.25-g packet
81 mg	4	2	2	Two 2.5-g packets	One 2.5-g packet	One 2.5-g packet
* Weight given as gel content of packet.						

k) Application recommendations for AndroGel(R) 1% 75-g pump are in the table below [5]:

Dosing Guidelines for the AndroGel(R) 1% 75-g Multi-Dose Pump	
Prescribed Testosterone Dose	Number of Pump Actuations
50 mg daily	4 pumps once daily
75 mg daily	6 pumps once daily
100 mg daily	8 pumps once daily

3) Fortesta(TM)

a) Prime the pump by depressing the actuator 8 times while canister is in upright position; safely discard the gel dispensed from the first 8 actuations; only necessary to prime pump before the first dose [21].

b) Apply to clean, dry, intact skin of the front and inner thighs; do not apply to genitals or other parts of the body; use one finger to apply gel [21].

c) After the application site is dry, site should be covered with clothing (with sufficient length to cover application site); wash hands thoroughly with soap and water after applying gel [21].

d) Children and women should avoid contact with unwashed or unclothed application site [21].

e) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [21].

f) If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [21].

g) Application recommendations for Fortesta(TM) are in the table below [21]:

Total Dose of Testosterone	Total Pump Actuations	Pump Actuations per Thigh	
		Thigh #1	Thigh #2
10 mg	1	1	0
20 mg	2	1	1
30 mg	3	2	1
40 mg	4	2	2
50 mg	5	3	2
60 mg	6	3	3
70 mg	7	4	3

4) Testim(R)

a) Apply to clean, dry, intact skin of shoulder or upper arm; do not apply to genitals or abdomen. Wash hands thoroughly with soap and water immediately after applying [24].

b) Do not wash application site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [24].

c) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [24].

d) Children and women should avoid contact with unwashed or unclothed application site [24].

e) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [24].

5) Vogelxo(TM)

a) With multidose bottle, prime the pump 3 times before first use (discard any product released). Depress pump 4 times or empty entire contents of 1 unit-dose tube or packet into palm of the hand and immediately apply to clean, dry, intact skin of shoulder and upper arm. When the daily dosage is 100 mg, repeat on the opposite shoulder [25].

b) Do not apply to abdomen or genitals. Wash hands thoroughly with soap and water immediately after applying [25].

c) Do not wash site for at least 2 hours after application. Cover the application site with clothing after the gel has dried. If unwashed or unclothed skin comes in direct contact with the skin of another person, wash the general area of contact on the other person with soap and water as soon as possible [25].

d) Prior to any anticipated skin-to-skin contact with another person, wash the application site thoroughly with soap and water [25].

e) Children and women should avoid contact with unwashed or unclothed application site [25].

f) Product contains alcohol and is flammable. Avoid fire, flames, or smoking until the gel has dried [25].

e) Transdermal route

1) Administration

a) Immediately after opening the pouch, apply the adhesive side of the Androderm(R) system to the back, abdomen, upper arm, or thigh in a clean, dry area of the skin. Press system firmly in

place, ensuring good contact with the skin, especially around the edges. Avoid application to oily, damaged, or irritated skin. Do not apply to the scrotum, and avoid bony prominences or areas of prolonged pressure during sitting or sleeping [19].

b) Avoid swimming, showering, or washing the administration site for at least 3 hours after application [19].

c) Rotate application sites, with at least 7 days between applications to the same site [19].

B) Testosterone Cypionate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle; it is not for IV injection [83].

b) If crystals formed because product was stored at lower than recommended temperatures, they can be dissolved by warming or shaking the vial [83].

C) Testosterone Enanthate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Administration

a) Administer IM injection slowly and deeply into the gluteal muscle, avoiding intravascular injection. Crystals formed during storage at lower than recommended temperatures can be dissolved by warming or shaking the vial. A wet syringe or wet needle may turn the solution cloudy but does not affect product potency [73].

c) Subcutaneous route

1) Administration

a) Xyosted(TM) is for subQ injection in the abdominal region only. Avoid IM or intravascular injection. Do not use if the liquid in the syringe is cloudy or if visible particles are present; an air bubble is normal. Do not use if the seal is broken [74].

D) Testosterone Undecanoate

1) Preparation

a) General Information

1) NIOSH Group 3 Non-antineoplastics With Reproductive Risks [50]

2) NIOSH: This drug presents a potential occupational hazard to men and women actively trying to conceive and women who are pregnant or may become pregnant, and are breast feeding, due to presence of the drug in breast milk [50].

3) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [50].

b) Intramuscular route

1) Preparation

a) Carefully remove gray plastic cap from vial; leave the aluminum metal ring and crimp seal around the gray rubber stopper [63].

b) Using an 18-gauge needle at a 45-degree angle with the bevel oriented upward, inject 3 mL of air through the gray rubber stopper to create positive pressure in the vial, and then withdraw 3 mL (750 mg) of solution [64].

c) Expel any air bubbles from the syringe and change the syringe needle to a new IM needle [63].

d) .

2) Administration

a) For IM use only [63]

b) Slowly (over 60 to 90 seconds) inject IM deep into the gluteal muscle; care must be taken to avoid intravascular administration as this may lead to pulmonary oil microembolism; also avoid the superior gluteal arteries and sciatic nerve [63].

c) Discard any unused portion [63].

d) Alternate injection sites between left and right buttock between consecutive injections [63].

c) Oral route

1) Administration

a) Give with food [53][57].

E) Testosterone

1) Buccal mucosa route

a) Patch, Extended Release

1) Store at 20 to 25 degrees C (68 to 77 degrees F). Protect from heat and moisture [108].

2) Intramuscular route

a) Solution

1) Store at room temperature. Warming and rotating the vial between hands will redissolve any crystals that may have formed when stored at lower temperatures [88].

3) Nasal route

a) Gel/Jelly

1) Store at a controlled room temperature between 20 and 25 degree C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [22].

4) Oral route

a) Capsule

1) Refrigerate between 2 and 8 degrees C before dispensing. Do not refrigerate after dispensing. The shelf life is 3 years before opening when stored between 2 and 8 degrees C and 90 days at room temperature after the container has been opened [208].

5) Topical application route

a) Gel/Jelly/Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [28][25]. Do not freeze [21].

2) Store upright at a controlled room temperature of 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 to 86 degrees F) [209][183].

6) Transdermal route

a) Patch, Extended Release

1) Store at 25 degrees C (77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [182].

F) Testosterone Cypionate

1) Injection route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F); protect from light [83].

G) Testosterone Enanthate

1) Intramuscular route

a) Solution

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F). If crystals form, warm and rotate vial between palms of hands to dissolve [73].

2) Subcutaneous route

a) Solution

1) Store in original carton at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 to 86 degrees F). Protect from light; do not refrigerate or freeze [74].

H) Testosterone Undecanoate

1) Intramuscular route

a) Solution

1) Store in original carton at a controlled room temperature of 25 degrees C (77 degrees F) , with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Discard any unused portion [59].

2) Oral route

a) Capsule

1) Store at a temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F). Store in a dry place and protect from moisture [57].

b) Capsule, Liquid Filled

1) Store at a controlled room temperature between 20 and 25 degrees C (68 and 77 degrees F), with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [53].

Trade Names

No results available

Regulatory Status

No results available

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TAB 175-26

ESTRADIOL

DRUGDEX Evaluations

DOSING/ADMINISTRATION

Adult Dosing

Normal Dosage

Estradiol

Insertion, vaginal

Dyspareunia, Moderate to severe - Menopause

1) Imvexxy(TM)

a) Use lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Reevaluate periodically as clinically appropriate to determine if treatment is still necessary [5].

b) Initial dosage: 4 mcg intravaginally once daily at the same time each day for 2 weeks [5]

c) Maintenance dosage: 4 or 10 mcg intravaginally twice weekly (every 3 to 4 days); adjust dose based on clinical response [5]

d) Concomitant medication: Consider a progestin in postmenopausal women with a uterus to reduce the risk of endometrial cancer [5].

Oral route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The initial dose of oral estradiol for the treatment of moderate to severe vasomotor symptoms is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on followed by 1 week off). Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended initial dosing regimen is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off). Adjust to the lowest dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
2) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Initial dosage: 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off) [7]
2) Titration: Adjust dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
3) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].
4) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [7].

Breast cancer, Metastatic; for palliation only

1) The dose of oral estradiol for the palliative treatment of breast cancer in appropriately selected women and men with metastatic disease is 10 mg orally 3 times daily for at least 3 months [7].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The initial dose of oral estradiol for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 1 to 2 mg orally daily. Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 2 to 6 mg orally daily with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Pl. Trial Ex. 026

Postmenopausal osteoporosis; Prophylaxis

1) The dose of oral estradiol for the prevention of postmenopausal osteoporosis is 0.5 mg orally daily for 23 days of a 28-day cycle. The lowest effective dose has not been established [7].
2) Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [7].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Prostate cancer, Advanced, Androgen-dependent; for palliation only

1) The dose of oral estradiol for the palliative treatment of advanced androgen-dependent prostate cancer is 1 to 2 mg orally 3 times daily. Determine the effectiveness of therapy by phosphatase levels as well as by symptomatic improvement [7].

Transdermal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Emulsion

a) The initial dose of estradiol topical emulsion for the treatment of moderate to severe vasomotor symptoms is one foil patch (1.74 g each) applied topically to clean, dry skin on each thigh daily for a total dose of 3.48 g (delivering 0.05 mg estradiol per day) [35].

2) Gel

a) Divigel(R)

1) Initial dosage: One 0.25 gram packet applied topically once daily, alternating between the right and left upper thigh. Apply to a 5x7-inch surface area and allow to dry before dressing. Do not wash application site within 1 hour after application [33].

2) Maximum dosage: Adjust dosage up to a MAX of 1.25 mg topically once daily as needed [33].

3) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [33]

b) Elestrin(R)

1) Initial dosage: Apply 0.87 g (1 pump, which delivers 0.52 mg estradiol) topically once daily via the metered-dose pump in a thin layer to the upper arm and shoulder area (approximately 320 cm(2)); adjust dose based on clinical response [34].

2) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [34]

c) Estrogel(R)

1) The initial dose of estradiol topical gel 0.06% (Estrogel(R)) for the treatment of moderate to severe vasomotor symptoms is 1.25 g/day (which delivers 0.75 mg estradiol) applied topically via the metered-dose pump to clean, dry, unbroken skin on the arm. Apply in a thin layer from wrist to shoulder and allow gel to dry for up to 5 minutes before dressing [13].

3) Patch
Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.0375 mg/day applied to the skin twice weekly	lower abdomen (below the umbilicus) or buttocks
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Dosage titration: Adjust dose based on clinical response, use lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10].
Alternative dose schedule: Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

a) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be

initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].

4) Spray

a) The initial dose of transdermal estradiol spray for the treatment of moderate to severe vasomotor symptoms is one spray (delivering 1.53 mg estradiol) applied to the forearm every morning. Dosage adjustment should be guided by the clinical response of the patient. If needed, the dose may be increased to 2 or 3 sprays daily based upon clinical response [36].

Atrophic vulva (Moderate to Severe) - Menopause

1) Gel

a) Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

2) Patch

The initial dose of transdermal estradiol patches for the treatment of vulvar atrophy is outlined in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][8][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19] [8][9][11][12].

b) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Gel

a) Usual dosage: Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [13].

2) Patch

Initial dosage is provided in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip

Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][9][11][12].
Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [19][8][9][11][12].

c) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

The initial dose of transdermal estradiol patches for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is outlined in the following table [19][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [19][8][9][11][12]. Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][9][11][12].
1) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 0.025 to 0.2 mg/day transdermally with or without antiandrogens or gonadotropin-releasing hormone agonist; replace patch every 3 to 5 days [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks

Minivelle(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen (below umbilicus) or buttocks
Vivelle-Dot(R)	0.025 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust according to severity of symptoms, response of the patient, biochemical markers, and measurements of bone mineral density. Adjust to lowest dose that will provide effective control [8][12].
May be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].
1) Concomitant therapy: Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [8][12].
2) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Vaginal route

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended dose of estradiol vaginal cream is 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period. A maintenance dose of 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Vaginal Cream

a) Initial dosage: 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period [14].

b) Maintenance dosage: 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [14].

2) Vaginal Ring

a) Usual dosage: 1 ring inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3 to 6 month intervals [15].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [15].

3) Vaginal Insert

a) Initial dosage: 1 vaginal insert (10 mcg) inserted vaginally once daily for 2 weeks, preferably at the same time each day. The recommended maintenance dose is 1 vaginal insert 10 mcg twice weekly. Reevaluate treatment, and attempt to taper or discontinue periodically [16].

Menopause - Urethral atrophy (Moderate to Severe)

1) The recommended dose of estradiol vaginal ring is 1 ring (contains 2 mg estradiol) inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3- to 6-month intervals [15].

General Dosage Information

a) In postmenopausal women with a uterus, initiate progestin with estrogen to reduce the risk of endometrial cancer [34][19][8][12][7][38][13][14][15][35][36]; women with a history of hysterectomy and endometriosis may need a progestin [34][16][29].

b) Use estrogen, alone or with a progestin, at the lowest effective dose and for the shortest duration consistent with individual treatment goals and risks; reevaluate periodically (generally at 3 to 6 month intervals) to determine if treatment is still necessary [34][16][29][19][8][12][7][38][13][14][15][35][36].

Estradiol Acetate

Vaginal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day inserted intravaginally every 3 months, dose adjusted based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals; reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day ring inserted intravaginally every 3 months and dose adjust based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals, and reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Estradiol Cypionate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The usual dose of estradiol cypionate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 1 to 5 milligrams injected intramuscularly every 3 to 4 weeks [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Decreased estrogen level - Female hypogonadism syndrome

1) The dose of estradiol cypionate for the treatment of hypoestrogenism due to hypogonadism is 1.5 to 2 milligrams injected intramuscularly at monthly intervals [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The dose of estradiol valerate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) The usual dose for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals

and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The dose of estradiol valerate for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 5 to 30 mg IM every 2 weeks OR 2 to 10 mg IM every week with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hormone sensitive prostate cancer, Advanced, for palliation only

1) The dose of estradiol valerate for the palliative treatment of advanced androgen-dependent prostate cancer is 30 milligrams or more injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 1 or 2 weeks [57].

Dosage in Renal Failure

A) No specific recommendations are available [10].

Dosage in Hepatic Insufficiency

A) Use is contraindicated in patients with hepatic impairment or disease [10].

Dosage in Other Disease States

A) Cardiovascular Disorders

1) Immediately discontinue estrogen with or without progesterone therapy immediately if DVT, pulmonary embolism, stroke, or myocardial infarction occurs [10].

B) Cholestatic Jaundice

1) Discontinue use if reoccurs [10]

C) Fluid Retention

1) Discontinue use if medically concerning [10]

D) Hypercalcemia

1) Discontinue use if occurs [10]

E) Pancreatitis

1) Discontinue use if occurs [10]

F) Visual Abnormalities

1) Permanently discontinue use if papilledema or retinal vascular lesions occur [10].

Pediatric Dosing

Normal Dosage

Estradiol

Oral route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 5 mcg/kg/day orally for 6 months; increase dose by 5 mcg/kg/day every 6 months to an adult dosage of 2 to 6 mg/day [1]

b) Postpubertal transgender female: Initial, 1 mg/day orally for 6 months, then 2 mg/day [1]

c) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Transdermal route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 6.25 to 12.6 mcg/24 hours applied every 3.5 days; increase dosage by 12.5 mcg/24 hours every 6 months to adult dosage of 50 to 200 mcg/24 hours to mimic physiological estradiol levels [1]

b) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

a) Safety and efficacy in pediatric patients have not been established [34][16][29][19][41][7][13][38][8][12][35][36][14][15].

Estradiol Acetate

1) Safety and efficacy of the vaginal ring and oral tablets has not been established in pediatric patients [59][61].

Estradiol Valerate

1) Safety and efficacy not established in pediatric patients [58].

FDA Uses

Estradiol

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets, topical gel and emulsion, transdermal patch and spray); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, transdermal patches, transdermal spray, topical gel, and topical emulsion are indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [34][33][29][19][7][8][12][36][13][35].

Evidence

Estradiol oral tablets, transdermal patches, transdermal spray, topical gel, and topical emulsion have been shown to be effective [34][33][29][19][7][8][12][36][13][35] Transdermal estrogen use in postmenopausal women was not associated with an increased risk of VTE compared with oral estrogen in the ESTHER study [37].

c) Adult:

1) Transdermal versus Oral

a) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of VTE among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% CI, 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar

results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Transdermal Emulsion

a) Estradiol topical emulsion was statistically better than placebo at 4 and 12 weeks for relief of both the frequency and severity of moderate to severe vasomotor symptoms [35]. Postmenopausal women (n=200; mean age 52 years) were randomized to receive estradiol topical emulsion 3.45 g (containing 2.5 mg of estradiol per g) or placebo daily for 12 weeks. Mean change in the number of hot flashes and mean change in severity score from baseline is summarized below:

	EstraSorb(R) 3.45 g/day	Placebo
Number of Daily Hot Flushes (Intent-to-Treat Population)		
Baseline Mean	13.05	13.63
Week 4 Mean	4.42	7.46
Mean Change at Week 4	-8.56 p less than 0.001	-5.97
Week 12 Mean	2	5.88
Mean Change at Week 12	-11.11 p less than 0.001	-7.2
Severity Score of Daily Hot Flushes (Intent-to Treat-Population, Most Recent Value Carried Forward)		
Baseline Mean	2.36	2.44
Week 4 Mean	1.47	1.99
Mean Change at Week 4	-0.89 p less than 0.001	-0.45
Week 12 Mean	0.92	1.88
Mean Change at Week 12	-1.44 p less than 0.001	-0.55

3) Transdermal Gel

a) Significant reductions in the daily mean frequency and severity of moderate to severe hot flushes were observed at 5 and 12 weeks with estradiol topical gel (Elestrin(R)) 0.87 g/day compared with placebo during a randomized 12-week trial involving postmenopausal women (n=484; mean age, 54 years; age range, 28 to 74 years). Following amendment to identify the lowest effective dose, patients were randomized to Elestrin(R) 0.87 g (containing 0.52 mg estradiol), 1.7 g (containing 1.04 mg estradiol) or placebo topically once daily for 12 weeks. The change from baseline in the mean daily frequency and severity of hot flushes is summarized in the following table [34].

	Elestrin(R) 0.87 g/day (n=136)	Elestrin(R) 1.7 g/day (n=142)	Placebo (n=137)
Frequency of Daily Hot Flushes			
Baseline (mean)	13.3	13.1	13.5
Week 4 (mean change)	-6.5*	-8	-5.1
Week 5 (mean change)	-7.5	-8.8	-5.1
Week 12 (mean change)	-8.5	-10	-5.4
Severity Score of Daily Hot Flushes			
Baseline Mean	2.4	2.4	2.4
Week 4 (mean change)	-0.5*	-0.7	-0.2
Week 5 (mean change)	-0.5	-0.8	-0.2
Week 12 (mean change)	-0.8	-1.2	-0.3
Key: *p-value non-significant			

b) Statistically significant reductions in the daily median frequency and severity of moderate to severe hot flushes were observed in patients receiving estradiol 0.1% topical gel (Divigel(R)) compared with placebo during a randomized, double-blind, 12-week trial involving postmenopausal women (n=495; mean age 54.6 years) [38]. Patients were randomized to Divigel(R) 0.25 g, 0.5 g, 1 g (containing 0.25, 0.5, and 1 mg estradiol, respectively) or placebo once daily to the thigh for 12 weeks. The change from baseline in the median daily frequency and severity of hot flushes is summarized in the following table:

	Divigel(R) 0.25 g/day	Divigel(R) 0.5 g/day	Divigel(R) 1 g/day	Placebo
Frequency of Daily Hot Flushes				
Baseline Median	9.72	9.24	9.64	9.32
Median Change at Week 4	-5 p=0.132	-5.73 p=0.011	-7.2 p less than 0.001	-3.63
Median Change at Week 7	-6.62 p less than 0.001	-7.14 p less than 0.001	-7.71 p less than 0.001	-4.37
Median Change at Week 12	-6.88 p less than 0.001	-7.29 p less than 0.001	-8.35 p less than 0.001	-4.48
Severity of Daily Hot Flushes				
Baseline Median	2.52	2.51	2.52	2.54
Median Change at Week 4	-0.07 p=0.283	-0.18 p less than 0.001	-0.47 p less than 0.001	-0.04
Median Change at Week 7	-0.24 p less than 0.001	-0.46 p less than 0.001	-1.06 p less than 0.001	-0.06
Median Change at Week 12	-0.33 p=0.021	-0.56 p=0.002	-1.69 p less than 0.001	-0.13

c) Statistically significant reductions in the daily mean frequency and severity of moderate to severe hot flushes were observed at 4 and 12 weeks in patients receiving estradiol 0.06% topical gel (EstroGel(R)) compared with placebo during a randomized 12-week trial involving postmenopausal women (n=145) [13]. Patients were randomized to EstroGel(R) 1.25 g (containing 0.75 mg estradiol) or placebo once daily for 12 weeks. The change from baseline in the mean daily frequency and severity of hot flushes is summarized in the following table:

	EstroGel(R) 1.25 g/day	Placebo
Frequency of Daily Hot Flushes		
Baseline Mean	10.33	11.01
Week 4 Mean	4.43	5.95
Mean Change at Week 4	-5.91 p=0.019	-5.06
Week 12 Mean	2.79	5.17
Mean Change at Week 12	-7.55 p=0.043	-5.84
Severity Score of Daily Hot Flushes		
Baseline Mean	2.36	2.3
Week 4 Mean	1.73	2
Mean Change at Week 4	-0.63 p=0.005	-0.31
Week 12 Mean	1.33	1.76
Mean Change at Week 12	-1.03 p less than 0.001	-0.54

4) Transdermal Patch

a) Transdermal estradiol patches (Alora(R)) were superior to placebo at 4 and 12 weeks for relief of the frequency and severity of vasomotor symptoms in a randomized, double-blind trial involving 268 postmenopausal women [8]. Women having estradiol and follicle stimulating hormone (FSH) serum concentrations in the postmenopausal range and who experienced an average of at least 60 moderate to severe hot flushes per week were randomized to either Alora(R) 0.05 or 0.01 milligram/day twice a week or placebo for 12 weeks. The mean changes in frequency of vasomotor symptoms from baseline are summarized below:

Week of Therapy	Alora(R) 0.05 mg/day	Alora(R) 0.1 mg/day	Placebo
Baseline mean frequency of moderate to severe vasomotor symptoms	90	85	92
4 Week mean change from baseline*	-57	-70	-45
8 Week mean change from baseline	-65	-77	-49
12 Week mean change from baseline*	-68	-79	-54

* Indicates a statistically significant difference between both treatment groups and placebo using an ANCOVA model

b) Transdermal estradiol (Climara(R)) 0.05 and 0.1 mg patches were statistically superior to placebo for the relief of the frequency of hot flushes in a randomized controlled trial involving 214 postmenopausal women. Women who experienced a minimum of 5 moderate to severe hot flushes per week or a minimum of 15 hot flushes of any severity per week, for 2 consecutive weeks, were randomized to treatment with 0.05 mg estradiol patch, 0.1 mg estradiol patch, or placebo in a cyclical regimen for 11 weeks. Data were available from 191 patients for efficacy analysis. In the 0.05 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 46 at baseline to 20. In the 0.1 mg estradiol group, the mean weekly hot flush rate across all treatment cycles decreased from 52 at baseline to 16. The mean weekly hot flush rate in the placebo group declined from 53 at baseline to 46. Compared with placebo, both estradiol treatment groups demonstrated a statistically significant greater mean decrease in hot flushes across all treatment cycles (p less than 0.05) [19].

c) Transdermal estradiol (Climara(R)) 0.025 mg/day was superior to placebo at 4 and 12 weeks for relief of the frequency and severity of moderate to severe vasomotor symptoms in a randomized, double-blind trial involving 187 postmenopausal women. Women were randomized to Climara(R) 0.025 mg/day or placebo continuously for up to three 28-day cycles. The mean changes in frequency of vasomotor symptoms from baseline are summarized below [19]:

Week of Therapy	Climara(R) 0.025 mg/day	Placebo
4 Week Mean Change*	-6.45 (p less than 0.002)	-5.11
8 Week Mean Change*	-7.69	-5.98
12 Week Mean Change*	-7.56 (p less than 0.003)	-5.98
*: from baseline in the number of moderate-to-severe vasomotor symptoms		

d) Transdermal estradiol (Vivelle(R)) 0.075 and 0.1 mg patches were superior to placebo in relieving vasomotor symptoms at week 4 and in maintaining relief through weeks 8 and 12 during two controlled trials (n=356) [11][12]. The original study demonstrated that the 0.0375 and 0.05 mg patches did not differ from placebo until approximately week 6, therefore, an additional 12-week placebo-controlled trial involving 255 postmenopausal women was performed with the intention of identifying the efficacy of the 0.0375 mg patch. The 0.0375 mg patch was superior to placebo in reduction of frequency and severity of hot flushes at week 4 and maintained efficacy through weeks 8 and 12. Results with regard to the mean change in mean number of daily hot flushes are summarized in the following table:

Mean change number of hot flushes	Vivelle(R) 0.0375 mg/day	Placebo
Week 4	-8.4 p less than 0.05	-4.9
Week 8	-9.4 p less than 0.05	-5.8
Week 12	-9.8 p less than 0.05	-6.6

e) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

5) Transdermal Spray

a) Estradiol transdermal spray was found to be an effective treatment for vasomotor symptoms in a 12-week, double-blind, randomized trial involving 454 postmenopausal women (mean age, 53 years) [36]. Patients were randomized to at least one dose of the transdermal spray (1, 2, or 3 sprays delivering 1.53 mg of estradiol/spray) or placebo. At baseline, the mean total frequency of moderate to severe vasomotor symptoms was 56 or more per week (8 or more per day). Efficacy was considered clinically and statistically significant when a difference of at least 2/day or 14/week reduction in hot flush frequency was achieved and when a statistically significant

reduction in severity occurred with estradiol spray compared with placebo. At weeks 4 and 12, 1 to 3 sprays of estradiol was superior to placebo in terms of frequency and severity of hot flushes.

	1 spray/day	2 sprays/day	3 sprays/day
Frequency of Daily Hot Flushes			
Baseline Median (estradiol, placebo)	11.81, 12.41	12.66, 12.13	10.78, 12.55
Mean Change at Week 4 (estradiol, placebo)	-6.26, -3.64 p=0.001	-7.30, -4.74 p=0.0027	-6.64, -4.54 p=0.0002
Mean Change at Week 12 (estradiol, placebo)	-8.10, -4.76 p=0.0004	-8.66, -6.19 p=0.0099	-8.44, -5.32 p less than 0.0001
Severity of Weekly Hot Flushes			
Baseline Median (estradiol, placebo)	2.53, 2.55	2.54, 2.54	2.58, 2.54
Mean Change at Week 4 (estradiol, placebo)	-0.47, -0.19 p=0.0573	-0.57, -0.25 p=0.016	-0.43, -0.13 p=0.0031
Mean Change at Week 12 (estradiol, placebo)	-1.04, -0.26 p less than 0.0001	-0.92, -0.54 p=0.0406	-1.07, -0.31 p less than 0.0001

6) Vaginal

a) An estradiol vaginal ring delivering 50 or 100 mcg of estradiol daily was effective in reducing the number and severity of vasomotor symptoms and improving urogenital symptoms, compared with placebo. In a double-blind trial, women with moderate to severe vasomotor symptoms were randomized to a vaginal ring delivering 50 mcg estradiol (n=113), or 100 mcg estradiol (n=112), or a placebo vaginal ring (n=108) daily for 13 weeks. Vasomotor symptoms significantly improved in both treatment groups compared with placebo (p less than 0.05). There was a trend toward greater improvement in patient assessment of urogenital signs with active treatment compared with placebo. For women with vaginal atrophy, the maturation index improved significantly in both the 50 and 100 mcg treatment groups compared with placebo (p=0.008 and p=0.003, respectively). Scores for climacteric symptoms also improved significantly (p less than 0.05) for both treatment groups compared with placebo. The vaginal rings were well tolerated [39]. Similar results were noted in a prospective, multicenter, randomized, double-blind trial comparing estradiol vaginal ring (delivering 50 mcg/day) with oral estradiol (1 mg/day). A total of 159 postmenopausal women were randomized to treatment for 24 weeks. Significant improvement in climacteric symptoms scores were noted at 12 and 24 weeks in both treatment groups (p less than 0.05). There was also significant improvement in scores of anxiety, depression, and sexual dysfunction for both groups (p less than 0.05). The frequency of hot flushes was significantly reduced (p less than 0.001) for both groups at 12 and 24 weeks. No significant between-group differences were noted [40].

Atrophic vulva (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablet, EstroGel(R), transdermal patch, vaginal cream); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, EstraGel(R), transdermal patches, and vaginal cream are indicated for the treatment of moderate to severe symptoms of vulvar atrophy associated with menopause [19][7][13][8][9][11][12][14]

Limitation of Use

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][7][13][8][9][11][12]

Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablet, EstroGel(R), transdermal patch, vaginal formulations); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets, topical gel EstroGel(R), transdermal patches, and vaginal cream, ring, and inserts are indicated for the treatment of moderate to severe symptoms of vaginal atrophy associated with menopause [16][19][7][13][8][9][11][12][14][15].

Limitation of Use

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][7][13][8][9][11][12]

c) Adult:

1) Transdermal

a) Transdermal estradiol (Alora(R)) improved vaginal atrophy in a placebo-controlled trial. Postmenopausal women were treated with transdermal estradiol 0.05 mg/day (n=54), transdermal estradiol 0.1 mg/day (n=45), or placebo (n=46). Vaginal cytology was obtained before treatment and at the last visit. The mean increase in superficial cells was 18.7%, 23.7%, and 8.7% for the estradiol 0.05 mg/day, 0.1 mg/day, and placebo groups, respectively. Additionally, corresponding reductions in basal/parabasal and intermediate cells were also noted [8].

b) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

2) Vaginal

a) After 12 weeks of treatment, estradiol 10 mcg vaginal inserts were significantly superior to placebo in decreasing the severity of a composite score of most bothersome symptoms associated with atrophic vaginitis (vaginal dryness, vaginal and/or vulvar irritation or itch, vaginal soreness, dysuria, dyspareunia, and vaginal bleeding associated with intercourse). A 12-month, randomized study enrolled 309 postmenopausal women who inserted one 10 mcg estradiol insert (or placebo) intravaginally daily for 14 days. They then used 1 insert twice weekly for 50 weeks. There was a significant increase in the percentage of vaginal superficial cells at week 12 with estradiol compared with placebo (13.2% compared with 3.8%), a significant decrease in parabasal cells at week 12 (-37% compared with -9.3%), and a significant mean reduction between baseline and week 12 in vaginal pH score (-1.3 compared with -0.4) [16].

b) The efficacy of estradiol vaginal ring (Estring(R)) for the treatment of postmenopausal vaginal atrophy was demonstrated in two controlled trials that compared estradiol vaginal ring with conjugated estrogens vaginal cream. Both studies concluded there was no difference in efficacy between the two treatments with respect to the physicians' and patients' assessment of vaginal symptom improvement after 12 weeks of treatment. In both studies, the treatments demonstrated similar efficacy in reduction of vaginal pH levels and maturation of vaginal mucosa after 12 weeks. Endometrial overstimulation occurred in 11% of patients receiving conjugated estrogens vaginal cream compared with 0% in patients receiving estradiol vaginal ring. Patients preferred the estradiol ring over the conjugated estrogens cream due to comfort and ease of use [15].

c) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or oestrogen cream. The 12-week treatment period consisted of a vaginal ring that uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period, no statistically

significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

d) Although estradiol vaginal cream and conjugated estrogen vaginal cream are similarly effective in treating postmenopausal vaginal atrophy, estradiol may be preferred because of decreased undesirable effects [24]. Conjugated estrogens, given intravaginally, were found to cause a significant elevation in estrone and estradiol levels and an increase in sex hormone binding globulin (SHBG) capacity. Estradiol induced no such changes. Histological examination in 2 patients from each group showed no evidence of endometrial hyperplasia in the patients receiving estradiol, while moderate hyperplasia was found in both patients receiving conjugated estrogens.

e) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms [25].

Breast cancer, Metastatic; for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol oral tablets are indicated as palliative treatment of metastatic breast cancer in appropriately selected men and women [7]

c) Adult:

1) A randomized study involving 328 patients with stage II/IIIA breast cancer found no improvements in relapse-free or overall survival when ethinyl estradiol was used to prime cancer cells prior to chemotherapy (Bontenbal et al, 2000). Patients received 4 cycles of fluorouracil 500 mg/meter squared, doxorubicin 50 mg/meter squared, and cyclophosphamide 500 mg/meter squared once every 4 weeks. Of the 328 patients, 162 received no estrogenic recruitment and 166 received 2 doses of 0.5 mg ethinyl estradiol, 24 hours prior to and at the time of chemotherapy. Within a median follow-up of 6.8 years, 177 patients relapsed, of which 123 died. There were no significant differences between the treatment groups related to relapse-free, local recurrence-free, distant metastasis-free, and survival. This conclusion supports the findings of other randomized studies.

2) Oral micronized estradiol 1 mg 3 times daily for days 0 through 20 every other month alternating with tamoxifen 20 mg twice daily for days 0 through 27, in addition to chemotherapy, resulted in an objective response rate of 39% (28% complete response and 11% partial response) among 25 patients with metastatic breast cancer [26]. This study protocol did not evaluate the role of estradiol in the priming of tumor cell proliferation in vivo nor its ultimate clinical effect by comparison with a control group. Overall, the treatment was nonaggressive and well-tolerated, suggesting that estradiol may play a useful role in the treatment of metastatic, estrogen receptor-positive breast cancer; however, further study is needed to define its optimal use.

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets and transdermal patches); Pediatric, no

Efficacy: Adult, Effective; Pediatric, Effective

Recommendation: Adult, Class I; Pediatric, Class IIb

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol oral tablets and transdermal patches are indicated for the treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure [19][7][8][9][11][12]

c) Adult:

1) Transdermal estradiol has been shown to be effective in inducing puberty in a study of 15 hypogonadal women [41]. The following protocol was used: transdermal estradiol 25 mcg/day patch applied twice weekly for 3 weeks of each month for 6 months, later adding oral medroxyprogesterone acetate 5 to 10 mg daily during the third week of each cycle, and finally increasing the estradiol dose of days 15 to 25 by substituting the 50 mcg/day patch. The patients ranged in age from 14 to 27 years, with the treatment period ranging from 0.5 to 3 years. No adverse effect on lipoprotein levels was seen. Transdermal estradiol appears to be safe and effective in this setting.

d) Pediatric:

1) Transdermal estradiol has been shown to be effective in inducing puberty in a study of 15 hypogonadal women [41]. The following protocol was used: transdermal estradiol 25 mcg/day patch applied twice weekly for 3 weeks of each month for 6 months, later adding oral medroxyprogesterone acetate 5 to 10 mg daily during the third week of each cycle, and finally increasing the estradiol dose of days 15 to 25 by substituting the 50 mcg/day patch. The patients ranged in age from 14 to 27 years, with the treatment period ranging from 0.5 to 3 years. No adverse effect on lipoprotein levels was seen. Transdermal estradiol appears to be safe and effective in this setting.

Dyspareunia, Moderate to severe - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (Imvexxy(TM) vaginal insert); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol vaginal insert (Imvexxy(TM)) is indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause [5].

Evidence

In a randomized trial, estradiol vaginal inserts significantly improved dyspareunia severity scores at week 12 compared with placebo. The percentages of superficial and parabasal cells and vaginal pH were also significantly improved; as well as vaginal dryness and vulvar and/or vaginal irritation or itching [6].

c) Adult:

1) In a randomized trial (REJOICE), estradiol vaginal inserts significantly improved dyspareunia severity scores at week 12 compared with placebo in postmenopausal women with vulvar and vaginal atrophy (N=764). Mean change from baseline of the dyspareunia severity scores was -1.52, -1.69, and -1.69 for 4-, 10-, and 25-mcg doses vs -1.28 for placebo. At week 12, the percentage of vaginal superficial cells significantly increased for all doses (17% to 23% vs 6% for placebo), the percentage of vaginal parabasal cells significantly decreased (41% to 46% vs 7% for placebo), and vaginal pH was significantly improved. Vaginal dryness and vulvar and/or vaginal irritation or itching were also significantly improved. Dyspareunia was identified as the most bothersome symptom and was associated with vulvar and vaginal atrophy. Included women also had 5% or less superficial cells on vaginal smear and a vaginal pH of greater than 5. Headache was the most commonly reported treatment-emergent adverse event. Patients self-administered digitally a 4-, 10-, or 25- mcg insert into the vagina once daily for 2 weeks, then twice weekly for 10 weeks [6].

Menopause - Urethral atrophy (Moderate to Severe)

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (vaginal ring); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol vaginal ring is indicated for the treatment of urogenital symptoms associated with postmenopausal atrophy of the lower urinary tract (urinary urgency and dysuria) [15].

c) Adult:

1) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or oestrogen cream. The 12-week treatment period consisted of a vaginal ring which uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period no statistically significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

Postmenopausal osteoporosis; Prophylaxis

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral tablets and transdermal patches); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indication

Estradiol transdermal patch is indicated for the prevention of postmenopausal osteoporosis [10][29][7][8][12].

Limitation of Use

Consider therapy only for women at significant risk of osteoporosis and for whom nonestrogen medications are not appropriate [29][19][7][8][12].

The mainstays for decreasing the risk of postmenopausal osteoporosis are weight-bearing exercise, adequate calcium and vitamin D intake, and when indicated, pharmacologic therapy [7][8][12].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

c) Adult:

1) General Information

a) Investigators looked at 670 white women in the Framingham Study cohort, with a mean age of 76 years, to determine whether bone mass in elderly women was affected by earlier estrogen, and how long women needed to take estrogen to have a beneficial effect on bone density as they get older. The bone mineral density of these women was measured at the femur, spine, shaft of the radius, and ultradistal radius. Density of the radius and ultradistal radius was significantly higher in women who had taken estrogen for at least 10 years. Bone mineral density of the spine was significantly higher only in women who had taken estrogen for 7 to 9 years; femoral bone density values were higher (but not significantly) in women who had used estrogen for 7 to 9 years, or 10 or more years. The women younger than 75 years old who had taken estrogen for at least 7 years had significantly higher bone mineral density than the women who had never taken estrogen. In the women older than 75 years who had taken estrogen for a comparable duration, the overall bone density was only slightly higher than in women who had never taken estrogen, although the bone mineral density in the shaft of the radius of estrogen takers was significantly higher. Among women younger than 75 years old, the bone mineral density was positively correlated with the duration of estrogen therapy; however, both the correlation and the benefits seem to be lost in women older than 75 years. This study suggests that for long-term preservation of bone mineral density, women should take estrogen for at least 7 years after menopause. This duration may still not be adequate to protect women 75 years and older from fracture [30].

2) Oral

a) Loss of vertebral bone mass was prevented in postmenopausal women who received oral estradiol during a randomized, double-blind, dose-ranging study. Patients were randomized to estradiol 0.5 mg daily or placebo for 23 days of a 28-day cycle for a total of 2 years. After estradiol was discontinued, bone mass declined at a rate similar to the immediate postmenopausal period. There was no evidence that treatment with estradiol was able to restore bone mass to premenopausal levels [7].

b) A 3-year study of early postmenopausal women (n=153) concluded that thinness and smoking are important risk factors for the development of osteoporosis, but are counteracted by hormone replacement therapy (Bjarnason and Christiansen, 2000). In the study, patients were randomized to receive 1 or 2 mg of oral estradiol daily or placebo. Baseline BMI was significantly (p less than 0.01) associated with bone resorption with a subsequent association between BMI and bone mineral density (BMD). A low BMI was associated with an increased rate of loss (p less than 0.01), while response to either 1 or 2 mg estradiol treatment was independent of BMI. Smoking was associated with a 4% lower BMD at baseline compared with that of nonsmokers and this effect was additive with that of BMI. The increase in serum estradiol during treatment for smokers was half that of nonsmokers. Serum follicle-stimulating hormone (FSH) was significantly less suppressed in smokers in the estradiol 1 mg treatment group, while the FSH serum concentrations were similar among smokers and nonsmokers in the placebo and 2 mg treatment group. The data suggest that osteoporosis screening strategies may benefit from including these risk factors.

c) Oral micronized estradiol 0.5 to 2 mg daily in cyclic fashion for 18 months was significantly better than placebo for prevention of bone loss in postmenopausal women in a double-blind, placebo-controlled study. During the double-blind phase, no significant increases in bone density were seen. Further data were obtained after switching the placebo group to treatment with 1 mg daily for an additional 18 months, during which time significant increases in bone density were seen (4.3% annually). Significant net gains in vertebral bone density with micronized estradiol were also reported (Munk-Jensen, 1988); however, estradiol was given continuously in this study rather than cyclically, a regimen less favored due to possible increased risk of endometrial cancer [31].

3) Transdermal

a) Treatment with transdermal estradiol (Alora(R)) patch was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized, double-blind study involving 355 hysterectomized, nonosteoporotic, postmenopausal women (mean age, 53.2 years). The study participants were randomized to transdermal estradiol (Alora(R)) 0.025, 0.05, or 0.075 mg/day every 3 or 4 days or placebo. Additionally, all patients received oral elemental calcium 1000 mg daily. The primary endpoint was the percent change in BMD from baseline to year 2. The average lumbar spine T-score at baseline was 0.64. A total of 196 patients were included in the completer population while 258 patients were included in the intent-to-treat, last observation carried forward (LOCF) population. All doses of transdermal estradiol were statistically superior to placebo in terms of percent change in BMD from baseline. The mean percent changes in BMD at 2 years (LOCF) were 1.45%, 3.39%, 4.24%, and -0.8% for estradiol 0.025, 0.05, 0.075 mg/day and placebo, respectively [8].

b) Treatment with transdermal estradiol (Climara(R)) was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized study involving 175 hysterectomized, nonosteoporotic, postmenopausal women. The study participants were randomized to transdermal estradiol (Climara(R)) 0.025, 0.05, 0.06, or 0.1 mg/day (n=129) or placebo (n=46). The primary endpoint was the percent change in anterior-posterior lumbar spine BMD from baseline to year 2. Of the patients randomized, a total of 134 contributed to the last observation carried forward (LOCF) population. All doses of transdermal estradiol demonstrated a statistically significant overall treatment effect at each timepoint compared with placebo, which implied bone preservation versus bone loss for all active treatment groups. The percent change in total hip BMD was statistically significant for all estradiol treatment groups compared with placebo [19].

c) Treatment with transdermal estradiol (Vivelle(R)) was superior to placebo with regard to effects on bone mineral density (BMD) during a 2-year, randomized, double-blind study involving 261 hysterectomized and nonhysterectomized, postmenopausal women with no evidence of osteoporosis (mean age, 52 years). The study participants were randomized to transdermal estradiol (Vivelle(R)) 0.025, 0.0375, 0.05, or 0.1 mg/day (n=194) or placebo (n=67). Additionally, all patients received oral elemental calcium 1000 mg daily and nonhysterectomized women received oral medroxyprogesterone acetate 2.5 mg daily. The primary endpoint was the percent change in BMD of the AP lumbar spine from baseline to year 2. Of the 261 women randomized, 232 contributed to the last observation carried forward (LOCF) population. All doses of transdermal estradiol were associated with an increase in BMD of the AP lumbar spine while placebo was associated with a decrease in BMD. All estradiol doses, with the exception of 0.05 mg/day, were significantly superior to placebo (p less than 0.05) at all time points and the highest dose of transdermal estradiol was superior to the 3 lower doses. Additionally, all doses of transdermal estradiol were significantly superior to placebo (p less than 0.05) with regard to percent change in BMD of the femoral neck from baseline to year 2, a secondary efficacy endpoint. Again, the highest transdermal estradiol dose was superior to the 3 lower doses for the secondary endpoint [11][12].

d) Transdermal estradiol 0.025 to 0.1 mg daily demonstrated efficacy in the prevention of postmenopausal bone loss. A multicenter, randomized, placebo-controlled, parallel-group study evaluated the efficacy, safety, and tolerability of an estradiol transdermal system over 2 years for the prevention of postmenopausal bone loss. Postmenopausal women (n=261) were randomized to apply the estradiol transdermal system (0.025,

0.0375, 0.05, or 0.1 mg per day) or matching placebo twice a week for 2 years. After 2 years of treatment, there were significant differences at all doses of estradiol in bone mineral density of the L1-L4 anteroposterior lumbar spine when compared to placebo (0.1 and 0.05 mg/day, p less than 0.001; 0.0375 mg/day, p equal to 0.024; 0.025 mg/day, p equal to 0.002). There were also significant differences in the bone mineral density of the femoral neck (all, p less than or equal to 0.044). All doses of the transdermal estradiol system were well tolerated [32].

Prostate cancer, Advanced, Androgen-dependent; for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (oral only); Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol oral tablets are indicated for palliative treatment of advanced androgen-dependent prostate cancer [7].

In the multicenter, randomized, open-label, phase 2 Prostate Adenocarcinoma: TransCutaneous Hormones versus luteinizing-hormone-releasing hormone agonists (PATCH) trial (n=254), 92% of patients with locally advanced or metastatic prostate cancer who received transdermal estrogen achieved castrate testosterone concentrations at 3 months. Cardiovascular events occurred in 10.1% of patients at a median of 19 months [27].

Transdermal estradiol produced an effective tumor response, was associated with minimal cardiovascular toxicity, prevented andropause symptoms, and improved quality-of-life scores [28].

c) Adult:

1) Transdermal Patch

a) In the multicenter, randomized, open-label, phase 2 Prostate Adenocarcinoma: TransCutaneous Hormones versus luteinizing-hormone-releasing hormone agonists (PATCH) trial (n=254), 92% of patients with locally advanced or metastatic prostate cancer who received transdermal estrogen achieved castrate testosterone concentrations at 3 months, with cardiovascular events occurring in 10.1% of patients at a median of 19 months. Men (median age, 74 years; interquartile range, 69 to 79 years; metastatic disease, 36%) with testosterone levels of 6 nanomoles/liter (nmol/L) or higher were randomized 1:2 to receive a luteinizing-hormone-releasing hormone agonist (LHRHa) prescribed according to local practice (n=85) or transdermal estrogen 3 patches (100 mcg/24 hours) changed twice weekly for 4 weeks, then (if serum testosterone levels were 1.7 nmol/L or lower) 2 patches changed twice weekly (regimen 1; n=33) or 4 patches changed twice weekly for 4 weeks followed by 3 patches changed twice weekly when castrate testosterone levels were reached (regimen 2; n=136). Radical radiotherapy to the prostate was initially not permitted in the study but was later allowed to demonstrate changes in practice. Second-line therapy was permitted in cases of disease progression, including changing to the nonassigned study treatment. At 3 months, 93% and 92% of patients in the LHRHa group and estrogen group, respectively, achieved testosterone levels of 1.7 nmol/L or lower; at 6 months, the percentages were 88% and 95%, respectively. After a median followup of 19 months, cardiovascular events (primary endpoint) occurred in 7.1% (95% CI, 2.7% to 14.9%) of patients who received LHRHa and 10.1% (95% CI, 6% to 15.6%) of patients who received estrogen. The rate of cardiovascular events was 2.9% higher (95% CI, -4.2 to 10.1) in the estrogen group compared with LHRHa; however, this study was not powered to detect a difference between treatment groups. At 6 months, among patients still receiving the study drug and who did not receive additional therapy, mean fasting glucose and mean fasting cholesterol levels were increased in the LHRHa group by 2% and 7.6% and decreased in the estrogen group by 2.1% and 1.2%, respectively (p less than 0.035 and p less than 0.0001, respectively). Other adverse events included gynecomastia, which occurred more frequently in the estrogen group compared with LHRHa, and hot flushes, which occurred more often in the LHRHa group [27].

b) Data from a pilot study involving 20 men with advanced prostate cancer who received transdermal estradiol indicate transdermal therapy produced an effective tumor response, was associated with minimal cardiovascular toxicity, prevented andropause symptoms, and improved quality-of-life scores. The men applied 6 transdermal estradiol (7.8 mg) patches weekly for 8 weeks and then reduced the number of patches to maintain castrate levels of testosterone. Median follow-up was 15 months. All patients achieved castrate levels of testosterone within 3 weeks and had biochemical evidence of disease regression. One patient died of disease at 14 months, and only 1 cardiovascular

complication (fluid retention) occurred. Mild to moderate gynecomastia occurred in 80% of patients. No patient reported hot flashes [28].

Estradiol Acetate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Estradiol acetate vaginal ring 0.05 mg/day or 0.1 mg/day significantly decreased the frequency and severity of moderate to severe vasomotor menopause symptoms compared with placebo at weeks 4 and 12 in a randomized trial (N=333) [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes (vaginal ring); Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Efficacy of estradiol acetate vaginal ring for the treatment of vulvar and vaginal atrophy in postmenopausal women was demonstrated in a randomized trial (N=333). At week 13, vaginal superficial cells increased by a mean of 16.0% and 18.9% for estradiol acetate vaginal ring 0.05 mg/day and 0.1 mg/day, respectively, compared with 1.11% for placebo, and there was a reduction in parabasal cells. Vaginal pH decreased by a mean of 0.73 and 0.60 for estradiol acetate vaginal ring 0.05 mg/day and 0.1 mg/day, respectively, compared with mean decrease of 0.25 for placebo [60][59].

Estradiol Cypionate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol cypionate is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [55]

Decreased estrogen level - Female hypogonadism syndrome

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol cypionate is indicated for the treatment of female hypoestrogenism due to hypogonadism [55]

Estradiol Valerate

Abnormal vasomotor function (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol valerate is indicated for the treatment of moderate to severe vasomotor symptoms associated with menopause [57]

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Effective

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol valerate injection is indicated for treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause [57]

When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with estrogen therapy [57]

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIa

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure [57]

Hormone sensitive prostate cancer, Advanced, for palliation only

FDA Labeled Indication

a) Overview

FDA Approval: Adult, yes; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Indicated for treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only) [57]

Non-FDA Uses

Estradiol

Alzheimer's disease; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A cohort-based study (n=221,406) with an average follow-up of more than 5 years demonstrated that current estrogen replacement therapy in postmenopausal women did not reduce the risk of developing Alzheimer disease (Seshardri et al, 2001)

The Baltimore Longitudinal Study of Aging, a prospective study of postmenopausal or perimenopausal women (n=472), showed a reduced risk of Alzheimer disease in women who had reported the use of estrogen [45]

An observational, cohort study of elderly women (n=1124) demonstrated that estrogen may delay the onset and decrease the risk of developing Alzheimer disease (AD) [46]

A case-control study nested within a prospective cohort study of postmenopausal women (n=8877) demonstrated that estrogen replacement therapy may be useful for preventing or delaying the onset of Alzheimer disease (Paganini-Hill and Henderson, 1996)

c) Adult:

1) A cohort-based study with an average follow-up of more than 5 years demonstrated that current estrogen replacement therapy (ERT) in postmenopausal women did not reduce the risk of developing Alzheimer disease (AD). The population-based nested case-control study involved 2 base cohorts, one of women who received (ERT) (n=112,481) and another who did not (n=108,925). Fifty-nine newly diagnosed cases of AD and 221 matched control subjects were identified from the 2 cohorts. The risk for developing AD was determined to be equal for women who received ERT for at least 1 year and for nonusers, as 25% of the newly diagnosed AD patients and 24% of controls currently used ERT (relative risk estimate (OR) of 1.18; 95% CI, 0.59 to 2.37). Smoking (current and past) was not an independent risk factor for AD but body mass index was and appropriate adjustments in the relative risks were made. When past ERT recipients and current users were combined, the risk of developing AD did not significantly change (OR, 1.19; 95% CI, 0.62 to 2.27). Additionally, the duration of ERT use did not account for significant differences in the risk as users for 5 years or longer were compared with nonusers (OR 1.05; 95% CI, 0.32 to 3.44). There was also no difference for estrogen recipients who received estrogen alone or combined with a progestin (Seshardri et al, 2001).

2) The Baltimore Longitudinal Study of Aging was a prospective study of 472 postmenopausal or perimenopausal women that showed a reduced risk of Alzheimer disease (AD) in women who had reported the use of estrogen. Of the 472 women enrolled, 45% had used oral or transdermal estrogen replacement therapy (ERT) at any time (excluding premenopausal oral contraceptives). Thirty-four cases of AD were diagnosed during the 16-year follow-up, which included 9 ERT users. The relative risk for AD in ERT users versus nonusers was 0.46 (95% CI, 0.209 to 0.997), which indicates a reduced risk of AD for women who had reported the use of estrogens. Level of education, age at menopause and menarche, years of natural cyclic estrogen exposure, menopause duration, and surgical menopause did not affect the results of the study, and there was no effect related to duration of ERT therapy [45].

3) An observational, cohort study of elderly (mean age 74 years) women (n=1124) demonstrated that estrogen may delay the onset and decrease the risk of developing

Alzheimer disease (AD). Initially, all of the women were free of AD but during follow-up (1 to 5 years), 167 women developed the disease. Women who developed AD were older and had fewer years of education than those who did not, but age at menopause was similar for both groups. Estrogen use after the onset of menopause was reported in 156 of the 1124 enrolled women, with an average duration of 6.8 years. The age at onset of AD was significantly later in women who had taken estrogen than those who did not (p less than 0.01). The relative risk (RR) of AD associated with a history of estrogen use was 0.40 (95% CI, 0.22 to 0.85; p=0.01). Adjustment for ethnicity, years of education, apolipoprotein-E genotype, and participation group (senior housing versus Medicare sample) did not significantly change the RR. In addition, women who received estrogen for longer than 1 year (average, 13.6 years) had a greater reduction in risk (RR 0.13, 0.02 to 0.92; p less than 0.01) [46].

4) A case-control study nested within a prospective cohort study of 8,877 women demonstrated that estrogen replacement therapy (ERT) may be useful for preventing or delaying the onset of Alzheimer disease (AD) in postmenopausal women. Of the 8,777 cohort patients, 248 women who died with AD or other dementia diagnoses were identified and 5 controls were matched to each case based on year of death and year of birth (+/-1 year). The risk of AD and related dementia was significantly reduced in estrogen users (both oral and nonoral preparations) compared with nonusers (odds ratio (OR), 0.65; 95% CI, 0.49 to 0.88). Both increasing dosage and duration of conjugated estrogen were associated with a significant decrease in risk (p equal to 0.01 for both). The lowest observed risk was observed in long-term (at least 15 years) users who received high doses (at least 1.25 mg daily) (OR, 0.48; 95% CI, 0.19 to 1.17) (Paganini-Hill and Henderson, 1996).

Dementia

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Results from Women's Health Initiative Memory Study (WHIMS) demonstrated that conjugated equine estrogen therapy alone did not reduce the incidence of dementia or mild cognitive impairment and increased the risk for both end points combined [47]

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Conjugated equine estrogen (CEE) therapy alone did not reduce the incidence of dementia or mild cognitive impairment (MCI) and increased the risk for both end points combined. The Women's Health Initiative Memory Study (WHIMS), a double-blind ancillary study of the Women's Health Initiative, randomized 2947 postmenopausal women (aged 65 to 79 years) to CEE 0.625 mg daily or placebo. All women were free of probable dementia at baseline and incidence of probable dementia and MCI was measured by the Modified Mine-Mental State Examination (3MSE) at baseline and annually thereafter. After a period of 5.21 years, 47 patients were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (hazard ratio (HR), 1.49; 95% CI, 0.83 to 2.66) [47]; this correlates to an estimated event rate difference of 12 per 10,000 woman-years with estrogen-only versus placebo (95% CI, -4 to 41) [43]. The incidence rates for probable dementia in the estrogen-alone trial were not significantly different from those in the estrogen plus progestin trial (45 vs 22 per 10000 person-years for CEE plus progestin versus placebo). When data for estrogen alone and estrogen plus progestin were pooled, the risk of probable dementia was significantly increased versus placebo (HR, 1.76; 95% CI, 1.19 to 2.60). In the estrogen-alone trial, 76 patients in the CEE group were diagnosed with MCI versus 58 in the placebo group (HR, 1.34; 95% CI, 0.95 to 1.89). In the combined data, the HR was similar (HR, 1.25; 95% CI, 0.97 to 1.6). In the estrogen-alone trial, 93 patients in the CEE group were diagnosed with either probable dementia or MCI compared to 69 in the placebo group (HR, 1.38; 95% CI, 1.01 to 1.89) [47].

Disorder of cardiovascular system; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence is inconclusive

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category A

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

There was no significant difference in coronary events with estrogen versus placebo in pooled analysis of the EPAT, PEPI, and WHI trials of postmenopausal women who had undergone hysterectomy [42]

The risk of stroke was significantly greater with estrogen versus placebo in the WHI study [42].

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Coronary Heart Disease

a) Pooled analysis of the Estrogen in the Prevention of Atherosclerosis Trial (EPAT), the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, and Women's Health Initiative (WHI) trial (n=11,310; high quality evidence) reported no significant difference in coronary events with estrogen versus placebo (3.6% vs 3.8%; relative risk [RR], 0.95; 95% CI, 0.79 to 1.14) with a mean follow-up of 6.8 years among women who had undergone hysterectomy. In the WHI trial, there was no significant difference in cardiovascular risk with hormone therapy versus placebo 3.9 years after treatment discontinuation (hazard ratio [HR], 0.97; 95% CI, 0.75 to 1.25) [42].

b) Results from the WHI trial showed no significant difference in cardiovascular risk with hormone therapy versus placebo 3.9 years after treatment discontinuation (hazard ratio [HR], 0.97; 95% CI, 0.75 to 1.25). Estrogen therapy did not significantly affect the risk of coronary heart disease in subgroups based on age, race/ethnicity, hypertension, diabetes, high cholesterol that required medication, coronary risk factors, years since oophorectomy or hysterectomy, or body mass index. The risk for coronary heart disease with estrogen increased with age: Ages 50 to 59 years, HR 0.6 (95% CI, 0.35 to 1.04); ages 60 to 69 years, HR, 0.95 (95% CI, 0.72 to 1.24); ages 70 to 79 years, HR, 1.09 (95% CI, 0.8 to 1.49). Time since menopause also did not have a significant effect on the risk of coronary heart disease with estrogen-only therapy versus placebo [42].

2) Stroke

a) The risk of stroke was significantly higher with estrogen-only therapy versus placebo (3.2% vs 2.4%; hazard ratio [HR], 1.35; 95% CI, 1.07 to 1.7) after a median treatment duration of 7.2 years in the Women's Health Initiative (WHI) study (N=10,739; moderate quality evidence) [42]; this correlated to an estimated event rate difference of 11 per 10,000 woman-years (95% CI, 2 to 23 events) [43]. Stroke risk was similar between arms 3.9 years after treatment discontinuation. At 10.7 years of follow-up, cumulative stroke risk was higher with estrogen-only (4.4% vs 3.8%; HR, 1.15; 95% CI, 0.97 to 1.37). Results on stroke risk from the Estrogen in the Prevention of Atherosclerosis Trial (EPAT) and the Estrogen Replacement and Atherosclerosis (ERA) study were inconclusive due to low event rates [42].

b) In a study of 664 postmenopausal women (mean age, 71 years) who had recently had an ischemic stroke or transient ischemic attack, estradiol 1 mg/day did not reduce mortality or the recurrence of stroke. Over a follow up period of 2.8 years, 48 deaths and 51 nonfatal strokes occurred in the estradiol group versus 41 deaths and 52 nonfatal strokes in the placebo group. During the first 6 months, 3 fatal strokes and 18 nonfatal strokes occurred in women in the estradiol group, compared with 1 fatal stroke and 8 nonfatal strokes in women in the placebo group. Women receiving estradiol were more likely to have vaginal bleeding and endometrial hyperplasia and a more frequent need for hysterectomy [44].

Gender dysphoria - Male-to-female transsexual

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy; Pediatric, Evidence favors efficacy

Recommendation: Adult, Class IIb; Pediatric, Class IIa

Strength of Evidence: Adult, Category B; Pediatric, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adolescents)

After puberty suppression with triptorelin, administration of daily oral estrogen to adolescent transgirls (N=28) produced breast development within the first year and increased hip circumference and decreased the waist/hip ratio over 3 years of treatment [2].

Evidence (Adults)

Estradiol, as ethinyl estradiol and 17-beta estradiol, may be effective in changing the physical external appearance for male to female transsexuals [3][4].

Guidelines (Adolescents)

Initiation of gender-affirming hormone therapy, at gradually increasing doses, is recommended in adolescents with confirmed persistence of gender dysphoria/gender incongruence who request such therapy and who have sufficient mental capacity to give informed consent, usually by age 16 years. Compelling reasons may exist to initiate therapy younger than 16 years, but studies in this population are minimal. Initial therapy to undergo suppression of pubertal development is suggested at Tanner stage G2/B2. Neither puberty suppression nor gender-affirming hormone therapy is recommended in prepubertal children [1].

Guidelines (Adults)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender [1].

Estrogen options include oral or transdermal 17-beta estradiol and oral conjugated estrogens; it is suggested that ethinyl estradiol not be used as it may have a higher risk of VTE than other preparations. Treatment with physiologic doses of estrogen alone does not suppress testosterone levels into the normal range for females; multiple adjunctive medications are available [1].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Pediatric:

1) Administration of daily oral estrogen to 28 adolescent transgirls produced breast development within the first year and increased hip circumference and decreased the waist/hip ratio over 3 years of treatment. Results for selected outcomes are shown in the table below. Subjects had received triptorelin alone for a median of 24.8 months (range, 6.4 to 51.6 months) before initiation of estrogen at a median age of 16 years (range, 13.9 to 18.9 years); estrogen was initiated in 5 patients with tall stature (greater than 180 cm) before 15.5 years. Median Tanner breast development stage was 1 at treatment initiation, 3 after 1 year, 4 after 2 years, and 5 after 3 years. Gonadotropin levels were suppressed in all patients, with the exception of one who was noncompliant with gonadotropin-releasing hormone analog therapy. Estradiol levels increased with increasing doses, and the adult dose of 2 mg administered for a median of 2 years (range, 3 to 30 months) resulted in a median serum estradiol level of 100 picomole/L. There were no significant changes over time in median prolactin levels, Hb, HCT, HbA1c, or liver enzymes. Study subjects had lifelong extreme gender dysphoria, were psychologically stable, and lived in a supportive environment. For transgirls who had started triptorelin before 16 years, the starting dose of estradiol was 5 mcg/kg/day once daily, increased by 5 mg/kg/day every 6 months until an adult dose of 2 mg/day was reached. For transgirls who started triptorelin at 16 years or older and had complete endogenous puberty, the starting estradiol dose was 1 mg orally daily, which was increased to 2 mg after 6 months. Two patients received 200 mcg ethinylestradiol and 4 received estradiol 6 mg to limit growth [2].

Estrogen-Induced Changes in Tanner Stage and Anthropometric Parameters

	Baseline	After 3 Years of Treatment	Standard Deviation at 3 Years (Female Adolescent Reference)
Tanner breast stage, median	1	5 (range, 2 to 5)	-
Testicular volume, median	8 mL	6.5 mL	-
Height, mean	178 cm	180 cm*	1.53 +/- 1.5
Body mass index, mean	20.8 kg/m(2)	21.5 kg/m(2)*	-0

Waist circumference, mean	73.9 cm	73.7 cm	0.22 /- 1.29
Hip circumference, mean	93.9 cm	97.4 cm*	0.42 +/- 0.98
Waist/hip ratio, mean	0.79	0.75*	-0.04 +/- 1.01
Bone age, median	14.3 years (range, 13 to 18 years)	18 years (range, 16 to 19 years)	-
Fat percentage, mean	26%	25.9%	-
Lean body mass percentage, mean	119%	125%	-
*significant difference from baseline			

Impaired cognition

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Ineffective

Recommendation: Adult, Class III

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence

Results from Women's Health Initiative Memory Study (WHIMS) demonstrated that conjugated equine estrogen therapy alone did not reduce the incidence of dementia or mild cognitive impairment and increased the risk for both end points combined [47]

Guidelines

Do not use estrogen alone for the primary prevention of chronic conditions in asymptomatic postmenopausal women. There is moderate certainty that estrogen-only prophylaxis provides no net benefit or that the harms outweigh the benefits in postmenopausal women who have had a hysterectomy [43].

c) Adult:

1) Conjugated equine estrogen (CEE) therapy alone did not reduce the incidence of dementia or mild cognitive impairment (MCI) and increased the risk for both end points combined. The Women's Health Initiative Memory Study (WHIMS), a double-blind ancillary study of the Women's Health Initiative, randomized 2947 postmenopausal women (aged 65 to 79 years) to CEE 0.625 mg daily or placebo. All women were free of probable dementia at baseline and incidence of probable dementia and MCI was measured by the Modified Mine-Mental State Examination (3MSE) at baseline and annually thereafter. After a period of 5.21 years, 47 patients were diagnosed with probable dementia, of whom 28 were assigned to CEE and 19 to placebo (hazard ratio (HR), 1.49; 95% CI, 0.83 to 2.66) [47]; this correlates to an estimated event rate difference of 12 per 10,000 woman-years with estrogen-only versus placebo (95% CI, -4 to 41) [43]. The incidence rates for probable dementia in the estrogen-alone trial were not significantly different from those in the estrogen plus progestin trial (45 vs 22 per 10,000 person-years for CEE plus progestin versus placebo). When data for estrogen alone and estrogen plus progestin were pooled, the risk of probable dementia was significantly increased versus placebo (HR, 1.76; 95% CI, 1.19 to 2.60). In the estrogen-alone trial, 76 patients in the CEE group were diagnosed with MCI versus 58 in the placebo group (HR, 1.34; 95% CI, 0.95 to 1.89). In the combined data, the HR was similar (HR, 1.25; 95% CI, 0.97 to 1.6). In the estrogen-alone trial, 93 patients in the CEE group were diagnosed with either probable dementia or MCI compared to 69 in the placebo group (HR, 1.38; 95% CI, 1.01 to 1.89) [47].

Menstrual migraine

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A double-blind, randomized, crossover trial (n=35) suggested that perimenstrual estradiol supplement can be of benefit in preventing menstrual migraine attacks, but discontinuation of estradiol supplement led to an increase in migraine attacks [50]

c) Adult:

1) In a double-blind, randomized, crossover trial (n=35), the use of perimenstrual estradiol gel 1.5 mg was more effective than placebo in preventing menstrual migraines; however, there was a rise in migraine attacks upon discontinuation of estradiol supplement. Women aged between 29 and 50 years (mean 43 years) were given indistinguishable gels (estradiol or placebo), and instructed to alternate and apply 1.5 mg gel to the upper arms or thighs daily from approximately 6 days before the first full day of bleeding up to and including the second full day of bleeding for 6 cycles. This therapeutic approach resulted in 133 and 171 migraine days while women were using estradiol and placebo, respectively (p=0.03). Estradiol gel was associated with a 22% reduction in migraine days per woman relative to placebo (relative risk (RR) 0.78; 95% CI, 0.62 to 0.99; p=0.04), and the attacks were less severe (RR 0.73; 95% CI, 0.54 to 0.97; p=0.03). However, the occurrence of migraine attack increased by 40% in the 5 days following estradiol use compared with placebo (RR 1.4; 95% CI, 1.03 to 1.92; p=0.03). Although the risk of migraine disappeared 5 to 10 days post estradiol use (RR 1.04; 95% CI, 0.67 to 1.62; p=0.92), the potential benefit of perimenstrual estradiol supplement was offset by the occurrence of deferred post-gel migraine attacks associated with estradiol withdrawal [50].

Mental distress

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Transdermal estradiol reduced response to mental stress in a small, crossover study of postmenopausal women (n=10) [48]

c) Adult:

1) A blinded, crossover study of 10 postmenopausal women demonstrated that transdermal estradiol reduced the response to mental stress, as measured by plasma epinephrine levels, diastolic blood pressure, and the overall cardiac sympathetic tone. The women were randomized to receive transdermal estradiol (50 mcg daily) or placebo for 3 weeks, with a 3-week wash-out between the 2 treatments. At the conclusion of each treatment, the subjects underwent a mental stress test during which circulating levels of catecholamines and other hormonal and biochemical variables were measured. The epinephrine response was less marked during estradiol treatment compared to placebo and the difference in effects of placebo and estradiol on stress-induced epinephrine responses were significantly different (p less than 0.05). While there were no effects of treatment on stress-induced systolic blood pressure, mean diastolic blood pressure was significantly increased from baseline during placebo treatment (p less than 0.002), but not during estrogen treatment (p equal to 0.64). In addition, a decrease in the responses of some measures of stress-induced cardiac sympathetic tone was also measured with estradiol treatment. More studies are warranted to determine the influence of estrogens on sympathoadrenal functioning [48].

Migraine; Prophylaxis

See Drug Consult reference: Migraine Prophylaxis and Treatment in Adults - Clinical Practice Guidelines

Postpartum depression

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

A small, open-label study (n=23) showed that depression symptoms may be rapidly reduced in patients with postpartum depression by treatment with estradiol [49]

c) Adult:

1) A small (n=23) open-label study showed that treatment with sublingual estradiol for 8 weeks rapidly reduced depression symptoms in women diagnosed with postpartum depression. All patients were severely depressed and had a low serum estradiol concentration (mean=79.8 picomoles per liter (pmol/L)). Ten patients received psychotherapy and 4 patients received antidepressant medication prior to estradiol therapy without benefit. Micronized estradiol was given sublingually at a dose of 1 mg 3 to 8 times daily depending on daily serum estradiol concentrations. At a mean dose of 3.9 mg during the first week of treatment, significant mood improvement was noted (p less than 0.001) which was measured using a clinician-rated depression symptom scale (the Montgomery-Asberg Depression Rating Scale (MADRS)). Improvement continued at a mean dose of 4.8 mg during the second week, and by the end of the week, the MADRS scores correlated with clinical recovery in 83% of patients. Further studies are needed to determine the optimum treatment duration, dose, and central mechanism of action of estradiol [49].

Urinary tract infectious disease; Prophylaxis

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Estradiol-releasing vaginal ring prolonged the time to next recurrence and decreased the number per year of urinary tract infections among postmenopausal women [51].

c) Adult:

1) The time to next recurrence was prolonged in postmenopausal women with recurrent urinary tract infection using an estradiol-releasing vaginal ring. In a multicenter, randomized, open parallel-group study, women (n=53) were assigned to the estradiol-releasing vaginal ring or to the control group (n=55). Women were included in the study if they were menopausal greater than 2 years and had greater than 3 urinary tract infections treated during the previous 12 months. One ring was carried vaginally for a 12-week period. The duration of treatment was 36 weeks for the estradiol group and 36 weeks or until the first recurrence for the control group. A recurrence of urinary tract infection occurred in 51% (n=27) of the estradiol group and 80% (n=44) in the control group [51].

Estradiol Acetate

Migraine; Prophylaxis

See Drug Consult reference: Migraine Prophylaxis and Treatment in Adults - Clinical Practice Guidelines

Estradiol Cypionate

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Gender dysphoria - Male-to-female transsexual

a) Overview

FDA Approval: Adult, no; Pediatric, no

Efficacy: Adult, Evidence favors efficacy

Recommendation: Adult, Class IIb

Strength of Evidence: Adult, Category B

See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

b) Summary:

Evidence (Adults)

In male-to-female transsexual adults, hormone treatment with estradiol valerate and goserelin acetate for 2 years before sex reassignment surgery significantly increased body mass index, total fat mass, and lumbar spine bone mineral density and significantly decreased lean mass [56].

Guideline (Adults)

Gender transition treatment can be initiated in adults with confirmed persistent gender dysphoria/gender incongruence who have the capacity to make fully informed decisions and have well-controlled, if any, mental health concerns. The goals of therapy are to suppress endogenous sex hormones of the designated gender and to replace these with endogenous sex hormones of the affirmed gender [1].

Estradiol valerate or cypionate or transdermal preparations are options to oral estradiol that may have an advantage in older transgender females who may have a higher risk of VTE. it is suggested that ethinyl estradiol not be used as it may have a higher risk of VTE than other preparations. Treatment with physiologic doses of estrogen alone does not suppress testosterone levels into the normal range for females; multiple adjunctive medications are available [1].

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

c) Adult:

1) In male-to-female transsexual adults (N=84), hormone treatment with estradiol valerate and goserelin acetate for 2 years before sex reassignment surgery significantly increased body mass index, total fat mass, and lumbar spine bone mineral density and significantly decreased lean mass. There were significant increases in median levels of estrogen and sex hormone-binding globulin and significant decreases in median levels of luteinizing hormone, follicle-stimulating hormone, and testosterone, with no significant change in median prolactin and dehydroepiandrosterone sulphate levels. Results for selected hormonal and anthropometric outcomes are shown in the table below. There were no significant changes in triglycerides, cholesterol, and LDL, but HDL was significantly increased from 54 to 70.1 mg/dL. One 49-year-old patient developed a DVT. Estradiol valerate 10 mg IM was administered every 10 days, and goserelin acetate 3.8 mg subQ was administered every 4 weeks to suppress androgen secretion [56].

Hormone-Induced Changes in Median Anthropometric and Endocrine Parameters

	Baseline	24 Months
BMI (kg/m(2))	22.3	23.3*
Fat mass (kg)	10.7	14.3*
Lean mass (kg)	59.6	55.4*
Femur BMD (g/cm(2))	1.09	1.09
L2-L4 BMD (g/cm(2))	1.20	1.30*
LH (international units/L)	2.9	0.2*
FSH (international units/L)	2.8	0.2*
Testosterone (nanomoles/L)	13.0	0.7*
Estrogen (picomoles/L)	55.5	697.8*
Prolactin (milli-international units/L)	230.2	244.4
DHEAS (micromoles/L)	7.0	4.3
SHBG (nanomoles/L)	37.2	118.0*

*significant change from baseline

BMD, bone mineral density; BMI, body mass index; DHEAS, dehydroepiandrosterone sulphate; FSH, follicle-stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone-binding globulin

Dose Adjustments

Adult Dosage

Normal Dosage

Estradiol

Insertion, vaginal

Dyspareunia, Moderate to severe - Menopause

1) Imvexxy(TM)

a) Use lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman. Reevaluate periodically as clinically appropriate to determine if treatment is still necessary [5].

b) Initial dosage: 4 mcg intravaginally once daily at the same time each day for 2 weeks [5]

c) Maintenance dosage: 4 or 10 mcg intravaginally twice weekly (every 3 to 4 days); adjust dose based on clinical response [5]

d) Concomitant medication: Consider a progestin in postmenopausal women with a uterus to reduce the risk of endometrial cancer [5].

Oral route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The initial dose of oral estradiol for the treatment of moderate to severe vasomotor symptoms is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on followed by 1 week off). Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended initial dosing regimen is 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off). Adjust to the lowest dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
2) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Initial dosage: 1 to 2 mg orally daily in a cyclical pattern (3 weeks on, 1 week off) [7]
2) Titration: Adjust dose as needed to control symptoms. The minimal effective dose for maintenance therapy should be determined by titration. Attempt to taper or discontinue therapy at 3 to 6 month intervals [7].
3) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [7].
4) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [7].

Breast cancer, Metastatic; for palliation only

1) The dose of oral estradiol for the palliative treatment of breast cancer in appropriately selected women and men with metastatic disease is 10 mg orally 3 times daily for at least 3 months [7].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The initial dose of oral estradiol for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 1 to 2 mg orally daily. Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [7].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 2 to 6 mg orally daily with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

1) The dose of oral estradiol for the prevention of postmenopausal osteoporosis is 0.5 mg orally daily for 23 days of a 28-day cycle. The lowest effective dose has not been established [7].
2) Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [7].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Prostate cancer, Advanced, Androgen-dependent; for palliation only

1) The dose of oral estradiol for the palliative treatment of advanced androgen-dependent prostate cancer is 1 to 2 mg orally 3 times daily. Determine the effectiveness of therapy by phosphatase levels as well as by symptomatic improvement [7].

Transdermal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Emulsion

a) The initial dose of estradiol topical emulsion for the treatment of moderate to severe vasomotor symptoms is one foil patch (1.74 g each) applied topically to clean, dry skin on each thigh daily for a total dose of 3.48 g (delivering 0.05 mg estradiol per day) [35].

2) Gel

a) Divigel(R)

1) Initial dosage: One 0.25 gram packet applied topically once daily, alternating between the right and left upper thigh. Apply to a 5x7-inch surface area and allow to dry before dressing. Do not wash application site within 1 hour after application [33].

2) Maximum dosage: Adjust dosage up to a MAX of 1.25 mg topically once daily as needed [33].

3) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [33]

b) Elestrin(R)

1) Initial dosage: Apply 0.87 g (1 pump, which delivers 0.52 mg estradiol) topically once daily via the metered-dose pump in a thin layer to the upper arm and shoulder area (approximately 320 cm(2)); adjust dose based on clinical response [34].

2) Treatment duration: Use the lowest effective dose for the shortest duration consistent with therapy goals [34]

c) Estrogel(R)

1) The initial dose of estradiol topical gel 0.06% (Estrogel(R)) for the treatment of moderate to severe vasomotor symptoms is 1.25 g/day (which delivers 0.75 mg estradiol) applied topically via the metered-dose pump to clean, dry, unbroken skin on the arm. Apply in a thin layer from wrist to shoulder and allow gel to dry for up to 5 minutes before dressing [13].

3) Patch

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.0375 mg/day applied to the skin twice weekly	lower abdomen (below the umbilicus) or buttocks
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Dosage titration: Adjust dose based on clinical response, use lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10].

Alternative dose schedule: Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

a) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].

4) Spray

a) The initial dose of transdermal estradiol spray for the treatment of moderate to severe vasomotor symptoms is one spray (delivering 1.53 mg estradiol) applied to the forearm every morning. Dosage adjustment should be guided by the clinical response of the patient. If needed, the dose may be increased to 2 or 3 sprays daily based upon clinical response [36].

Atrophic vulva (Moderate to Severe) - Menopause

1) Gel

a) Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

2) Patch

The initial dose of transdermal estradiol patches for the treatment of vulvar atrophy is outlined in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][8][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Gel

a) Usual dosage: Apply 1.25 g/day (which delivers 0.75 mg estradiol) topically via the metered-dose pump to clean, dry, unbroken skin on the arm. The gel should be applied in a thin layer from wrist to shoulder and allowed to dry for up to 5 minutes before dressing. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [13].

b) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [13].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [13].

2) Patch

Initial dosage is provided in the following table [19][8][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust dose based on clinical response, use the lowest dose needed to control symptoms, and attempt to taper or discontinue at 3 to 6 month intervals [10][9][11][12].

Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [9][11][12].

a) When prescribing solely for the treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered first due to the risks associated with oral estrogen therapy [19][8][9][11][12].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [19][8][9][11][12].

c) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

The initial dose of transdermal estradiol patches for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is outlined in the following table [19][9][11][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.05 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Estraderm(R)	0.05 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Vivelle(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen
Vivelle-Dot(R)	0.0375 mg/day applied to the skin twice weekly	trunk of body including buttocks and abdomen

Adjust dose according to severity of symptoms and response of the patient and adjust to lowest level that will provide effective control [19][8][9][11][12]. Estradiol transdermal patches may be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][9][11][12].

1) Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated one week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than one week [8][9][11][12].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 0.025 to 0.2 mg/day transdermally with or without antiandrogens or gonadotropin-releasing hormone agonist; replace patch every 3 to 5 days [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Postmenopausal osteoporosis; Prophylaxis

Initial dose: Outlined in the following table [29][19][8][12]:

Product	Dosing Regimen	Application Site
Alora(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen, upper quadrant of buttocks, outer hip
Climara(R)	0.025 mg/day applied to the skin once weekly	lower abdomen or upper quadrant of buttocks
Minivelle(R)	0.025 mg/day applied to the skin twice weekly	lower abdomen (below umbilicus) or buttocks
Vivelle-Dot(R)	0.025 mg/day applied to the skin twice weekly	abdomen

Dosage titration: Adjust according to severity of symptoms, response of the patient, biochemical markers, and measurements of bone mineral density. Adjust to lowest dose that will provide effective control [8][12].
May be administered in a continuous regimen in patients who do not have a uterus. In patients with a uterus who are not using concomitant progestin therapy, transdermal estradiol patches can be administered on a cyclic schedule (3 weeks on, 1 week off) [8][12].

1) Concomitant therapy: Postmenopausal women require an average of 1500 mg/day of elemental calcium. When calcium supplementation is not contraindicated, it may be useful for women with suboptimal dietary intake. Additionally, vitamin D supplementation of 400 to 800 international units daily may also be required to ensure adequate daily intake [8][12].

2) Switching from other formulations: Therapy with estradiol transdermal patches may be initiated at once in women not currently receiving oral estrogens or in women switching from topical or another transdermal estradiol therapy. Therapy with estradiol transdermal patches should be initiated 1 week after withdrawal of oral estrogens or sooner if menopausal symptoms reappear in less than 1 week [8][12].
See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy

Vaginal route

Atrophic vulva (Moderate to Severe) - Menopause

1) The recommended dose of estradiol vaginal cream is 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period. A maintenance dose of 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

Atrophy of vagina (Moderate to Severe) - Menopause

1) Vaginal Cream

a) Initial dosage: 2 to 4 g vaginally daily for 1 or 2 weeks, then gradually reduced to 50% of initial dose for a similar period [14].

b) Maintenance dosage: 1 g, administered 1 to 3 times a week, may be used after vaginal mucosa has been restored. Adjust dose as needed to control symptoms and attempt to taper or discontinue at 3 to 6 month intervals [14].

c) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [14].

2) Vaginal Ring

a) Usual dosage: 1 ring inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3 to 6 month intervals [15].

b) Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary [15].

3) Vaginal Insert

a) Initial dosage: 1 vaginal insert (10 mcg) inserted vaginally once daily for 2 weeks, preferably at the same time each day. The recommended maintenance dose is 1 vaginal insert 10 mcg twice weekly. Reevaluate treatment, and attempt to taper or discontinue periodically [16].

Menopause - Urethral atrophy (Moderate to Severe)

1) The recommended dose of estradiol vaginal ring is 1 ring (contains 2 mg estradiol) inserted as deeply as possible into the upper one-third of the vagina vault. The ring is to remain in place continuously for 3 months and then be removed. Replace with a new ring if additional therapy is appropriate. Attempt to taper or discontinue at 3- to 6-month intervals [15].

General Dosage Information

a) In postmenopausal women with a uterus, initiate progestin with estrogen to reduce the risk of endometrial cancer [34][19][8][12][7][38][13][14][15][35][36]; women with a history of hysterectomy and endometriosis may need a progestin [34][16][29].

b) Use estrogen, alone or with a progestin, at the lowest effective dose and for the shortest duration consistent with individual treatment goals and risks; reevaluate periodically (generally at 3 to 6 month intervals) to determine if treatment is still necessary [34][16][29][19][8][12][7][38][13][14][15][35][36].

Estradiol Acetate

Vaginal route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day inserted intravaginally every 3 months, dose adjusted based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals; reevaluate periodically to determine if treatment is necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) Usual dose: 0.05 mg/day ring inserted intravaginally every 3 months and dose adjust based on clinical response [59]
2) Use the lowest effective dose for the shortest duration consistent with treatment goals, and reevaluate periodically to determine if treatment is

necessary [59].
3) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. Women without a uterus generally do not need progestin therapy [59].

Estradiol Cypionate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The usual dose of estradiol cypionate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 1 to 5 milligrams injected intramuscularly every 3 to 4 weeks [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Decreased estrogen level - Female hypogonadism syndrome

1) The dose of estradiol cypionate for the treatment of hypoestrogenism due to hypogonadism is 1.5 to 2 milligrams injected intramuscularly at monthly intervals [55].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [55].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [55].

Gender dysphoria - Male-to-female transsexual

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Estradiol Valerate

Intramuscular route

Abnormal vasomotor function (Moderate to Severe) - Menopause

1) The dose of estradiol valerate for the treatment of moderate to severe vasomotor symptoms associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Atrophic vulva (Moderate to Severe) - Atrophy of vagina (Moderate to Severe) - Menopause

1) The usual dose for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Decreased estrogen level, Secondary to hypogonadism, castration, or primary ovarian failure

1) The dose of estradiol valerate for the treatment of female hypoestrogenism due to hypogonadism, castration, or primary ovarian failure is 10 to 20 milligrams injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 4 weeks [57].
2) When estrogen is prescribed for postmenopausal women with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin [57].
3) Use of estrogen, alone or with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual women. Patients should be re-evaluated at 3- to 6-month intervals to determine if treatment is still necessary [57].

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage

a) 5 to 30 mg IM every 2 weeks OR 2 to 10 mg IM every week with or without antiandrogens or gonadotropin-releasing hormone agonist [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Hormone sensitive prostate cancer, Advanced, for palliation only

1) The dose of estradiol valerate for the palliative treatment of advanced androgen-dependent prostate cancer is 30 milligrams or more injected intramuscularly deep into the upper, outer quadrant of the gluteal muscle every 1 or 2 weeks [57].

Dosage in Renal Failure

A) No specific recommendations are available [10].

Dosage in Hepatic Insufficiency

A) Use is contraindicated in patients with hepatic impairment or disease [10].

Dosage in Other Disease States

A) Cardiovascular Disorders

1) Immediately discontinue estrogen with or without progesterone therapy immediately if DVT, pulmonary embolism, stroke, or myocardial infarction occurs [10].

B) Cholestatic Jaundice

1) Discontinue use if reoccurs [10]

C) Fluid Retention

1) Discontinue use if medically concerning [10]

D) Hypercalcemia

1) Discontinue use if occurs [10]

E) Pancreatitis

1) Discontinue use if occurs [10]

F) Visual Abnormalities

1) Permanently discontinue use if papilledema or retinal vascular lesions occur [10].

Pediatric Dosage

Normal Dosage

Estradiol

Oral route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 5 mcg/kg/day orally for 6 months; increase dose by 5 mcg/kg/day every 6 months to an adult dosage of 2 to 6 mg/day [1]

b) Postpubertal transgender female: Initial, 1 mg/day orally for 6 months, then 2 mg/day [1]

c) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

Transdermal route

Gender dysphoria - Male-to-female transsexual

1) Guideline Dosage, Adolescents

a) Induction of female puberty: Initial, 6.25 to 12.6 mcg/24 hours applied every 3.5 days; increase dosage by 12.5 mcg/24 hours every 6 months to adult dosage of 50 to 200 mcg/24 hours to mimic physiological estradiol levels [1]

b) Maintenance dosage: Adjust to mimic physiological estradiol levels [1]

See Drug Consult reference: Gender Dysphoria/Gender Incongruence - Gender-Affirming Hormone Therapy Guidelines

General Dosage Information

a) Safety and efficacy in pediatric patients have not been established [34][16][29][19][41][7][13][38][8][12][35][36][14][15].

Estradiol Acetate

1) Safety and efficacy of the vaginal ring and oral tablets has not been established in pediatric patients [59][61].

Estradiol Valerate

1) Safety and efficacy not established in pediatric patients [58].

Administration

A) Estradiol

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

4) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [52].

b) Transdermal route

1) Emulsion

a) Apply and rub emulsion into thighs and calves for 3 minutes on each side until thoroughly absorbed. Rub excess on both hands and buttocks and allow to dry completely before covering with clothing. Wash hands after application [35].

2) Gel

a) Divigel(R)

1) Apply entire contents of the single-dose packet to clean, dry skin of left or right upper thigh. The gel should not be applied to face, breasts, in or around vagina, or to irritated skin. Avoid contact with eyes. Allow to dry before dressing and do not wash application site within 1 hour after application. Wash hands with soap and water after application [38].

b) Estrogel(R)

1) Prime the metered dose pump by fully depressing the spout 2 times for the 93 g pump or 3 times for the 50 and 25 g pumps prior to the first use. Collect gel into palm of hand and apply directly onto dry, clean, unbroken skin of the upper arm and shoulder area. The gel should not be applied directly to breast. Apply gel gently from wrist to shoulder and allow to dry for up to 5 minutes before dressing. It is not necessary to massage or rub in the ge. Wash hands with soap and water after application [13].

c) Elestrin(R)

1) To prime the pump, push the head down slowly and allow it to spring back automatically; repeat until gel comes out. Throw away the first amount of gel (not a full dose) into the trash. Once the pump head has come all the way back up, the pump is ready to use [34].

2) If taking a bath or shower or using a sauna, apply dose afterwards. Dry skin completely before application. Apply dose at the same time each day [34].

3) Hold the pump with the tip facing clean, dry, unbroken skin of the application area of the arm, and press the pump firmly and fully for each pump needed. Gently spread the gel over the entire area of the upper arm and shoulder using 2 fingers. Do not apply to the breast or in or around the vagina. Wash hands after application [34].

4) Allow the gel to dry for at least 5 minutes before dressing, and keep the area dry for as long as possible. Avoid fire, flame, or smoking until the gel has dried. Do not allow others to come in contact with the application area for at least 2 hours. If swimming, wait at least 2 hours before going into the water. Do not apply sunscreen to the area where the gel was applied for at least 25 minutes, and do not apply for 7 or more consecutive days [34].

5) If a dose is missed, do not double the dose. If the next dose is less than 12 hours away, wait and apply the dose the next day. If it is more than 12 hours until the next dose, apply the missed dose and resume normal dosing the next day [34].

3) Transdermal System

a) Place system on clean, dry skin, preferably on the lower abdomen, upper quadrant of the buttock, or outer aspect of the hip. Do not apply to the breasts or waistline. Rotate sites of application with 1 week allowed between applications to a particular site [29][19][8][12].

b) Press Climara (R) system firmly in place for at least 10 seconds, making sure there is good contact, especially around the edges [10]

c) If Climara(R) or Minivelle(R) system falls off reapply to different site; if reapplication not possible, apply new patch to another location for remainder of dosing interval [29][19]

d) Swimming, bathing, or using a sauna may decrease the adhesion of the Climara (R) system and the delivery of estradiol [10]

e) Remove Climara(R) system carefully and slowly, fold it in half, and throw it away. If any adhesive remains on the skin, allow the area to dry for 15 minutes, then gently rub with an oil-based cream or lotion to remove residue [10].

4) Spray

a) Prior to initial application, prime pump by spraying 3 sprays with the cover on. With container being held vertically upright, apply to adjacent, nonoverlapping areas on the inner surface of the forearm, starting near the elbow. Allow to dry for 2 minutes before covering with clothing, and do not wash the site for 1 hour after application. Women should cover the application site with clothing if another person may come into contact with that area of the skin after the spray dries [53].

c) Vaginal route

1) Cream

a) The prescribed dose should be measured using the supplied applicator. Gently insert applicator with measured dose deeply into vagina and press plunger downward to original position. Clean the applicator with mild soap and warm water after use [14].

2) Ring

a) The vaginal ring should be inserted as deeply as possible into the upper one-third of the vaginal vault; the exact position is not critical. To remove the ring, hook a finger through the ring and pull. If the ring is removed or falls out any time during the 90-day treatment period, rinse the ring in lukewarm water and reinsert [15].

3) Insert

a) Using the supplied applicator for Vagifem(R), gently insert into the vagina as far as it can comfortably go without force, or until half of the applicator is inside the vagina, whichever is less [16].

b) Insert Imvexxy(TM) intravaginally with the smaller end up for a depth of about 2 inches into the vaginal canal [5].

B) Estradiol Acetate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

b) Vaginal route

1) Administration

a) Wash hands thoroughly before and after inserting vaginal ring [59]

b) Press the opposite sides of the vaginal ring and insert into the vagina [59]

c) The patient may reposition estradiol acetate vaginal ring with finger if needed. If the ring is totally expelled from the vagina, it should be rinsed with lukewarm water and reinserted [59].

d) To remove, wash hands and hook finger through ring and gently pull downward [59].

C) Estradiol Cypionate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if

the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Preparation

a) If crystals form because estradiol cypionate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming and shaking the vial [55].

D) Estradiol Valerate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Administration

a) Estradiol valerate injection may be administered with a small gauge needle due to its low viscosity. A dry needle and syringe should be used since use of a wet needle or syringe may cause the solution to become cloudy [57].

b) Inject deep into the upper, outer quadrant of the gluteal muscle [57]

c) If crystals form because estradiol valerate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming [57].

d) Since the 40-milligram vial provides a high concentration in a low volume, particular care should be taken to administer the full prescribed dose [57].

E) Estradiol

1) Oral route

a) Tablet

1) Store at a controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F); protect from light and close lid tightly [62].

2) Topical application route, Transdermal route

a) Gel/Jelly

1) Store at a controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [74][520][65].

3) Transdermal route

a) Patch, Extended Release

1) Store between 20 and 25 degrees C (66 and 77 degrees F). Store in the protective pouch and apply immediately after removal [29][67][66][521][19]. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [29][521][19].

b) Spray

1) Store at room temperature, between 20 and 25 degrees C (68 and 77 degrees F); do not freeze. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [69].

4) Vaginal route

a) Cream

1) Store at room temperature; protect from temperatures above 40 degrees C (104 degrees F) [73].

b) Insert, Extended Release

1) Store at a controlled room temperature between 15 and 25 degrees C (59 and 77 degrees F) [5][142], with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [5].

c) Insert, Extended Release

1) Store at a controlled room temperature, 25 degrees C (77 degrees F); do not refrigerate. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [16].

F) Estradiol Acetate

1) Oral route

a) Tablet

1) Store estradiol acetate tablets at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [170].

2) Vaginal route

a) Insert, Extended Release

1) Store estradiol acetate vaginal ring at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [60].

G) Estradiol Cypionate

1) Intramuscular route

a) Oil

1) Store estradiol cypionate injection at controlled room temperature (20 to 25 degrees Celsius or 68 to 77 degrees Fahrenheit) [55].

H) Estradiol Valerate

1) Intramuscular route

a) Oil

1) Store estradiol valerate injection at room temperature [57].

Comparative Efficacy

Conjugated Estrogens

Abnormal vasomotor function (Moderate to Severe) - Menopause

a) Transdermal estradiol was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

b) Percutaneous estradiol (Oestrogel(R), a topical gel available in Europe) applied to the abdomen or thighs daily provided relief of menopausal symptoms equal to that of oral conjugated estrogens in a randomized, comparative study (Dupont et al, 1991). The topical gel resulted in a ratio of estradiol to estrone comparable to physiologic levels in the luteal phase of premenopausal women while oral conjugated estrogens did not (1.2 versus 0.1, respectively).

c) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks [25]. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms.

Atrophic vulva - Atrophy of vagina - Menopause

a) A 12-week comparison study involving the use of estradiol vaginal tablets (25 micrograms (mcg)) with conjugated estrogen cream (1 gram) daily in postmenopausal women with urogenital symptoms demonstrated that both treatments improved urogenital symptoms as well as vaginal health index and cytology. The improvements were noted after 4 weeks of treatment. Conjugated estrogen cream was superior in alleviating vaginal dryness and dyspareunia. Endometrial proliferation was noted in 2 patients after 12 weeks, but no hyperplasia or cancer was identified [522].

b) Transdermal estradiol (Estraderm(R)) was compared with conjugated estrogens in a controlled study involving 124 postmenopausal patients [20]. All patients were receiving conjugated estrogens prior to admission to the study; patients were then randomized to either continue conjugated estrogens or receive 0.1 mg daily of estradiol transdermally for 3 weeks. Doses of conjugated estrogens ranged from 0.625 to 1.25 mg daily. The estradiol system appeared equally effective as conjugated estrogens in controlling postmenopausal symptoms (hot flashes, sweating, headache, insomnia, vaginal discomfort, urge to urinate). Spotting or bleeding tendencies and breast tenderness were similar in both groups, and side effects were similar (less than 10%). However, skin irritation and rash occurred in several patients receiving the transdermal estradiol system, resulting in withdrawal of 13 patients from the study. No clinically significant differences were found in hemostatic parameters between women receiving transdermal estradiol or

oral conjugated estrogens [21]. Similar results were observed with oral conjugated estrogens 0.3 mg per day or an estradiol patch delivering 0.025 mg/day for 12 weeks in 193 postmenopausal women [22].

c) Women (n=176) with postmenopausal urogenital atrophy were evaluated for safety and efficacy using an estrogen vaginal ring or estrogen cream. The 12-week treatment period consisted of a vaginal ring which uniformly released estradiol 5 to 10 mcg/24 hours or nightly use of conjugated estrogen cream 0.625 mg for 3 weeks followed by one drug-free week; the conjugated estrogen cycle was repeated twice. Equivalence was demonstrated for vaginal dryness, dyspareunia, vaginal mucosal atrophy, and intercurrent vaginal bleeding. At the end of the treatment period no statistically significant difference was observed in the incidence of bleeding following the progestogen challenge test. Therapy with the estradiol vaginal ring was preferred over conjugated estrogen cream [23].

d) Although estradiol vaginal cream and conjugated estrogen vaginal cream are similarly effective in treating postmenopausal vaginal atrophy, estradiol may be preferred because of decreased undesirable effects [24]. Conjugated estrogens, given intravaginally, were found to cause a significant elevation in estrone and estradiol levels and an increase in sex hormone binding globulin (SHBG) capacity. Estradiol induced no such changes. Histological examination in 2 patients from each group showed no evidence of endometrial hyperplasia in the patients receiving estradiol, while moderate hyperplasia was found in both patients receiving conjugated estrogens.

e) In a double-blind trial involving 29 females with postmenopausal syndrome, estradiol vaginal cream (0.01%) was compared with conjugated estrogens vaginal cream, both given daily at bedtime for 2 weeks [25]. Marked improvement in vaginal and vasomotor symptoms was noted with both drugs after 7 to 14 days. Plasma estrone and estradiol concentrations were significantly increased after both drugs, although the increase was more marked with estradiol than with the conjugated estrogens. The maturational indices of the parabasal and superficial cells were also significantly improved with both drugs. Adverse effects were mild (primarily breast tenderness and abdominal bloating), occurring in 7 of 20 patients receiving estradiol and 2 of 9 patients receiving conjugated estrogens. The authors concluded that both preparations were effective in the treatment of postmenopausal symptoms.

Disorder of cardiovascular system; Prophylaxis

a) Plasminogen-activator inhibitor type 1 (PAI-1), which is an antagonist of fibrinolysis and inhibits tissue plasminogen activator and urokinase plasminogen activator, was reduced in postmenopausal women who received conjugated estrogen alone or in combination with medroxyprogesterone. Women (n=30) in group 1 were assigned conjugated estrogen 0.625 mg daily alone or in combination with medroxyprogesterone 2.5 mg daily for 1 month and then received the alternate therapy for 1 month. Women (n=20) in group 2 received transdermal estradiol 0.1 mg daily alone or in combination with medroxyprogesterone 2.5 mg daily. Plasma levels of PAI-1 were reduced from 32 ng/mL to 14 ng/mL following 1 month of conjugated estrogen therapy (p less than 0.001). One month after conjugated estrogen and medroxyprogesterone therapy, PAI-1 levels decreased from 31 ng/mL to 15 ng/mL (p=0.003). No significant differences in PAI-1 levels or in the degree of reduction from baseline were observed between the conjugated estrogen and the conjugated estrogen with medroxyprogesterone groups. LDL cholesterol levels decreased and HDL cholesterol levels increased in both groups. In the transdermal estradiol alone and estradiol with medroxyprogesterone groups there was no significant change in the PAI-1 levels from base line [525].

Postmenopausal osteoporosis; Prophylaxis

a) An 18-month trial comparing the effects of transdermal estradiol or oral conjugated estrogens vs placebo showed both active drug treatments to be associated with significant increases in bone mineral density (BMD) compared to no therapy. There were no significant differences in BMD between the two treatment groups [523].

b) Similar efficacy of micronized 17 beta-estradiol (Estrace(R)) 1 mg daily and conjugated estrogens (Premarin(R)) 0.625 mg daily in preventing bone loss in postmenopausal women (51 to 80 years of age) has been reported [524]. As protection from bone loss was demonstrated to persist as long as estrogen therapy with either compound was continued, these investigators recommend the early and continued use of hormonal replacement for life in postmenopausal women to prevent accelerated bone loss.

Adverse Effects

a) CARDIOVASCULAR EVENTS: In a case-control study of postmenopausal women (N=384), current use of oral conjugated equine estrogens (CEE) was associated with a significant 108% increase in the risk of venous thrombosis (VT) compared with current use of oral estradiol. Myocardial infarction (MI) risk was 87% higher, but the difference was not significant. Ischemic stroke risk was similar between groups. The women had no prior history of VT, MI, or ischemic stroke. Results were not influenced by age, daily estrogen dose, concomitant progestogen use, or timing of initiation of hormone therapy. CEE users had a greater likelihood of clotting than estradiol users, based on a 68% higher level of normalized activated protein C sensitivity ratio (nAPCsr). The difference in nAPCsr provided a possible biological mechanism for the observed difference in cardiovascular event risk [526].

Venlafaxine

Abnormal vasomotor function - Menopausal symptom

a) In the MsFLASH trial (N=339, midlife women), low-dose oral estradiol or low-dose venlafaxine decreased the mean frequency of vasomotor symptoms (VMS) associated with menopause at week 8 by 53% and 48%, respectively, a difference that was statistically significant compared with placebo (29%). Patients were randomized in a 2:2:3 ratio to 17-beta-estradiol 0.5-mg/day orally, venlafaxine XR 75 mg/day orally (titrated from 37.5 mg/day up to 75 mg/day over 1 week), or placebo for 8 weeks. The mean VMS frequency at baseline was 8.1/day [527].

Place In Therapy

A) Estradiol

1) Primary Prevention of Chronic Conditions in Postmenopausal Women

a) Use of estrogen alone has no net benefit for primary prevention of chronic conditions in most postmenopausal women who have had a hysterectomy and is therefore not recommended. These recommendations are applicable to the use of hormone therapy for primary prevention of chronic conditions in asymptomatic postmenopausal women. The statements do not apply in women considering hormone therapy to manage menopausal symptoms or in women who have had premature menopause (primary ovarian insufficiency) or surgical menopause. Decisions regarding therapy should be individualized to the specific patient or situation [43].

b) The following table summarizes evidence from randomized, placebo-controlled trials about the benefits and harms of estrogen-alone hormone therapy for prevention of chronic conditions in postmenopausal women [42]:

Outcome	Relative Benefit/Harm of HT	Relative Risk (95% Confidence Interval)*	Number of Trials	Number of Women	Strength of Evidence
Breast cancer (invasive)	NS	0.79 (0.61 to 1.01)	1^	10,739	Moderate
Colorectal cancer	NS	1.15 (0.81 to 1.63)	1^	10,739	Low
Lung cancer	NS#	1.04 (0.73 to 1.48)	1^	10,739	Low
Coronary heart disease	NS	0.95 (0.79 to 1.14)	3	11,310	High
Dementia (probable)	NS	1.49 (0.84 to 2.66)	1^	2947	Low
Diabetes, prevention	Benefit	0.87 (0.77 to 0.98)	1^	9917	Moderate
Fractures, prevention	Benefit	0.73 (0.65 to 0.8)	1^	10,739	High
Gallbladder disease	Harm	1.51 (1.32 to 1.73)	1^	8376	Moderate
Stroke	Harm	1.33 (1.06 to 1.67)	1^	10,739	Moderate
Urinary incontinence	Harm	1.53 (1.37 to 1.71)	1^	3073	Moderate
VTE	Harm	1.43 (1.11 to 1.85)	1^	10,739	Moderate
All-cause mortality	NS	1.01 (0.88 to 1.17)	3	11,961	High

KEY: HT=hormone therapy; NS=non-significant finding; VTE=venous thromboembolism

*Treatment with estrogen alone versus control.

^Estimates are based on the best available single study.

#Event rates were low, such that firm conclusions could not be made regarding difference between harm and benefit.

The absolute event rate difference for potential harms per 10,000 woman-years were estimated per each outcome as: Dementia (probable, 65 years or older), 12; gallbladder disease, 30; stroke, 11; VTE (DVT or pulmonary embolism), 11; urinary incontinence, 1261 [43].
The absolute event rate difference for potential benefits per 10,000 woman-years were estimated per each outcome as: Diabetes, -19; all fractures, -53; invasive breast cancer, -7 [43].

c) Although the review of randomized trials found no significant increase in the risk of invasive breast cancer with estrogen-only menopausal hormone therapy (MHT) [42], a meta-analysis of worldwide epidemiological data showed a significant increase in the risk of breast cancer in current estrogen users (except vaginal estrogens) compared with nonusers (RR, 1.37; 95% CI, 1.33 to 1.41). Results are based on 24 prospective studies and 61,383 cases of breast cancer; randomized studies did not have sufficient breast cancer cases for inclusion. The risk of breast cancer was greater with 5 through 14 years of estrogen use (RR, 1.33; 95% CI, 1.28 to 1.37) than with 1 through 4 years of use (RR, 1.17; 95% CI 1.1 to 1.26). Starting at age 50 years, the absolute 20-year breast cancer incidence rates were 7.4% with 10 years of estrogen use and 6.8% with 5 years

use versus 6.3% with no MHT use. There was no difference in risk between equine estrogen and estradiol or between oral and transdermal administration. In past users, excess duration-dependent risks continued for more than 10 years after MHT discontinuation. Of women who used estrogen-only MHT, 84% had received a hysterectomy [121].

2) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal vasomotor symptoms and symptoms of vaginal and vulval atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [16][7][13][38][8][92][12][36][14][15].

3) Estradiol Preparations

a) Oral estradiol is indicated for the treatment of moderate to severe menopausal vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, breast cancer in men and women with metastatic disease (palliation only), androgen-dependent prostate cancer (palliation only), and for the prevention of postmenopausal osteoporosis [7].

b) When prescribing oral estradiol solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women who are at a significant risk of developing osteoporosis and for whom non-estrogen medications are not considered to be appropriate [7].

c) Topical estradiol gel 0.06% (EstraGel(R)) is indicated for the treatment of moderate to severe menopausal vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause [13] while topical estradiol gel 0.1% (Divigel(R)) is indicated only for the treatment of moderate to severe menopausal vasomotor symptoms [38].

d) Estradiol is available as several different transdermal systems which vary by strength and whether they are applied once or twice weekly. All are to be applied to the lower abdomen or buttocks. The various estradiol transdermal systems are indicated for the treatment of moderate to severe menopausal vasomotor symptoms, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration or primary ovarian failure, and/or for the prevention of postmenopausal osteoporosis [29][8][92][12].

e) Estradiol is also available as a transdermal spray. The spray is approved for the treatment of moderate to severe menopausal vasomotor symptoms [36].

f) Estradiol may also be given vaginally using any of the following formulations: estradiol vaginal cream, estradiol vaginal ring, or estradiol vaginal inserts. The vaginal cream is indicated for the treatment of vulvar and vaginal atrophy [14], while the vaginal ring is indicated for the treatment of moderate to severe urogenital symptoms associated with postmenopausal atrophy of the vagina and/or the lower urinary tract [15]. The vaginal insert Vagifem(R) is indicated for the treatment of atrophic vaginitis [16]. The vaginal insert Imvexxy(TM) is indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause [5].

See Drug Consult reference: Osteoporosis - Prevention and Drug Therapy
See Drug Consult reference: Canadian: Management of Osteoporosis in Men and Women

B) Estradiol Acetate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) relieves postmenopausal symptoms and vaginal atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [170][60].

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Acetate

a) Oral estradiol acetate is indicated for the treatment of moderate to severe menopausal vasomotor symptoms while estradiol acetate vaginal ring is indicated for the treatment of moderate to severe menopausal vasomotor symptoms and moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause. However, if prescribing solely for the treatment of vulvar and vaginal atrophy, topical vaginal products should always be considered first [170][60].

C) Estradiol Cypionate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal symptoms and vaginal atrophy. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [55]. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use.

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Cypionate

a) Estradiol cypionate injection is indicated for the treatment of moderate to severe menopausal vasomotor symptoms associated with menopause and hypoestrogenism due to hypogonadism [55].

D) Estradiol Valerate

1) Estrogen Replacement Therapy

a) Estrogen replacement therapy (ERT) increases bone mineral density, reduces the risk of osteoporotic fracture, and relieves postmenopausal symptoms and vaginal atrophy. When used solely for vulvar and vaginal atrophy, topical estrogens, such as vaginal creams, should be used. Nonestrogen products should be used for the prevention of osteoporosis and estrogen should be used only in cases of significant risk of osteoporosis and the benefit outweighs the risks associated with estrogen use. Estrogens (alone or combined with progestins) should not be used for the prevention of cardiovascular disease or dementia. Proven risks associated with estrogen monotherapy includes stroke, deep vein thrombosis, and development of probable dementia. Proven risks of estrogen/progestin therapy include myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis, and development of probable dementia [57].

b) Many authorities recommend cyclical estrogen/progestin therapy for postmenopausal women. While this will decrease the risk of endometrial carcinoma, progestins may reverse the beneficial effects of estrogens on lipoproteins and risk of coronary atherosclerosis. Cyclic progestins may also affect compliance due to the return of withdrawal bleeding. There is no published data to suggest that women treated with cyclic estrogen/progestin regimens have a better overall mortality (or morbidity) than women treated with cyclic estrogens alone. There is also no basis for recommending that women without a uterus receive cyclic estrogen/progestin therapy, since these women have no risk of developing endometrial carcinoma.

c) There is no evidence that, in equipotent estrogenic doses, any one estrogen is superior to the others for treatment of menopausal symptoms or prevention of osteoporosis. The largest clinical experience, however, is with conjugated estrogens, followed by estradiol.

d) Use of estrogens for other menopausal problems such as skin or mood changes has not been proven effective.

2) Estradiol Valerate

a) Estradiol cypionate injection is indicated for the treatment of moderate to severe menopausal vasomotor symptoms associated with menopause, moderate to severe symptoms of vulvar and vaginal atrophy associated with menopause, hypoestrogenism due to hypogonadism, castration, or primary ovarian failure, and treatment of advanced androgen-dependent carcinoma of the prostate (palliation only) [57].

MEDICATION SAFETY

Contraindications

A) Estradiol

1) Known anaphylactic reaction, angioedema, or hypersensitivity to estradiol or any component of the product [70][71][64][72][66][74][75][76][19][69]

2) Active arterial thromboembolic disease (eg, stroke, myocardial infarction) or history of these conditions [70][64][5][72][66][74][69][76][7][14][75][19][8]

3) Breast cancer, whether known, suspected, or history of this condition [70][64][5][72][66][74][69][19][75]; except in appropriately selected patients being treated for metastatic disease [76][7][14][8]

4) Active DVT, pulmonary embolism, or history of these conditions [70][64][5][72][66][74][69][76][7][14][75][19][8]

5) Estrogen-dependent neoplasia, whether known or suspected [70][64][5][72][66][74][76][7][14][75][19][8]

6) Hepatic impairment or disease [70][64][5][72][66][74][69][76][7][14][75][19][8]

7) Pregnancy, whether known or suspected [72][69][76][7][14][75][8]

8) Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders [70][64][5][72][66][74][69][75][76][19]

9) Undiagnosed abnormal genital bleeding [70][64][5][72][66][74][69][76][7][14][75][19][8]

B) Estradiol Acetate

1) Active or history of arterial thromboembolic disease (eg, stroke, myocardial infarction) [59][61]

2) Active or history of DVT or pulmonary embolism [59][61]

3) Anaphylactic reaction or angioedema to Femring(R) [59]

4) Breast cancer (known, suspected, or history of) [59][61]

5) Estrogen-dependent neoplasia [59][61]

6) Hypersensitivity to estradiol acetate or product ingredients [59][61]

7) Liver dysfunction or disease [59][61]

8) Pregnancy [59][61]

9) Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders [59]

10) Undiagnosed abnormal genital bleeding [59][61]

C) Estradiol Cypionate

1) Arterial thromboembolic disease (stroke, myocardial infarction) (active or recent) [55]

2) Breast cancer (known, suspected or history of) [55]

3) Deep vein thrombosis/pulmonary embolism (active or a history of these conditions) [55]

4) Estrogen-dependent neoplasia (known or suspected) [55]

5) Genital bleeding, undiagnosed abnormal [55]

6) Hypersensitivity to estradiol cypionate or product ingredients [55]

7) Liver dysfunction or disease [55]

8) Pregnancy (known or suspected) [55]

D) Estradiol Valerate

1) Undiagnosed abnormal genital bleeding [58]

2) Known, suspected, or history of breast cancer [58]

3) Known or suspected estrogen-dependent neoplasia [58]

4) Active or history of deep vein thrombosis or pulmonary embolism [58]

5) Active or recent (within the past year) arterial thromboembolic disease (eg, myocardial infarction, stroke) [58]

6) Liver disease or dysfunction [58]

7) Known hypersensitivity to estradiol valerate [58]

8) Known or suspected pregnancy [58]

Precautions

A) Estradiol

1) Angioedema: Hereditary angioedema; estrogens may exacerbate symptoms of angioedema [16][29][66][74][69][75][76][19]

2) Application: Fire, flame, and smoking should be avoided until applied alcohol-based products are

dried [74][69][76][75]

3) Cardiovascular: Arterial vascular disease risk factors (eg, hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity) increase the risk of cardiovascular disorders [5][16][29][72][66][74][69][76][7][14][75][19][8]; discontinue therapy in all patients if pulmonary embolism, DVT, stroke or myocardial infarction are suspected [68][10][33] or occur [71]

4) Cardiovascular: VTE risk factors (eg, personal or family history of VTE, obesity, systemic lupus erythematosus) increase the risk of cardiovascular disorders [68][10][5][29][72][74][69][76][7][14][75][8]; discontinue therapy in all patients if pulmonary embolism, DVT, stroke or myocardial infarction are suspected [68][10][33] or occur [71].

5) Cardiovascular: Men given large doses of estrogen (conjugated estrogens 5 mg/day) may have increased risk of myocardial infarction, pulmonary embolism, or thrombophlebitis [7][14][8]

6) Cardiovascular: Elevated blood pressure may occur [5][29][74]; monitoring recommended [19]

7) Cardiovascular: Hypertension may occur or worsen; monitoring recommended [72][66][76][7][14][15][75][19][8]

8) Endocrine and metabolic: Severe hypercalcemia may occur in women with bone metastases from breast cancer; discontinue [5][16][29][72][66][74][69][76][7][14][14][75][19][8]

9) Endocrine and metabolic: Triglyceride elevation leading to pancreatitis or other complications may occur in patients with preexisting hypertriglyceridemia [5][16][29][72][66][74][69][76][7][14][75][8]; discontinue if pancreatitis occurs [63][71][68][10]

10) Endocrine and metabolic: Hypothyroidism; estrogen increases thyroid-binding globulin levels which may require a dosage increase in thyroid replacement therapy; monitoring recommended [5][16][29][72][66][74][69][76][7][14][75][19][8]

11) Endocrine and metabolic: Premature puberty/breast development (females) and gynecomastia (males) have been reported in children from inadvertent skin exposure to transdermal spray; contact with unwashed or unclothed application sites should be avoided [69]

12) Endocrine and metabolic: Fluid retention may be exacerbated in patients with conditions affected by fluid retention (cardiac or renal dysfunction); monitoring recommended [63][68][10][5][16][29][72][69][76][7][14][75][8]; discontinuation may be necessary [10][33]. Discontinue estrogen-alone therapy with evidence of medically concerning fluid retention [63][71][68].

13) Endocrine and metabolic: Hypocalcemia may occur in patients with hypoparathyroidism [5][16][29][72][66][74][69][75][76][19]

14) Endocrine and metabolic: Diabetes mellitus exacerbation may occur [5][16][29][72][66][74][69][76][7][14][75][19][8]

15) Endocrine and metabolic: Prepubertal boys; estrogen treatment may modify the normal pubertal process and induce gynecomastia [7][14][8][12]

16) Endocrine and metabolic: Prepubertal children; large and repeated doses of estrogen over an extended time period may accelerate epiphyseal closure, which could result in short adult stature [66][7][14][8]

17) Gastrointestinal: Gallbladder disease requiring surgery; estrogens reported to increase risk in postmenopausal women [5][16][29][72][66][74][69][76][7][14][75][19][8]

18) Hematologic: Surgeries associated with an increased risk of thromboembolism or periods of prolonged immobilization; discontinuation at least 4 to 6 weeks prior to surgery recommended [5][16][29][72][66][74][69][76][7][14][75][19][8]

19) Hematologic: Porphyria may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

20) Hepatic: Hepatic impairment or history of cholestatic jaundice with past estrogen use or pregnancy; discontinue if cholestatic jaundice recurs [5][16][29][72][66][74][69][76][7][14][75][19][8]

21) Hepatic: Hepatic hemangiomas may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

22) Immunologic: Anaphylaxis and angioedema have been reported [29][66]

23) Immunologic: Systemic lupus erythematosus may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

24) Immunologic: Tartrazine (FD&C Yellow No. 5) sensitivity, especially with aspirin sensitivity; oral tablets may cause allergic-type reaction [7]

25) Neurologic: Epilepsy or migraines may be exacerbated [5][16][29][72][66][74][69][76][7][14][75][19][8]

26) Ophthalmic: Retinal vascular thrombosis has been reported; discontinuation may be necessary [5][16][29][72][66][74][69][76][7][14][75][19][8]

27) Ophthalmic: Visual abnormalities may occur; discontinue therapy if papilledema or retinal vascular lesions occur [63][71][68][10]

28) Reproductive: Prolonged therapy; increased risk of breast or endometrial [5][29][16] or ovarian cancer with duration of use [29][72][66][74][69][76][7][14][75][19][8]

29) Reproductive: Ovarian cancer; estrogens with or without progestin may increase risk [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

30) Reproductive: Endometriosis may be exacerbated in patients with residual, post-hysterectomy endometriosis treated with estrogen alone; consider adding a progestin [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

31) Reproductive: Prepubertal girls; estrogen treatment induces premature breast development and vaginal cornification, and may induce vaginal bleeding [66][7][14][8]

32) Reproductive: Abrasions induced by the Vagifem(R) applicator have been reported, particularly in women with severely atrophic vaginal mucosa [16]

33) Reproductive: Vaginal infection; treat before initiating or continuing therapy with vaginal ring or vaginal insert [72]

34) Reproductive: Vaginal irritation (narrow, short or stenosed vagina); irritation or ulceration may occur with vaginal ring use [72]

35) Respiratory: Asthma exacerbations may occur [5][29][16][29][72][66][74][69][76][7][14][75][19][8]

36) Sunscreen use: Absorption of transdermal and topical formulations may be affected [69][76][13][75]

37) Systemic absorption: May occur with vaginal insert use; precautions associated with systemic estrogen alone therapy should be taken into account [5]

B) Estradiol Acetate

1) Angioedema: Hereditary angioedema may be exacerbated [59][61]

2) Cardiovascular: Monitor patients with risk factors for arterial vascular disease (eg, hypertension, diabetes, tobacco use, hypercholesterolemia, obesity) or VTE (eg, personal or family history of VTE, obesity, systemic lupus erythematosus) due to increased risk of cardiovascular disorders with use of estrogen mono- or combination therapy [59][61]

3) Cardiovascular: Significant blood pressure increases have occurred with estrogen use [59][61]

4) Cardiovascular: Conditions affected by fluid retention (eg, cardiac or renal dysfunction) may worsen; monitoring recommended [59][61]

5) Endocrine and metabolic: Hypothyroid patients treated with thyroid hormone replacement therapy require monitoring and possible thyroid hormone dose adjustment due to increased thyroid-binding globulin levels [59][61]

6) Endocrine and metabolic: Severe hypercalcemia may occur in women with breast cancer and bone metastases; discontinue if condition develops [59][61]

7) Endocrine and metabolic: Triglyceride elevations have been reported, which may progress to pancreatitis in women with preexisting hypertriglyceridemia; discontinuation may be required [59][61]

8) Endocrine and metabolic: Hypoparathyroidism; use with caution as hypocalcemia may occur with estrogen use [59][61]

9) Endocrine and metabolic: Diabetes may be exacerbated; use with caution [59][61]

10) Gastrointestinal: A 2 to 4-fold increased risk of gallbladder disease requiring surgery has been reported in postmenopausal women with estrogen use [59][61]

11) Hematologic: Porphyria may be exacerbated; use with caution [59][61]

12) Hepatic: Liver impairment; poor estrogen metabolism may occur [59][61]

13) Hepatic: Use caution in patients with a history of cholestatic jaundice and discontinue if condition recurs [59][61]

14) Hepatic: Hepatic hemangioma may be exacerbated; use with caution [59][61]

15) Immunologic: Systemic lupus erythematosus may be exacerbated; use with caution [59][61]

16) Neurologic: Epilepsy may be exacerbated; use with caution [59][61]

17) Neurologic: Migraines may be exacerbated; use with caution [59][61]

18) Ophthalmic: Retinal vascular thrombosis has been reported; interrupt therapy if condition is suspected and permanently discontinue if confirmed [59][61]

19) Reproductive: Estrogen mono- or combination therapy may increase risk of ovarian cancer [59][61]

20) Reproductive: Vaginal form may not be suitable for women susceptible to vaginal irritation or ulceration or with conditions that increase the risk of expulsion (eg, vaginal stenosis, narrow vagina, vaginal infection, cervical prolapse, rectoceles, cystoceles) [59][61]

21) Reproductive: Endometriosis exacerbation may occur with estrogen alone; consider adding a progestin in patients known to have residual endometriosis posthysterectomy [59][61]

22) Respiratory: Asthma may be exacerbated; use with caution [59][61]

23) Surgery: If possible, discontinue estrogens at least 4 to 6 weeks before prolonged bedrest or elective surgery associated with thromboembolism risk [59][61]

C) Estradiol Cypionate

1) Endometrial cancer; unopposed estrogen use increases the risk in women with intact uteri [55]

2) Cardiovascular disorders; estrogens with or without progestins should not be used for the prevention of cardiovascular disease [55]

3) Myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, deep vein thrombosis; conjugated estrogens plus progestin increased the risk in postmenopausal women aged 50 to 79 years; risk should be assumed to be similar with all doses of conjugated estrogens with medroxyprogesterone acetate and with other combinations and dosage forms of estrogens and progestins [55]

4) Dementia; conjugated estrogens in combination with medroxyprogesterone increased the risk of probable dementia in postmenopausal women aged 65 years and older and should not be used for the prevention of dementia; risk should be assumed to be similar with all doses of conjugated estrogens with medroxyprogesterone acetate and with other combinations and dosage forms of estrogens and progestins [55]

5) Addition of a progestin to estrogen therapy; lowers incidence of endometrial hyperplasia in women with a uterus but may also increase risk of breast cancer, affect lipoprotein metabolism, and impair glucose tolerance [55]

6) Arterial vascular disease risk factors (hypertension, diabetes mellitus, tobacco use, hypercholesterolemia, obesity); increased risk of cardiovascular events [55]

7) Asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, and hepatic hemangiomas; estrogen therapy may cause exacerbation [55]

8) Breast cancer and bone metastases; increased risk for severe hypercalcemia [55]

9) Conditions affected by fluid retention (cardiac or renal dysfunction); estrogens may exacerbate condition [55]

10) Endometriosis; estrogen therapy may cause exacerbation [55]

11) Gallbladder disease requiring surgery; estrogens increases risk 2- to 4-fold in postmenopausal women [55]

12) Hypertension; estrogen therapy may increase blood pressure [55]

13) Hypertriglyceridemia; may elevate plasma triglycerides leading to pancreatitis and other complications [55]

14) Hypocalcemia, severe; estrogens should be used with caution [55]

15) Hypothyroidism; estrogen increases thyroid-binding globulin levels which may require a dosage increase in thyroid replacement therapy [55]

16) Impaired liver function or history of cholestatic jaundice; decreased estrogen metabolism [55]

17) Ovarian cancer; estrogens with or without progestin may increase risk [55]

18) Prolonged therapy; estrogen-plus-progestin combination therapy increases risk of breast cancer with duration of use [55]

19) Retinal vascular thrombosis has been reported in patients receiving estrogens; discontinue conjugated estrogens if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine [55]

20) Surgeries associated with an increased risk of thromboembolism or periods of prolonged immobilization; increased risk of thromboembolism [55]

21) Venous thromboembolism risk factors (personal or family history, obesity, systemic lupus erythematosus); increased risk of developing venous thromboembolism [55]

D) Estradiol Valerate

1) Cardiovascular: Blood pressure elevations may occur; monitoring recommended [58]

2) Cardiovascular: Fluid retention may occur. Use caution in patients with conditions affected by fluid retention (eg, cardiac or renal dysfunction); monitoring recommended [58]

3) Endocrine and metabolic: Exacerbation of diabetes mellitus may occur [58]

4) Endocrine and metabolic: Exercise caution in patients with severe hypocalcemia [58]

5) Endocrine and metabolic: Increased doses of thyroid replacement therapy may be required in patients dependent on thyroid hormone replacement therapy; monitoring recommended [58]

6) Endocrine and metabolic: Preexisting hypertriglyceridemia increases risk of triglyceride elevations leading to pancreatitis [58]

7) Endocrine and metabolic: Severe hypercalcemia may occur in the presence of breast cancer and bone metastases; discontinue use [58]

8) Gastrointestinal: Increased risk of gallbladder disease requiring surgery has been reported [58]

9) Hematologic: Exacerbation of porphyria may occur [58]

10) Hematologic: Hypercoagulability, primarily related to decreased antithrombin activity, may occur [58]

11) Hepatic: Exacerbation of hepatic hemangiomas may occur [58]

12) Hepatic: Impaired liver function; poor metabolism of estrogens may occur [58]

13) Hepatic: Use caution in patients with a history of cholestatic jaundice associated with past estrogen use or pregnancy; if reoccurrence occurs discontinue use [58]

14) Immunologic: Exacerbation of systemic lupus erythematosus may occur [58]

15) Neurologic: Exacerbation of epilepsy may occur [58]

16) Neurologic: Exacerbation of migraine may occur [58]

17) Neurologic: Increased risk of stroke among women 50 years of age or older; discontinue if stroke occurs or is suspected [58]

18) Ophthalmic: Retinal vascular thrombosis has been reported; discontinuation may be necessary [58]

19) Reproductive: Abnormal uterine bleeding and/or mastodynia may occur [58]

20) Reproductive: Addition of a progestin during estrogen administration when a woman has not had a hysterectomy may decrease incidence of endometrial hyperplasia [58]

21) Reproductive: Exacerbation of endometriosis may occur and lead to malignant transformation of residual implants post-hysterectomy with estrogen therapy alone; consider addition of progestin therapy [58]

22) Reproductive: Increased risk of ovarian cancer [58]

23) Respiratory: Exacerbation of asthma may occur [58]

24) Surgery: Discontinue 4 to 6 weeks before surgery that is associated with increased risk of VTE, or during prolonged immobilization [58]

Adverse Effects

Cardiovascular Effects

Estradiol

Coronary arteriosclerosis

a) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 59% decreased risk of coronary artery disease in ever-users of unopposed estrogen or estrogen plus progestin therapy compared with never-users [103]

Edema

a) Incidence: Transdermal system, 0.5% to 13% [19]

b) General Information

1) Edema has been reported with estrogen and/or progestin therapy [76][7][38][35][8][19][11][12][36][14][15].

c) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 0.5% to 13% vs 6% with placebo [19]

Heart disease

a) General Information

1) No cardiovascular benefit occurred with estrogen mono- or combination therapy [29][69]

2) No overall effect on coronary heart disease events was reported with estrogen monotherapy [29][69]

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [29][69]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Do not use estrogen alone or with progestin to prevent cardiovascular disease [29][69]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Risk of all coronary heart disease (CHD) events (ie, nonfatal myocardial infarction, CHD death) with conjugated estrogen plus medroxyprogesterone acetate was increased non-significantly vs placebo. In a subgroup analysis, a nonsignificant reduction in CHD events was seen in women treated less than 10 years after menopause [29][69]

2) Hormone replacement therapy (oral route): No cardiovascular benefit was seen in postmenopausal women with heart disease with conjugated estrogen plus medroxyprogesterone acetate therapy. There were more cardiovascular heart disease (CHD) events in the first year compared with placebo, but not after year 1 [69][76][7][13][38][35][8][19][11][12][14][15].

Hypertension

a) General Information

1) May produce or exacerbate hypertension in some women, especially with higher-dose estrogens used in contraceptives, in older menopause-treatment regimens, and in cancer treatment [97][98][99][100][101]

2) Substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens in some cases, but a generalized effect of estrogen on blood pressure was not demonstrated in a large randomized trial [29][76][7][38][35][8][19][11][12][36][14][15]

Ischemic heart disease, Mortality

a) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): death due to ischemic heart disease, 1% in current users, 3% in former users, and 3.7% in never users [104]

Myocardial infarction

a) General Information

1) Increased risk with estrogen and progestin combination therapy [29][69][74]

2) Risk for myocardial infarction or coronary death was reduced by 39% with estrogen monotherapy among women aged 50 to 59 years and 14% among women aged 60 to 69 years; 10% increased risk among women aged 70 to 79 years [93].

3) Risk of all coronary heart disease (CHD) events (ie, nonfatal myocardial infarction, CHD death) was not significantly higher with estrogen alone vs placebo [29][69]

4) A nonsignificant reduction in CHD events was seen in women treated less than 10 years after menopause [29][69]

5) Increased risk of nonfatal myocardial infarction in men with larger doses of conjugated estrogens for palliative care [7][13][38][35][8][11][12][14][15][94].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [69][74][76][19]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Oral administration was associated with a more than 2-fold increase in C-reactive protein (CRP) levels in 1 study; transdermal administration had no effect on CRP [95]

4) Discontinue immediately if condition occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route), Non-fatal myocardial infarction, estrogen monotherapy: Risk was 9% lower with conjugated estrogens vs placebo [69][74]

2) Hormone replacement therapy (oral route), Non-fatal myocardial infarction, estrogen-progestin therapy: Risk was 28% higher with conjugated estrogens plus medroxyprogesterone acetate vs placebo [29][69][74]

3) Estrogen replacement (oral, transdermal routes), C-reactive protein levels: Oral conjugated estrogen was linked to a more than 2-fold increase in highly sensitive C-reactive protein levels from baseline; transdermal estrogen had no effect [95]

4) Estrogen replacement: The prothrombin 20210 G A variant increased myocardial infarction risk among hypertensive women treated with hormone replacement therapy (HRT) compared with HRT-treated women without the prothrombin variant [96]

Myocardial ischemia

a) Postmarketing

1) Has been reported [74]

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 19.1% with unopposed estrogen replacement therapy; 9.8% with estrogen plus progesterone; 8.4% with no estrogen therapy [102]

Thrombophlebitis

a) Postmarketing

1) Has been reported [66][72]

Estradiol Acetate

Edema

a) Edema has been reported with estrogen and/or progestin therapy [170].

Heart disease

a) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93][143][144].
b) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [170][145].
c) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].
d) Results from the Heart and Estrogen/progestin Replacement Study (HERS) indicated that treatment with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily provided no cardiovascular benefit in postmenopausal women with documented heart disease (n=2763, mean age 66.7 years). During an average follow-up of 4.1 years, treatment did not reduce the overall rate of coronary heart disease (CHD) events. In year one, there were more CHD events in the estrogen/progestin treated group compared with placebo but this was not the case in subsequent years. In the open-label extension of HERS (HERS II, n=2321), after an additional follow-up of 2.7 years (6.8 years total), rates of CHD events were comparable among women in the estrogen/progestin group and the placebo group in the HERS, HERSII, and overall [170].

Hypertension

a) In a small number of cases, substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens. However, in a large, randomized, controlled trial, a generalized effect of estrogen on blood pressure was not demonstrated [170].
b) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) Summary

1) The data on risk of myocardial infarction (MI) in postmenopausal women receiving estrogen replacement is not definitive. The Women's Health Initiative (WHI) Estrogen Alone trial comparing estrogen to placebo was unable to demonstrate a significant difference in the risk of myocardial infarction or coronary death [93][144]. However, data from the WHI Estrogen Plus Progestin trial

involving estrogen plus progestin demonstrated an increased risk of nonfatal myocardial infarction after an average follow-up of 5.2 years (hazard ratio 1.32, 95% confidence interval 1.02 to 1.72) in postmenopausal women with a uterus who received estrogen and progestin therapy [170][145].

b) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

c) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE), but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk for MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

d) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [170].

e) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

f) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

Raynaud's phenomenon

a) Incidence: 19.1% [102]

b) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Estradiol Cypionate

Edema

a) Edema has been reported with estrogen and/or progestin therapy [55].

Heart disease

a) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93][143][144].

b) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [55][145].

c) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].

Increased blood pressure

a) In a small number of cases, substantial increases in blood pressure were reported as idiosyncratic reactions to estrogens. However, in a large, randomized, controlled trial, a generalized effect of estrogen on blood pressure was not demonstrated [55].

b) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) General Information

1) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

2) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE), but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205).

Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk for MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [55].

4) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

5) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

a) Transgender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Estradiol Valerate

Edema

a) General Information

1) Edema has been reported with estrogen and/or progestin therapy [57].

Heart disease

a) General Information

1) Final reports from the Women's Health Initiative (WHI) Estrogen Alone trial indicate that estrogen only provided no overall protection against myocardial infarction or coronary death, however, there seemed to be a trend toward lowering the risk of coronary heart disease in women who were 50 to 59 years of age at baseline. The estrogen only study was halted after 6.8 years of follow-up [93] [143][144].

2) At an average of 5.2 years follow-up, results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicated conjugated estrogens 0.625

milligrams (mg) plus medroxyprogesterone acetate 2.5 mg daily lead to a significant increase in coronary heart disease (hazard ratio (HR) 1.29, 95% confidence interval (CI) 1.02 to 1.63). After an average follow-up of 6.8 years in the WHI Estrogen-alone substudy, the relative risk of conjugated estrogens therapy versus placebo was 0.95 (95% CI 0.79 to 1.16) [57][145].

3) A secondary analysis of the Women's Health Initiative (WHI) Estrogen Plus Progestin trial identified a nonsignificant reduction in risk of coronary heart disease (CHD) among women who initiated hormone therapy closer to menopause compared with women who initiated hormone therapy more distant from onset of menopause. The hazard ratio (HR) for CHD in women who initiated hormone therapy within 10 years since menopause was 0.76 (95% confidence interval (CI), 0.50 to 1.16) compared to 1.10 (95% CI, 0.84 to 1.45) and 1.28 (95% CI, 1.03 to 1.58) for women who initiated therapy within 10 to 19 years and 20 or more years, respectively (p=0.02). The estimated absolute risk for CHD was -6 per 10,000 person-years for women within 10 years of menopause, 4 per 10,000 person-years for 10 to 19 years since menopause, and 17 per 10,000 person-years for 20 or more years from menopause. When the risk of CHD was analyzed by age, the number of events increased with age but there was no statistically significant additional effect of hormone therapy by age. The HR for CHD in women aged 50 to 59 years was 0.93 (95% CI, 0.65 to 1.33) compared with 0.98 (95% CI, 0.79 to 1.21) for women aged 60 to 69 years and 1.26 (95% CI, 1.00 to 1.59) in women aged 70 to 79 years (p=0.16). There was, however, a reduction in total mortality in women aged 50 to 59 years (HR, 0.70; 95% CI, 0.51 to 0.96) and a nonsignificant trend for increasing HRs across age groups was noted (p=0.06). The risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146].

Increased blood pressure

a) General Information

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2) Estrogen therapy can produce or exacerbate hypertension in some women. This effect is consistently found with the higher doses of estrogens used in contraceptives, in older menopause-treatment regimens, and in treatment of cancer [101][100]; [99][98][97].

Myocardial infarction

a) General Information

1) Final results from the Women's Health Initiative (WHI) Estrogen Alone trial involving unopposed estrogen therapy for coronary prevention, demonstrated no overall protection against myocardial infarction (MI) or coronary death in postmenopausal women without a uterus. The subjects (n=10,739, mean age 63.6 years) were randomized to oral conjugated equine estrogens (CEE) 0.625 milligrams or placebo daily. After a mean duration follow-up of 7.1 years, there were 201 coronary heart disease (CHD) events among women using CEE compared with 217 events among women receiving placebo (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.79 to 1.16). The primary outcome (MI or coronary death) hazard ratios for patients aged 50 to 59 years, 60 to 69 years, and 70 to 79 years at baseline were 0.61 (95% CI, 0.25 to 1.50), 0.86 (95% CI, 0.60 to 1.25), and 1.10 (95% CI, 0.69 to 1.73), respectively. Additionally, coronary revascularization was less frequent in women aged 50 to 59 years who were receiving CEE (HR, 0.55; 95% CI, 0.35 to 0.86). This group was also associated with less frequent composite outcomes, such as HR for MI, coronary death, coronary revascularization, and confirmed angina (HR, 0.66; 95% CI, 0.45 to 0.96) [93].

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milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Larger doses of estrogen (5 milligrams conjugated estrogens daily) used in palliation therapy of prostate and breast cancer have been shown to increase the risk of nonfatal myocardial infarction during a large prospective clinical trial involving men [57].

4) Oral conjugated estrogens (CEE) but not transdermal estradiol was found to increase C-reactive protein (CRP) levels in a randomized, crossover, placebo-controlled trial. Postmenopausal women (n=29) were randomized to CEE 0.625 milligrams/day, transdermal estradiol 100 micrograms/day, or placebo for 8 weeks. CRP, a marker of systemic inflammation and predictor of myocardial infarction and cardiovascular mortality, was measured before and after 8 weeks of therapy. Oral estrogen therapy caused a more than two-fold increase in highly sensitive CRP (p less than 0.01 versus baseline and placebo). In the same women, transdermal estrogen had no effect on CRP. The data suggests the route of estrogen replacement therapy may be an important consideration in minimizing the adverse effects of estrogen therapy on cardiovascular outcomes [95].

5) In a population-based, case-control study of 232 postmenopausal hypertensive women, the association between hormone replacement therapy (HRT) and myocardial infarction (MI) risk differed between those with and without the prothrombin 20210 G A variant. The prothrombin variant was a risk factor for MI among hypertensive women. In addition, there was a significant interaction between the use of HRT and the prothrombin variant on the risk of MI among women with hypertension. These findings need to be confirmed in other settings [96].

a) Trangender

1) The risk of myocardial infarction was increased 2.64-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations over a mean follow-up of 9.07 years (median, 5.95 years) and was increased 3.69-fold in transmen receiving THT with testosterone compared with reference women over a mean follow-up of 8.1 years (median, 4.1 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of myocardial infarction in either transwomen or transmen compared with reference men [86].

Raynaud's phenomenon

a) Incidence: 19.1% [102]
b) Adult Clinical Trials

1) There was an association between postmenopausal patients using unopposed estrogen replacement therapy and Raynaud's phenomenon (19.1%) in women from the Framingham Offspring Cohort. The incidence was 9.8% among women receiving estrogen plus progesterone and 8.4% among those women not receiving estrogen. It has been suggested that estrogens may affect the pathogenesis of certain vascular disorders [102].

Dermatologic Effects

Estradiol

Application site irritation

a) Incidence: Transdermal spray, 1.3% [36]; transdermal system, 5.7% to 56.7% [29][8]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1.3% [36]

2) Estrogen replacement (transdermal route): Up to 3.2% [29]

3) Estrogen replacement (transdermal route): 5.7% to 56.7% vs 58.6% with placebo [8]

c) Postmarketing

1) Topical gel: Application site dryness, pain, discoloration, rash, and reaction have been reported [74]

Chloasma

a) General Information

1) May persist after discontinuation of estrogen and/or progestin therapy [76][7] [38][35][8][11][12][36][14][15]

Erythema multiforme

a) Postmarketing

1) Has been reported [76]

Hirsutism

a) General Information

1) Hirsutism has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Loss of scalp hair

a) General Information

1) Loss of scalp hair has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Persistent erythema of skin

a) Incidence: Transdermal system, less than or equal to 3.2% [29]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): Less than or equal to 3.2% [29]

Pruritus

a) Incidence: Topical emulsion, 4% [35]
b) General Information

1) Pruritus has been reported with estrogen and/or progestin therapy [76][7][38][35][8][92][11][12][36][14][15]

c) Adult Clinical Studies

1) Estrogen replacement (topical route): 4% with estradiol topical emulsion vs 0% with placebo [35]; topical gel, noted in clinical studies [74]

d) Postmarketing

1) Has been reported [29]

Estradiol Acetate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [170].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [170].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [170].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [55].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [55].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [55].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [55].

Estradiol Valerate

Chloasma

a) Chloasma or melasma that may persist when the drug has been discontinued has been reported during the use of estrogen and/or progestin therapy [57].

Hirsutism

a) Hirsutism has been reported during the use of estrogen and/or progestin therapy [57].

Loss of scalp hair

a) Loss of scalp hair has been reported during the use of estrogen and/or progestin therapy [57].

Pruritus

a) Pruritus has been reported during the use of estrogen and/or progestin therapy [57].

Endocrine/Metabolic Effects

Estradiol

Body fluid retention

a) General Information

1) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [29][69][76][7][13][38][35][8][19][11][12][14][15][94].

b) Prevention and Management

1) Discontinue with evidence of fluid retention [68]

Galactorrhea

a) General Information

1) Has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Gynecomastia

a) Adult Case Reports

1) Gynecomastia and impotence have been reported in 2 men after regular use of an estrogen-containing hair lotion (50 mg estradiol/100 mL alcoholic solution). Although one patient had return of libido and regression of the gynecomastia 4 weeks after discontinuing the hair lotion, the other patient had no regression of his gynecomastia. This patient underwent bilateral mastectomy 6 months after discontinuation of the hair product [109].

b) Pediatric Case Reports

1) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother. The indirect exposure also resulted in rapid changes in growth and advanced bone age [110].

Hypercalcemia

a) General Information

1) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [29][74][76][7][13][38][35][8][19][11][12][36][14][15][94]

b) Prevention and Management

1) Discontinue use [29][76][19] and treat hypercalcemia [29][74].

Hypertriglyceridemia

a) General Information

1) Estrogen therapy may be associated with elevations in plasma triglycerides, possibly leading to pancreatitis [68]

b) Prevention and Management

1) Discontinue if pancreatitis occurs [68]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Triglyceride levels increased with estrogen with or without medroxyprogesterone [111]

2) Hormone replacement therapy (transdermal route): No significant triglyceride elevation with estradiol plus oral progesterone [112]

3) Hormone replacement therapy (IM route): Significant increase in triglyceride levels with estradiol valerate plus dehydroandrosterone enanthate [113]

Hypocalcemia

a) General Information

1) Has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

2) Increased risk in women with hypoparathyroidism [29][69][19]

Syndrome of carbohydrate intolerance

a) General Information

1) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [76][7][13][38][35][8][11][12][36][14][15].

Thyroid-binding globulin high

a) Prevention and Management

1) Increased doses of thyroid replacement therapy may be required in women receiving estrogens and thyroid hormone therapy [68]

Weight decreased

a) General Information

1) Weight loss has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15].

Weight increased

a) Incidence: Transdermal system, up to 8.5% [29]

b) General Information

1) Weight increase has been reported with estrogen and/or progestin therapy [29] [76][7][38][35][8][19][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 0% to 8.5% vs 1.9% with placebo [29]

Estradiol Acetate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [170].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number

of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26; 95% confidence interval, 1.00 to 1.59) [170].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Diabetes mellitus

a) Estrogen therapy may cause an exacerbation of diabetes mellitus [170].

Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [170].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [170].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [170].

c) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].

d) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [170].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [170].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [55].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

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10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

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3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [55].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-

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b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens

only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

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Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [55].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [55].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [55].
c) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].
d) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [55].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [55].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [55].

Estradiol Valerate

Body fluid retention

a) Estrogens may cause some degree of fluid retention and may exacerbate conditions affected by fluid retention, such as cardiac or renal dysfunction [57].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26

to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [57].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of

developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755

women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Diabetes mellitus

a) Estrogen therapy may cause an exacerbation of diabetes mellitus [57].

Galactorrhea

a) Galactorrhea has been reported with the use of estrogen and/or progestin therapy [57].

b) Three prepubertal boys presented with gynecomastia and elevated estradiol levels as a result from indirect exposure to a custom-compounded preparation of estrogen cream being used by each child's mother [110]. The indirect exposure also resulted in rapid changes in growth and advanced bone age. It is recommended that women requiring estrogen therapy use an alternate form of estrogen delivery (transdermal or oral) if they are in frequent contact with children.

Hypercalcemia

a) Administration of estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases [57].

Hypertriglyceridemia

a) Summary

1) Estrogens generally cause an increase in HDL cholesterol and a decrease in LDL cholesterol, as well as an increase in serum triglycerides. The overall effect of these lipid changes is probably to reduce the risk of atherosclerosis. However, simultaneous use of progestins may prevent these benefits, and result in additional increases in LDL cholesterol. In addition, postmenopausal women with coronary disease who have the estrogen receptor alpha IVS1-401 C/C genotype or other closely related genotype have an augmented response of HDL cholesterol to hormone replacement therapy [156].

b) Estrogen therapy in patients with pre-existing hypertriglyceridemia may cause elevations of plasma triglycerides which may lead to pancreatitis and other complications [57].

c) A case of severe hypertriglyceridemia and pancreatitis was reported in a 30-year-old woman being treated with estradiol valerate for endometrial preparation for cryopreserved embryo transfer. Four days after the patient's third injection of intramuscular estradiol valerate 6 milligrams biweekly, the patient presented with lower abdominal pain, nausea, vomiting, fever and diffuse right quadrant tenderness. Blood work revealed a significantly elevated triglyceride level (8062 milligrams/deciliter (mg/dL)) and a total cholesterol level of 1186 mg/dL. Estrogen therapy was discontinued and the patient was admitted for supportive care. The patient was discharged on day 4 with complete resolution of clinical symptoms and a total cholesterol and triglyceride level of 300 mg/dL and 780 mg/dL, respectively. After 2 months on a low-fat diet and gemfibrozil therapy, the patient was able to maintain a normal cholesterol level under 200 mg/dL and triglyceride levels of 300 to 500 mg/dL. The use of oral estradiol during subsequent cryothaw pregnancies did not produce the same degree of hyperlipidemia as did treatment with injectable estradiol [168].

d) Lower doses of both conjugated equine estrogens (CEE) alone and CEE plus medroxyprogesterone (MPA) were associated with favorable changes in lipids and lipid proteins compared to higher doses and placebo. Postmenopausal women (n=749) were randomized to CEE 0.3 to 0.625 milligrams (mg) daily or the combined regimen of CEE (range 0.3 to 0.625 mg) with MPA (range 1.5 to 2.5 mg) daily. After one year, all of the regimens were associated with an increase in high-density lipoprotein cholesterol, with similar increases between CEE 0.45 mg with MPA 1.5 mg and CEE 0.625 mg with MPA 2.5 mg. Low-density lipoprotein

cholesterol was reduced in all treatment groups with the exception of CEE 0.3 mg with MPA 1.5 mg at cycle 13. Triglyceride levels increased in all groups as did apolipoprotein A-1 levels. Apolipoprotein B levels decreased in all groups [111].
e) The Lipid Research Clinics Program found a statistically insignificant trend towards increased LDL-cholesterol in 30 women under 45 years treated with estrogens (compared to 74 controls). This trend was not seen in older women receiving estrogen preparations, in whom a significant decrease in LDL-cholesterol was seen [157]. A statistically significant decrease in total serum cholesterol was seen in older women treated with estrogens, while the younger group showed a significant increase. Both HDL-cholesterol and triglycerides were increased in both old and young treatment groups, with a significant increase in VLDL-cholesterol seen only in the younger women (a statistically insignificant increase was noted in the older women). The treatment and control groups were comparable in terms of obesity, smoking, and alcohol usage. The reason for the differences between younger and older women with respect to LDL is not clear, though the authors speculate that the younger group may not all have been estrogen deficient, particularly as compared to the postmenopausal group.

Hypocalcemia

a) Hypocalcemia has been reported with the use of estrogen and/or progestin therapy [57].

Syndrome of carbohydrate intolerance

a) Reduced carbohydrate tolerance has been reported with the use of estrogen and/or progestin therapy [57].

Weight gain

a) Increases or decreases in weight has been reported with the use of estrogen and/or progestin therapy [57].

Gastrointestinal Effects

Estradiol

Abdominal pain

a) Incidence: Topical gel, 7.7% [13]; transdermal system, up to 16% [19]; vaginal cream, 2% [15]; vaginal ring, 4% [15]; vaginal tablets, 7% [94]
b) General Information

1) Abdominal cramps have been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15][94].

c) Adult Clinical Trials

1) Estrogen replacement (vaginal route): 4% with estradiol vaginal ring vs 2% with estradiol vaginal cream [15]; 7% with estradiol vaginal tablets vs 4% with placebo [94]

2) Estrogen replacement (transdermal route): 0% to 16% vs 8% with placebo [19]

Bloating symptom

a) General Information

1) Bloating has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Diarrhea

a) Incidence: Topical gel, 4.2% [13]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.2% vs 0% with placebo [13]

c) Postmarketing

1) Has been reported [29]

Disorder of gallbladder

a) General Information

1) A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported [29][74][76][7][38][35][8][19][11][12][36][14][15][94]

Flatulence

a) Incidence: Topical gel, 5.4% [74]; transdermal system, 1% to 7% [19]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% with estradiol vs 4.1% with placebo [74]

2) Estrogen replacement (transdermal route): 1% to 7% vs 1% with placebo [19]

Nausea

a) Incidence: Transdermal system, up to 6.2% [29][19]
b) General Information

1) Can be minimized by administration with meals; often disappears with continued administration [114].

c) Estrogen replacement (transdermal route): 0% to 6.2% vs 3.2% with placebo [29]

d) Estrogen replacement (transdermal route): 1% to 6% vs 3% with placebo [19]

Vomiting

a) General Information

1) Vomiting has been reported with estrogen and/or progestin therapy [76][7][38] [35][8][19][11][12][36][14][15]

Estradiol Acetate

Bloating symptom

a) Incidence: 2.7% to 7.1% [60]

b) Bloating has been reported with the use of estrogens and/or progestin therapy [170].

c) The incidences of abdominal distension reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 2.7% and 7.1%, respectively [60].

Bowel obstruction

a) Bowel obstruction has been reported in post-marketing surveillance during vaginal ring use [173].

Disorder of gallbladder

a) A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported [170].

b) Estrogen use in postmenopausal women can produce greater cholesterol saturation in the bile due to changes in hepatic excretory function, thus predisposing patients to gallstone formation. However, results of studies have been mixed with regard to replacement therapy and the risk of gallbladder disease, specifically cholelithiasis [158]. One report described that the risk of surgically confirmed gallbladder disease was increased 2.5 times during conjugated estrogen therapy [159]. Another report indicated that estrogen replacement therapy increased the risk of cholesterol cholelithiasis, as did obesity [160]. However, another report indicated that the occurrence of gallbladder disease was significantly lower in estrogen users as compared to a control group [100]. A higher, although insignificant, incidence of cholelithiasis in patients receiving estrogen and progestin therapy has been reported [161].

Nausea

a) Incidence: 2.1% to 2.3% [170]

b) Nausea has been reported with the use of estrogens and/or progestin therapy [170].

Pancreatitis

a) A case of recurrent acute pancreatitis occurring in conjunction with intermittently used estrogen therapy over 7 years has been reported. The patient presented to the emergency room on 4 separate occasions complaining of sudden epigastric or upper abdominal pain. Alcohol use was denied on all occasions and severe dyslipidemia was not present. Medications included oral estrogen for menopausal symptoms and propranolol for migraines. The patient was managed with conservative care during all episodes and was discharged 4 to 10 days after presenting. Estrogen was discontinued and restarted after the third episode 5 years later and pancreatitis recurred after 6 weeks. Again, after conservative therapy, the patient was discharged and estrogens were permanently discontinued [162].

Stomach cramps

a) Abdominal cramps have been reported with the use of estrogens and/or progestin therapy [170].

Vomiting

a) Vomiting has been reported with the use of estrogens and/or progestin therapy [170].

Estradiol Cypionate

Bloating symptom

a) Bloating has been reported with the use of estrogens and/or progestin therapy [55].

Disorder of gallbladder

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Vomiting

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Estradiol Valerate

Bloating symptom

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Disorder of gallbladder

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Vomiting

a) Vomiting has been reported with the use of estrogens and/or progestin therapy [57].

Hematologic Effects

Estradiol

Blood coagulation pathway finding

a) General Information

1) Procoagulant effects of oral estrogen may be more pronounced during initial treatment period [78] and with higher doses [79][80][81]

b) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Procoagulant effects have been described [82][83][84][78]

2) Hormone replacement therapy (transdermal route): No effect on coagulation markers [82][83][84]

Deep venous thrombosis

a) General Information

1) Increased risk with estrogen monotherapy and with estrogen and progestin combination therapy [29][69][74]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for VTE (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][74][19][76]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

3) Discontinue (when possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolic risk [29][69][74][76]

4) Discontinue immediately if event occurs or is suspected [29][69][74][19][76]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): 47% higher risk with conjugated estrogens compared with placebo [29][69][74][76]

2) Hormone replacement therapy (oral route): 95% higher risk with conjugated estrogens plus medroxyprogesterone acetate compared with placebo [29][69][74][76]

Porphyria

a) General Information

1) Estrogen therapy may exacerbate porphyria [29][74][76][7][38][35][19][92][11][12][36][14][15]

Thrombocytopenic purpura

a) Adult Case Reports

1) Thrombotic thrombocytopenic purpura has been reported in 2 cases with the use of transdermal estradiol. Transdermal estradiol was used for 5 years and 6 months, respectively, prior to the diagnosis [85].

Venous thromboembolism

a) General Information

1) Increased risk of VTE (DVT and pulmonary embolism) with estrogen monotherapy and with combination estrogen and progestin therapy [29][74]

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for VTE (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][76][19]

2) Factor V Leiden significantly enhances hormone-associated risk of thrombosis [87].

3) Transdermal estrogen appears not to increase the risk of thromboembolism among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy [37]

4) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

5) Discontinue (if possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolism risk [29][69]

6) Discontinue immediately if occurs or is suspected [29][69][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Though risk of pulmonary embolism among women (mean age, 63) treated with conjugated estrogens 0.625 mg/day monotherapy for a mean 7.1 years was not significantly greater than placebo, risk of DVT was 47% higher with conjugated estrogen monotherapy versus placebo. Increased VTE risk occurred during the first 2 years of therapy [69]

2) Hormone replacement therapy (oral route): Risk of DVT and pulmonary embolism were significantly greater than placebo in women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69]

3) Hormone replacement therapy (oral and transdermal route): Risk of VTE was 4.2-fold higher with oral estrogen therapy compared with placebo, while users of transdermal estrogen showed no significant difference. Additionally, risk of VTE was nearly 4-fold higher among users of norpregnane derivatives (nomegestrol acetate or promegestone) but showed no difference with use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) compared with placebo [37]

4) Hormone replacement therapy (oral route): Increased risk of DVT and VTE associated with conjugated estrogen monotherapy was 2- to nearly 3-fold higher compared with placebo during the first 2 years of therapy over 7.1 years of followup. Age, body mass index or other risk factors for VTE did not appear to influence risk. However, risk compared with placebo was lower with estrogen monotherapy (34% higher) versus with estrogen plus progestin combination therapy (more than 2-fold higher) [88].

5) Hormone replacement therapy (oral route): Risk of venous thromboembolism (VT) significantly increased with age and weight. Risk increased from about 2-fold higher with hormone replacement therapy (HRT) than with placebo among women aged 50 to 59 years and 60 to 69 years to more than 4-fold higher with HRT therapy than with placebo among women aged 70 to 79 years. VT risk rose from more than 2-fold higher with HRT than with placebo among women with a BMI between 25 and 30 to nearly 3-fold higher with HRT than with placebo among women with a BMI greater than 30. In addition, Factor V Leiden enhanced the hormone-associated risk of thrombosis with a nearly 7-fold higher risk than placebo in patients without the mutation [87].

6) Hormone replacement therapy (oral route): In more than 7 years of followup, women treated continuously with conjugated equine estrogen (CEE) showed a 65% greater risk of venous thromboembolism (VT) than placebo-treated women. No increased risk of VT compared with placebo was seen in women treated with esterified estrogen. Among estrogen users, women treated with CEE had a significant 78% higher risk of VT than women treated with esterified estrogen with continuous use [89].

7) Hormone replacement therapy (oral and transdermal routes): Estimated risk for venous thromboembolism was a significant 4-fold higher among current users of oral estrogen replacement therapy (ERT) compared with transdermal ERT users [90].

8) Hormone replacement therapy (oral route): In the Heart and Estrogen-progestin Replacement Study (HERS), women with coronary heart disease treated with conjugated estrogens and progestin showed a nearly 3-fold higher risk of venous thromboembolism than with placebo . Risk decreased with aspirin or statin use [91].

Venous thromboembolism, Recurrent

a) Adult Clinical Studies

1) Hormone replacement therapy (oral route): 6.4-fold higher risk of recurrent VTE in postmenopausal women [77]

2) Hormone replacement therapy (transdermal route): No increased risk of recurrent VTE in postmenopausal women[77]

Estradiol Acetate

Blood coagulation pathway finding

a) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups

may be at increased risk).

b) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) Estrogen therapy may cause an exacerbation of porphyria [170].

Venous thromboembolism

a) Summary

1) Results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to significant increases in the risk of venous thromboembolism in postmenopausal women with a uterus and health risks exceeded benefits [87]. Results from the WHI Estrogen Alone trial involving postmenopausal women without a uterus indicate the risk of venous thromboembolism was increased for women receiving estrogen (hazard ratio 1.32, 95% confidence interval 0.99 to 1.75) compared with placebo but to a lesser degree than compared to the risk associated with estrogen plus progestin [88]. Transdermal estrogen appears not to increase the risk of thromboembolism among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy [37].

b) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

c) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

d) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27

(95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported. When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

e) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

f) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

g) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

h) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors [81]. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected.

Estradiol Cypionate

Blood coagulation pathway finding

a) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups may be at increased risk).

b) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) Estrogen therapy may cause an exacerbation of porphyria [55].

Venous thromboembolism

a) General Information

1) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

3) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27 (95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported.

When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

4) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

5) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

6) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

7) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected [81].

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or reference men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Estradiol Valerate

Blood coagulation pathway finding

a) General Information

1) Estrogens can increase the concentrations of certain clotting factors. This effect is more obvious at higher dosages (greater than 1.25 mg/day conjugated estrogen equivalent). The dose-response relationship is not well-defined, and published

studies on this problem in postmenopausal women are not definitive [79][80][81]. However, data suggests no overall increased risk of thromboembolic complications associated with lower replacement doses of estrogens (although certain subgroups may be at increased risk).

2) It has been reported that long-term therapy with various estrogens did not affect clotting factors (thrombin time, prothrombin time, kaolin partial thromboplastin time) in 390 postmenopausal women. Many of these patients were on cyclic therapy or combination estrogen plus progestin therapy in varying doses and combinations. One patient in the treatment group developed deep venous thrombophlebitis and another had a myocardial infarction. No vascular complications occurred in the 110 patients who did not receive hormone therapy [79].

Porphyria

a) General Information

1) Estrogen therapy may cause an exacerbation of porphyria [57].

Venous thromboembolism

a) General Information

1) Results from the Estrogen and Thromboembolism Risk (ESTHER) study indicate that transdermal estrogen use is not associated with an increased risk of venous thromboembolism (VTE) among postmenopausal women compared with oral estrogen use and may be a safe alternative for women requiring hormone therapy. The multicenter, case-control study enrolled 271 consecutive cases of first documented episodes of idiopathic VTE and 610 matched community and hospital controls. The majority of current users of estrogen received 17-beta-estradiol. After adjusting for confounding factors, the odds ratios (OR) of VTE in current users of oral estrogen was 4.2 (95% confidence interval (CI), 1.5 to 11.6) compared with nonusers. The OR in current users of transdermal estrogen was 0.9 (95% CI, 0.4 to 2.1) compared with nonusers. Additionally, there was no significant association of VTE with the use of micronized progesterone or pregnane derivatives (including medroxyprogesterone acetate) while there was a 4-fold increase in OR of VTE (OR 3.9; 95% CI, 1.5 to 10.0) among users of norpregnane derivatives (nomegestrol acetate or promegestone). Stratification by dose and duration of estrogen therapy revealed similar results. There was no association between past estrogen use and VTE risk (OR, 1.1; 95% CI, 0.6 to 1.7) [37].

2) Final adjudicated results from the Women's Health Initiative (WHI) Estrogen Alone trial concluded there is an increased risk of venous thromboembolism (VT) in women receiving estrogen, particularly within the first 2 years, but the risk increase is less than the risk associated with the combination of estrogen plus progestin. Postmenopausal women without a uterus (n=10,739) were randomized in a double-blind trial to receive 0.625 milligrams (mg) of CEE or placebo. After a mean follow-up of 7.1 years, 111 women receiving CEE developed VT compared with 86 women receiving placebo (hazard ratio (HR), 1.32; 95% confidence interval (CI), 0.99 to 1.75). Deep vein thrombosis (DVT) occurred in 85 women receiving CEE compared with 59 women receiving placebo (HR, 1.47; 95% CI, 1.06 to 2.06). The HR for pulmonary embolism (PE) was similar between the two groups (1.37; 95% CI, 0.90 to 2.07). The increased risk of DVT, PE, and VT associated with CEE compared with placebo appeared to be greater within the first 2 years of therapy (HR, 2.79, 95% CI 1.24 to 6.27; HR, 2.21, 95% CI, 0.77 to 6.36; HR, 2.22, 95% CI, 1.12 to 4.39, respectively). Age, body mass index or other VT risk factors did not appear to have a significant effect on the interaction between estrogen use and risk of VT. Comparison of results from the WHI Estrogen Alone trial and the WHI Estrogen Plus Progestin trial indicates the HR for CEE is significantly lower than the HR for estrogen plus progestin (1.34, 95% CI, 1.01 to 1.77 versus 2.09, 95% CI 1.59 to 2.74) [88].

3) Final results from the Women's Health Initiative (WHI) Estrogen Plus Progestin trial indicate estrogen plus progestin therapy leads to a doubling in the rates of venous thromboembolism (VT) in postmenopausal women with a uterus. The WHI was a double-blind, controlled trial of 16,608 postmenopausal women who were randomized to oral conjugated equine estrogen (CEE) 0.625 milligrams (mg) daily plus oral medroxyprogesterone acetate (MPA) 2.5 mg daily or placebo. In a nested case-control study, baseline gene variants related to thrombosis risk were measured in the first 147 women who developed thrombosis and in 513 controls who were matched for age, randomization date, presence of baseline vascular disease, and time to follow-up. With a mean follow-up of 5.6 years, VT occurred in 167 women taking estrogen plus progestin and in 76 women taking placebo (3.5 per 1000 person-years and 1.7 per 1000 person-years, respectively; hazard ratio (HR), 2.06, 95% confidence interval (CI), 1.57 to 2.7). The risk of VT associated with hormone replacement therapy (HRT) was higher when compared to placebo and as age increased. The HR for women aged 50 to 59 receiving HRT was 2.27 (95% CI, 1.19 to 4.33) with an annualized rate per 1000 person years of 0.8 for placebo and 1.9 for HRT. Women aged 60 to 69 had an annualized rate of 1.9 and 3.5 per 1000 person-years when receiving placebo and HRT, respectively. The associated HR was 4.28 (95% CI, 2.38 to 7.72) for HRT and 2.31 (95% CI, 1.23 to 4.35) for placebo. Women aged 70 to 79 had an annualized rate per 1000-person

years of 2.7 if receiving placebo and 6.2 if receiving HRT, with a HR of 3.37 (95% CI, 1.72 to 6.6) for placebo and 7.46 (95% CI, 4.32 to 14.38) for HRT. As weight increased, the incidence of VT also increased. The annual incidence of VT per 1000 person-years was 1.5 (when receiving placebo) and 3.5 (when receiving HRT) for women with a body mass index (BMI) between 25 and 30. A HR of 1.63 (95% CI, 0.83 to 3.2) for placebo and 3.8 (95% CI, 2.08 to 6.94) for HRT was reported. When BMI was greater than 30, the annual incidence per 1000 person-years increased to 2.5 (when receiving placebo) and 5.1 (when receiving HRT) with a corresponding HR of 2.87 (95% CI, 1.52 to 5.4) for placebo and 5.61 (95% CI, 3.12 to 10.11) for HRT. In addition, Factor V Leiden (n=17) enhanced the hormone-associated risk of thrombosis with a 6.69-fold increased risk compared with women in the placebo group (n=35) without the mutation (95% CI, 3.09 to 14.49) [87].

4) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

5) When oral and transdermal estrogen replacement therapy (ERT) were compared in a multicenter, hospital-based, case-control study of postmenopausal women, oral ERT was associated with a risk of venous thromboembolism (VTE). Consecutive cases with a first documented episode of idiopathic VTE were recruited (n=155). During this same period, 381 controls matched for age and center were recruited. Overall, 22% and 7% of cases and controls, respectively, were current users of oral ERT while 19% and 24% of cases and controls, respectively, were current users of transdermal ERT. After adjustment for potential confounding variables (body mass index, family history of VTE, history of varicose veins, and education level), the odds ratio of VTE in current users of oral and transdermal ERT compared with non-users was 3.2 (95% confidence interval (CI) 1.8 to 6.8) and 0.9 (0.5 to 1.6), respectively. Estimated risk for VTE in current users of oral ERT compared with transdermal ERT users was 4.0 (95% CI 1.9 to 8.3) [90].

6) Data analyzed from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin is associated with an increased risk for venous thromboembolism in women with coronary heart disease. With a mean follow-up of 4.1 years, 34 of 1380 women receiving HRT developed venous thromboembolic events compared to 13 of 1383 women receiving placebo (relative hazard (RH) 2.7; 95% confidence interval (CI) 1.4 to 5.0). The risk was increased among women with lower- extremity fractures, cancer and for 90 days after inpatient surgery or nonsurgical hospitalization. Decreased risk was associated with aspirin or statin use [91].

7) Estrogen replacement in hospitalized postmenopausal women was not an associated risk factor for venous thrombosis in a case-control study which included women with prior thrombotic risk factors [81]. This retrospective study included 121 thromboembolic cases and 236 controls which were matched for age, year of admission, admitting service, and socioeconomic status. The sample was of sufficient size to have a 95% probability of detecting a two-fold or greater increase in the proportion of estrogen users. Thus, a smaller but still significant increase in risk for estrogen use could have gone undetected.

a) Transgender

1) The risk of VTE was increased 5.52-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 4.55-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of VTE in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Hepatic Effects

Estradiol

Cholestatic jaundice syndrome

a) General Information

1) Cholestatic jaundice has been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15][94]

b) Prevention and Management

1) Discontinue if condition recurs [68][29][76][19]

Hemangioma of liver

a) General Information

1) Exacerbation of hepatic hemangiomas may occur [29]

b) Postmarketing

1) Enlargement of hepatic hemangiomas has been reported[76].

Hepatitis

a) Postmarketing

1) Acute hepatitis has been reported [74]

Estradiol Acetate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [170].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [170].

Estradiol Cypionate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [55].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [55].

Estradiol Valerate

Cholestatic jaundice syndrome

a) Cholestatic jaundice has been reported during the use of estrogen and/or progestin therapy [57].

Hemangioma of liver

a) Estrogen therapy may cause an exacerbation or enlargement of hepatic hemangiomas and should be used with caution [57].

Immunologic Effects

Estradiol

Anaphylaxis

a) General Information

1) May involve the skin, respiratory tract, and/or digestive tract [29]

b) Postmarketing

1) Anaphylactoid and/or anaphylactic reactions have been reported with the postmarketing use of estrogen and/or progestin therapy [29][66][19][76][7][38][35][8][11][36][14][15]

Systemic lupus erythematosus

a) General Information

1) May exacerbate systemic lupus erythematosus; use with caution [29][19][76][7][13][38][35][8][11][12][36][14][15]

b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 2.1-fold increased risk in postmenopausal estrogen ever users compared with never users; 1.8-fold increased risk in past users compared with never users [119].

Estradiol Acetate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [170].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [170].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Estradiol Cypionate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [55].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [55].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Estradiol Valerate

Anaphylaxis

a) Anaphylactoid and/or anaphylactic reactions have been reported with the use of estrogen and/or progestin therapy [57].

Systemic lupus erythematosus

a) Estrogen therapy may cause an exacerbation of systemic lupus erythematosus and should be used with caution in these patients [57].
b) A cohort of 69,435 women was followed to examine the relationship between postmenopausal hormone use and development of systemic lupus erythematosus (SLE). Risk of SLE was determined by comparing ever-users of postmenopausal hormones to never-users. The age-adjusted relative risk (RR) for SLE was 2.1 for ever-users (RR equal 2.5 for current users, RR equal 1.8 for past users). There was a direct relationship between risk and duration of use of postmenopausal hormones [119].

Musculoskeletal Effects

Estradiol

Arthralgia

a) Incidence: Transdermal system, 0% to 8.5% [29][19]
b) General Information

1) Joint pain has been reported with estrogen and/or progestin therapy [19][7] [38][35][8][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 5% vs 3% with placebo [19]

2) Estrogen replacement (transdermal route): 0% to 8.5% vs 5.7% with placebo [29]

Backache

a) Incidence: 4% to 10.6% [29][19][15][15][94][94]
b) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 4% to 10.6% vs 6% to 6.4% with placebo [29][19]

2) Estrogen replacement (vaginal route): 6% to 8% [15]

3) Estrogen replacement (oral route): 7% vs 6% with placebo [94]

Leg cramp

a) General Information

1) Leg cramps have been reported with estrogen and/or progestin therapy [76][7] [38][35][8][11][12][36][14][15]

Osteoarthritis

a) Incidence: 34.5% [118]
b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 34.5% in postmenopausal women using estrogen for at least 1 year vs 31% among nonusers [118].

Estradiol Acetate

Arthralgia

a) Joint pain has been reported during the use of estrogen and/or progestin therapy [170].

Backache

a) Incidence: 2.1% to 3.0% [170]
b) Back pain has been reported with the use of oral estradiol acetate at a dosage of 0.9 milligrams/day and 1.8 milligrams/day 2.1% to 3.0% [170].

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [170].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Estradiol Cypionate

Arthralgia

a) Joint pain has been reported during the use of estrogen and/or progestin therapy [55].

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [55].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Estradiol Valerate

Leg cramp

a) Leg cramps have been reported during the use of estrogen and/or progestin therapy [57].

Osteoarthritis

a) Postmenopausal estrogen use was associated with a higher incidence of osteoarthritis (OA). Women (n=638) in the study had used postmenopausal estrogen for at least 1 year (average duration of 14.6 years). The incidence of OA was 34.5% among women who had used estrogen for at least 1 year and 31% among women who did not use estrogen (age adjusted p=0.02). When adjusted for age, body mass index, smoking, exercise, and type of menopause, estrogen users were more likely to have hip OA and hand OA. Knee OA prevalence did not differ by estrogen use (p greater than 0.05) [118].

Neurologic Effects

Estradiol

Cerebrovascular accident

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combination therapy [29][69][74]

2) Increased risk of ischemic stroke was observed in users of oral estrogens in a dose-dependent fashion, and users of norpregnane derivatives in a retrospective case-control study [106].

3) No significant differences in distribution of stroke subtypes or severity, including fatal strokes, were seen in women treated with estrogen monotherapy compared with placebo [29][69].

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-

up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

b) Prevention and Management

1) Appropriately manage risk factors for arterial vascular disease (eg, obesity, high cholesterol, tobacco use, diabetes, hypertension) [29][69][74]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

3) Do not use estrogen mono- or combination therapy to prevent stroke [29][69]

4) Discontinue immediately if event occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Overall adjusted risk of ischemic stroke was increased by 58% in a case (n=3144)-control (n=12158) study of French women aged 51 to 62 years [106]

2) Hormone replacement therapy (oral route): Overall stroke risk was 33% higher among women aged 50 to 79 years old treated with conjugated estrogens 0.625 mg/day for a mean of 7.1 years than among placebo-treated women, but there was no increased risk of stroke in women 50 to 59 years old [29][69][74]

3) Hormone replacement therapy (oral route): Ischemic stroke risk was 55% higher among women aged 50 to 79 years old treated with conjugated estrogens 0.625 mg/day for a mean of 7.1 years than among placebo-treated women, [29] [69]

4) Hormone replacement therapy (oral route): In a Women's Health Initiative substudy, overall stroke risk was 31% higher among women aged 50 to 79 years treated with conjugated estrogens 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day for a mean 5.6 years than among placebo-treated women [29] [69]

5) Hormone replacement therapy (oral route): Over a mean 7.1 years, overall stroke risk was 37% higher with conjugated equine estrogen therapy 0.625 mg compared with placebo. Risk of ischemic stroke was 55% higher and risk of hemorrhagic stroke was 64% higher than placebo [107]

6) Hormone replacement therapy (unspecified route): Decreased risk with noncontraceptive estrogen compared with women with no history of estrogen treatment, particularly in women under age 60; women treated with estrogen/progestin combination therapy also had a lower stroke risk [108]

Dementia

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combined therapy among postmenopausal women aged 65 or older [29][69][74]

2) Unknown if increased risk applies to younger postmenopausal women [29][69] [74]

b) Prevention and Management

1) Do not prescribe for dementia prophylaxis [29][69][74]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): In the Women's Health Initiative Memory Study (WHIMS) of women aged 65 to 79 years, a nonsignificant increase in dementia risk occurred with a mean 5.2 years of conjugated estrogens 0.625 mg/day monotherapy compared with placebo. However, risk was more than 2-fold higher than placebo with a mean 4 years of daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg combination therapy. Pooled risk among both groups treated with hormone replacement therapy was a significant 76% higher than among placebo-treated women. It is unknown if these findings may be generalized to younger postmenopausal women [29][69][74][76] [7][38][35][8][19][11][12][14][15][47]

Headache

a) Incidence: Topical gel, 9.5% [74]transdermal spray, 9% to 12% [36]; transdermal system, 5% to 50% [29][19][11][12]; vaginal cream, 16% [15]; vaginal insert, 2.6% to 3.7% [5]; vaginal ring, 13% [15]; vaginal tablets, 9% to 10% [94]

b) Adult Clinical Trials

1) Dyspareunia (vaginal route): 3.7% with estradiol 4-mcg insert and 2.6% with estradiol 10-mcg insert vs 3.1% with placebo [5]

2) Estrogen replacement (vaginal route): 13% with estradiol ring vs 16% with estradiol cream [15]; 9% to 10% with estradiol tablets vs 6% with placebo [94]

3) Estrogen replacement (topical route): 9.5% with estradiol vs 2.7% with placebo [74]

4) Estrogen replacement (transdermal route): 9% to 12% with estradiol spray vs 5% to 9% with placebo [36]; 5% to 50% with estradiol patch vs 10% to 23.6% with placebo [29][19][11][12]

Impaired cognition

a) Adult Clinical Study

1) Hormone replacement therapy (route unknown): 47% increased risk of having a 10-unit decrease in Modified Mini-Mental State Examination (3MSE) score compared with placebo [105]

Meningioma

a) Postmarketing

1) Has been reported [74]

Migraine

a) General Information

1) Estrogen therapy can exacerbate preexisting migraine conditions [29]

b) Prevention and Management

1) Sudden onset of migraine may be associated with retinal vascular thrombosis; consider interruption of therapy pending evaluation [29]

c) Adult Clinical Studies

1) Perimenstrual headache (topical route): 40% rise in migraine attacks due to estradiol withdrawal within 5 days immediately following discontinuation of estradiol gel compared with placebo [50]

d) Postmarketing

1) Has been reported [29]

Estradiol Acetate

Cerebrovascular accident

a) Summary

1) A significant increase in the risk of stroke was reported during the Women's Health Initiative (WHI) Estrogen Plus Progestin trial involving estrogen and progestin (hazard ratio 1.41, 95% confidence interval 1.07 to 1.85) [171] and in the WHI Estrogen Alone trial that compared estrogen only to placebo (hazard ratio 1.37, 95% confidence interval 1.09 to 1.73) [143][144]. A secondary analysis of the WHI Estrogen Plus Progestin trial demonstrated the risk of stroke was increased with hormone therapy (HR, 1.32; 95% CI, 1.12 to 1.56) but the risk did not vary significantly by age or time since menopause [146]. In several other studies, the relative risk (RR) of stroke among HRT users varied from 0.23 to 1.46, with one study reporting a RR of 2.6. Initiation and continuation of HRT should be based on established noncoronary benefits and risks, possible coronary benefits and risks, and patient preference. Use should be based on factors other than stroke risk [172].

b) Final results from the Women's Health Initiative Estrogen Alone trial indicate that conjugated equine estrogen (CEE) therapy increases the risk of ischemic stroke in postmenopausal women who are generally healthy and the risk is not differentiated among patient subgroups. The WHI Estrogen Alone trial randomized 10,739 healthy postmenopausal women (aged 50 to 79 years) without a uterus to CEE 0.625 milligrams (mg) (n=5310) or placebo (n=5429) daily. After an average follow-up of 7.1 years, a total of 168 and 127 strokes occurred in the CEE and placebo groups, respectively. The intention-to-treat hazard ratio (HR) for all stroke subtypes (ischemic, hemorrhagic, and other strokes) for CEE versus placebo was 1.37, 95% confidence interval (CI) 1.09 to 1.73. The HR for ischemic stroke was 1.55 (95% CI 1.19 to 2.01) while the HR for hemorrhagic stroke was 0.64 (95% CI 0.35 to 1.18). Ischemic strokes attributed for 80% of all strokes and hemorrhagic strokes accounted for 15%. The HRs for ischemic stroke were consistent among patient subgroups based on age, race, years since menopause, prior cardiovascular disease, hypertension or diabetes mellitus status, body mass index, smoking, prior hormone use, or statin or aspirin use at baseline. This indicated excess risk existed in all subgroups of women examined [107].

c) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE) but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval

(CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk of MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

d) Analyzed data from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin had no significant impact on the risk for stroke among postmenopausal women (n=2763) with coronary disease. The women were randomized to HRT or placebo. With a mean follow-up of 4.1 years, 149 women experienced 1 or more strokes (85% ischemic) which resulted in 26 deaths. The relative hazard (RH) for nonfatal stroke associated with HRT was 1.18; 95% confidence interval (CI) 0.83 to 1.66. The RH for fatal stroke was 1.61; 95% CI 0.73 to 3.55. More direct risks for stroke in this study were increased age, hypertension, diabetes, cigarette smoking, and atrial fibrillation [148].

e) A study in approximately 23,000 Swedish women was conducted to determine the relative risk of stroke in women who had been prescribed noncontraceptive estrogens. The cohort was followed for 6 years. The primary endpoint was the occurrence of a first stroke; secondary endpoints included the occurrence of subtypes of stroke such as subarachnoid hemorrhage (classified as acute stroke), intracerebral hemorrhage, cerebral infarction, cerebral embolism, and transient ischemic attack. For all endpoints, the risk of stroke was decreased in estrogen users compared to never users, particularly in those women under 60 years of age. This is the first study to show that women who were prescribed the progestin-estrogen regimen also had a lowered risk for stroke, which may indicate that progestins do not attenuate or eliminate the protective effects of estrogen alone [108]. The mechanisms of a possible protective effect of estrogen therapy against stroke is not known.

Dementia

a) Results of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens (CE) 0.625 milligrams (mg) alone and during 4 years of treatment with CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo. Findings from the estrogen-alone WHIMS indicated that conjugated equine estrogen (CEE) therapy alone did not reduce dementia or mild cognitive impairment in postmenopausal patients but increased the risk for both endpoints combined. Women aged 65 to 79 years (n=2947) participated in the estrogen-alone WHIMS, which compared CEE 0.625 mg with placebo. During follow-up, the hazard ratio (HR) of probable dementia for women receiving CEE compared to placebo was 1.49 (95% Confidence Interval (CI), 0.83 to 2.66). This negative trend did not reach statistical significance (p=0.18) and it is unknown whether this finding applies to younger postmenopausal women. The HR for probable dementia in the CEE/MPA substudy group compared to placebo was 2.05 (95% CI, 1.21 to 3.48). When data were pooled for estrogen alone and estrogen plus progestin therapy, the overall HR for probable dementia was 1.76 (95% CI, 1.19 to 2.60; p=0.005) [170][47].

Epilepsy

a) Estrogen therapy may cause an exacerbation of epilepsy [170].

Headache

a) Incidence: 3 to 5% [170]

b) Headache has been reported with estrogen and/or progestin therapy [170].

Impaired cognition

a) Conjugated equine estrogen (CEE) therapy did not improve global cognitive function but actually had an adverse effect on cognition. Women aged 65 to 79 years who participated in the Women's Health Initiative Memory Study (WHIMS), which compared CEE with placebo, demonstrated a trend toward an increased risk of probable dementia and/or mild cognitive impairment. The relative risk of having a 10-unit decrease in Modified Mini-Mental State Examination (3MSE) scores for women assigned to CEE compared with placebo was estimated to be 1.47 (95% Confidence Interval, 1.04 to 2.07) [105].

Migraine

a) Estrogen therapy may cause an exacerbation of migraine headaches [170].

Estradiol Cypionate

Cerebrovascular accident

a) General Information

1) Final results from the Women's Health Initiative Estrogen Alone trial indicate that conjugated equine estrogen (CEE) therapy increases the risk of ischemic stroke in postmenopausal women who are generally healthy and the risk is not differentiated among patient subgroups. The WHI Estrogen Alone trial randomized 10,739 healthy postmenopausal women (aged 50 to 79 years) without a uterus to CEE 0.625 milligrams (mg) (n=5310) or placebo (n=5429) daily. After an average follow-up of 7.1 years, a total of 168 and 127 strokes occurred in the CEE and placebo groups, respectively. The intention-to-treat hazard ratio (HR) for all stroke subtypes (ischemic, hemorrhagic, and other strokes) for CEE versus placebo was 1.37, 95% confidence interval (CI) 1.09 to 1.73. The HR for ischemic stroke was 1.55 (95% CI 1.19 to 2.01) while the HR for hemorrhagic stroke was 0.64 (95% CI 0.35 to 1.18). Ischemic strokes attributed for 80% of all strokes and hemorrhagic strokes accounted for 15%. The HRs for ischemic stroke were consistent among patient subgroups based on age, race, years since menopause, prior cardiovascular disease, hypertension or diabetes mellitus status, body mass index, smoking, prior hormone use, or statin or aspirin use at baseline. This indicated excess risk existed in all subgroups of women examined [107].

2) Results of a population-based, case-control study indicated there was no difference in risk of myocardial infarction (MI) or stroke associated with the use of oral conjugated equine estrogen (CEE) or esterified estrogens (EE) but there was a suggested higher risk of ischemic stroke associated with CEE use alone and higher risk of MI associated with recent initiation of CEE. A total of 2724 postmenopausal women (mean age 67 to 70 years) with an incident MI (n=1644) or stroke (n=1080) were identified. The control group was comprised of a random sample of age-matched postmenopausal women without MI or stroke (n=4205). Compared with no use of hormone therapy, use of CEE or EE, with or without progestin, demonstrated little or no difference in risk of MI, ischemic stroke, or hemorrhagic stroke. When CEE and EE were compared, the use of CEE was not associated with any increased risk of MI (adjusted odds ratio (OR), 0.93; 95% confidence interval (CI), 0.65 to 1.31) or ischemic stroke (adjusted OR, 1.31; 95% CI, 0.88 to 1.97). The additional adjustment for progestin use had little impact on OR for either therapy. When CEE and EE use (without progestin) were compared to each other, there was no difference in risk of MI, but there was a suggestion of higher risk of ischemic stroke associated with the use of CEE alone (OR, 1.57; 95% CI, 0.98 to 2.53; p=0.06). There was also a suggestion of higher risk of MI and ischemic stroke associated with CEE when high daily doses (greater than 0.625 milligrams) of CEE and EE were compared, however, the number of subjects was small and the CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

3) Analyzed data from the Heart and Estrogen-progestin Replacement Study (HERS) showed that hormone replacement therapy (HRT) with conjugated estrogens and progestin had no significant impact on the risk for stroke among postmenopausal women (n=2763) with coronary disease. The women were randomized to HRT or placebo. With a mean follow-up of 4.1 years, 149 women experienced 1 or more strokes (85% ischemic) which resulted in 26 deaths. The relative hazard (RH) for nonfatal stroke associated with HRT was 1.18; 95% confidence interval (CI) 0.83 to 1.66. The RH for fatal stroke was 1.61; 95% CI 0.73 to 3.55. More direct risks for stroke in this study were increased age, hypertension, diabetes, cigarette smoking, and atrial fibrillation [148].

4) A study in approximately 23,000 Swedish women was conducted to determine the relative risk of stroke in women who had been prescribed noncontraceptive estrogens. The cohort was followed for 6 years. The primary endpoint was the occurrence of a first stroke; secondary endpoints included the occurrence of subtypes of stroke such as subarachnoid hemorrhage (classified as acute stroke), intracerebral hemorrhage, cerebral infarction, cerebral embolism, and transient ischemic attack. For all endpoints, the risk of stroke was decreased in estrogen users compared to never users, particularly in those women under 60 years of age. This is the first study to show that women who were prescribed the progestin-estrogen regimen also had a lowered risk for stroke, which may indicate that progestins do not attenuate or eliminate the protective effects of estrogen alone [108]. The mechanisms of a possible protective effect of estrogen therapy against stroke is not known.

a) Transgender

1) The risk of stroke was increased 2.42-fold in transwomen receiving transgender hormone therapy (THT) with estrogen with or without androgens compared with reference women in the general Dutch or Norwegian populations and a 1.8-fold increased risk compared with reference men over a mean follow-up of 9.07 years (median, 5.95 years) in a retrospective review of transwomen (n=2517) and transmen (n=1358) receiving THT. There was no increased risk of stroke in transmen receiving testosterone compared with reference women or men over a mean follow-up of 8.1 years (median, 4.1 years) [86].

Dementia

a) Results of the Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with conjugated estrogens (CE) 0.625 milligrams (mg) alone and during 4 years of treatment with CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo. Findings from the estrogen-alone WHIMS indicated that conjugated equine estrogen (CEE) therapy alone did not reduce dementia or mild cognitive impairment in postmenopausal patients but increased the risk for both endpoints combined. Women aged 65 to 79 years (n=2947) participated in the estrogen-alone WHIMS, which compared CEE 0.625 mg with placebo. During follow-up, the hazard ratio (HR) of probable dementia for women receiving CEE compared to placebo was 1.49 (95% Confidence Interval (CI), 0.83 to 2.66). This negative trend did not reach statistical significance (p=0.18) and it is unknown whether this finding applies to younger postmenopausal women. The HR for probable dementia in the CEE/MPA substudy group compared to placebo was 2.05 (95% CI, 1.21 to 3.48). When data were pooled for estrogen alone and estrogen plus progestin therapy, the overall HR for probable dementia was 1.76 (95% CI, 1.19 to 2.60; p=0.005) [55][47].

Epilepsy

a) Estrogen therapy may cause an exacerbation of epilepsy [55].

Headache

a) Headache has been reported with estrogen and/or progestin therapy [55].

Impaired cognition

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Migraine

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Estradiol Valerate

Cerebrovascular accident

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CIs were wide (OR, 2.22; 95% CI, 0.82 to 5.97; p=0.12 and OR, 2.59; 95% CI, 0.83 to 8.07; p=0.10, respectively). Lastly, when estrogen therapy was initiated within 6 months, a higher risk of MI was associated with CEE versus EE (OR, 2.33; 95% CI, 0.93 to 5.82; p=0.07) [147].

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Epilepsy

a) General Information

1) Estrogen therapy may cause an exacerbation of epilepsy [57].

Headache

a) General Information

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Impaired cognition

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Migraine

a) General Information

1) Estrogen therapy may cause an exacerbation of migraine headaches [57].

Ophthalmic Effects

Estradiol

Disorder of cornea associated with contact lens

a) Postmarketing

1) Intolerance to contact lenses has been reported during the postmarketing use of estrogen and/or progestin therapy [19][76][7][38][35][8][11][12][36][14][15]

Dry eye syndrome

a) Incidence: 9% [115]

b) Adult Clinical Studies

1) Hormone replacement therapy (route unknown): 9% with estrogen alone; 6.7% with estrogen plus progestin; 5.9% with no hormone use [115]

Thrombosis of retinal vein

a) General information

1) Retinal vascular thrombosis has been reported in patients receiving estrogens [29][74][19][76][7][38][35][8][11][12][36][14][15][94]

b) Prevention and Management

1) Consider interruption of therapy and evaluation if sudden partial or complete loss of vision occurs, or with sudden onset of proptosis, diplopia, or migraine [29]

2) Permanently discontinue if exam reveals papilledema or retinal vascular lesions [68][29][19][76]

c) Postmarketing

1) Retinal vein occlusion has been reported [74]

Estradiol Acetate

Disorder of cornea associated with contact lens

a) Intolerance to contact lenses has been reported during the use of estrogen and/or progestin therapy [170].

Dry eye syndrome

a) Data from the Women's Health Study suggest hormone replacement therapy (HRT) is associated with the risk of developing dry eye syndrome and the risk appears to be greater with HRT using estrogen alone. Among data provided by 25,389 women, the prevalence for dry eye syndrome among women who used no HRT was 5.9%, compared to 9% for those who used estrogen alone and 6.7% for those who used estrogen and progestin combined therapy [115].

Eye / vision finding

a) Results of a cross-sectional study of women suggest that estrogen rather than age is the primary predictive factor for changes in vascular resistance distal to the ophthalmic artery. Three groups of women were identified for the study. Group 1 (n=20) consisted of young women (20- to 26-years-old); group 2 (n=16) was comprised of postmenopausal women at least 50-years-old who had never used estrogen replacement therapy (ERT); and group 3 had 16 postmenopausal women who were receiving ERT. Color Doppler imaging analysis of flow velocities in the ophthalmic, central retinal, and nasal and temporal posterior ciliary arteries revealed that young women and postmenopausal women on estrogen had reduced resistance indexes compared to postmenopausal women not receiving estrogen (p less than 0.001). Flow velocities in the central retinal artery were similar among the 3 groups while young women demonstrated greater peak systolic and end- diastolic velocities at similar resistance index (p less 0.05) in the posterior ciliary arteries [163].

Thrombosis of retinal vein

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Estradiol Cypionate

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Thrombosis of retinal vein

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Psychiatric Effects

Estradiol

Anxiety

a) Incidence: Topical gel, 1.8% [13]; transdermal system, 0% to 10% [29][8]
b) Estrogen replacement (topical route): 1.8% vs 0% with placebo [13]
c) Estrogen replacement (transdermal route): 0% to 10% vs 2.5% to 3.4% with placebo [29][8]

Depression

a) Incidence: Transdermal system, 0% to 10.6% [29][19]
b) General Information

1) Depression has been reported with estrogen and/or progestin therapy [19][76][7][38][35][8][11][12][36][14][15]

c) Adult Clinical Studies

1) Estrogen replacement (transdermal route): 0% to 10.6% vs 0% to 3.8% with placebo [29][19].

Disturbance in mood

a) Postmarketing

1) Mood disturbances have been reported with the postmarketing use of estrogen

and/or progestin therapy [29][19][76][7][13][38][35][8][11][12][36][14][15].

Estradiol Acetate

Depression

a) Depression has been reported with the use of estrogen and/or progestin therapy [170].

Disturbance in mood

a) Mood disturbances have been reported with the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Depression

a) Depression has been reported with the use of estrogen and/or progestin therapy [55].

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Depression

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Disturbance in mood

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Renal Effects

Estradiol Acetate

Device adherence, To bladder wall

a) General Information

1) May make vaginal ring removal difficult [174].

2) Bladder wall ulceration or erosion have been reported [174].

b) Management

1) Evaluate for bladder wall ulceration or erosion [174].

2) Consider not replacing ring until healing is complete [174].

c) Postmarketing Reports

1) Cases of ring adherence to the bladder wall have been reported [174].

Reproductive Effects

Estradiol

Abnormal cervical smear

a) Incidence: 5.4% [13]

b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% vs 2.7% with placebo [13]

Abrasion of vagina

a) General Information

1) May manifest as vaginal irritation, erythema, abrasion, or spotting [142]

b) Prevention and Management

1) Carefully evaluate if occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to the healing tissue [142].

c) Postmarketing

1) Vaginal erosion has been reported [142].

Breast cancer

a) General Information

1) Increased risk with conjugated estrogen monotherapy or with estrogen and progestin combined therapy [29][69][74], though no significant increased risk with estradiol monotherapy was reported in a systematic review/meta-analysis [120]

2) Tumors were larger, more advanced, and more likely node-positive with combination conjugated estrogen/progestin therapy than with placebo treatment [29][69][74]

3) Risk increases with duration of use [29][69][74]

4) Risk may occur earlier when given with progestins [29][69][74]

5) More abnormal mammograms may occur [29][69][74]

b) Prevention and Management

1) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69][74].

c) Adult Clinical Studies

1) Risk Among Healthy Women

a) Estrogen replacement, estrogen monotherapy (oral or transdermal route): Significantly increased risk in current estrogen users (except vaginal estrogens) vs nonusers (RR, 1.37; 95% CI, 1.33 to 1.41) in a meta-analysis of worldwide epidemiological data (24 prospective studies and 61,383 cases of breast cancer; randomized studies did not have sufficient breast cancer cases for inclusion); 1 through 4 years of use (RR, 1.17; 95% CI 1.1 to 1.26); 5 through 14 years of estrogen use (RR, 1.33; 95% CI, 1.28 to 1.37). Starting at age 50 years, the absolute 20-year breast cancer incidence rates were 7.4% with 10 years of estrogen use and 6.8% with 5 years use versus 6.3% with no MHT use. There was no difference in risk between equine estrogen and estradiol or between oral and transdermal administration. In past users, excess duration-dependent risks continued for more than 10 years after MHT discontinuation [121]

b) Estrogen replacement, estradiol monotherapy (oral or transdermal route): No significant difference in the odds of developing breast cancer between users of estradiol-only hormone replacement therapy (HRT) compared with non-use of estradiol HRT, according to a systematic review and meta-analysis or 12 studies. The odds of breast cancer were increased with estradiol/progestogen combinations based on the type of progestogen [120].

c) Estrogen replacement, conjugated estrogen monotherapy (oral route): A non-significant decrease in invasive breast cancer was seen in women (mean age, 63) treated with conjugated estrogens 0.625 mg/day monotherapy for a mean of 7.1 years compared with placebo-treated women. However, the risk was 24% higher than among placebo-treated patients in women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years. Compared with placebo, the risk was 86% higher with a history of hormone replacement therapy (HRT) and 9% higher with no prior history of HRT [69][74][76].

d) Estrogen replacement, estrogen monotherapy: Risk was 38% to 42% higher with estrogen monotherapy than with no history of estrogen use [122][123]; when stratified by duration of estrogen use, however, women treated with estrogen monotherapy for 10 years or more had the greatest increase in risk (6% to 42%) [123].

e) Estrogen replacement, combination therapy: Risk was 96% higher with current use of estrogen and progestin vs 38% higher with current use of estrogen monotherapy than among women who had never used hormone therapy (HT). Risk remained 8% higher among former HT users for up to 4 years vs 68% higher with current HT use [122].

2) Risk Among Breast Cancer Survivors

a) Estrogen replacement: One trial was discontinued early after results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events [124].

b) Estrogen replacement, estrogen monotherapy: Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors [125].

c) Estrogen replacement (oral and intravaginal routes): Rate of recurrence was 50% lower and breast cancer mortality 34% lower with use of hormone replacement therapy (HRT) than with non-use (O'Meara et al, 2001).

Breast tenderness

a) Incidence: Topical gel, 2.5% to 8.8% [76][38]; transdermal spray, 5% to 7% [36]; transdermal system, 6.5% to 17.0% [29][11]

b) General Information

1) Breast tenderness and pain have been reported with estrogen and/or progestin therapy [76][7][38][35][8][19][11][12][36][14][15]

c) Adult Clinical Trials

1) Estrogen replacement (topical route): 2.5% to 8.8% vs 1.6% to 3.6% with placebo [76][38].

2) Estrogen replacement (transdermal route): 5% to 7% vs 0% to 5% with placebo [36]

3) Estrogen replacement (transdermal route): 6.5% to 17% vs 0% with placebo [29][11][12]

Candida vaginitis

a) Incidence: Topical gel, 0.8% to 6.4% [38]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 0.8% to 6.4% vs 3.2% with placebo [38]

Candidiasis

a) Incidence: Vaginal cream, 7% [15]; vaginal ring, 6% [15]; vaginal tablets, 5% [94]
b) Adult Clinical Trials

1) Estrogen replacement (vaginal route); genital moniliasis, 6% with vaginal ring, 7% with vaginal cream [15], 5% with vaginal tablet vs 2% with placebo [94]

Disorder of menstruation

a) General Information

1) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [66][76][7][38][35][8][19][11][12][36][14][15]

Endometrial cancer

a) General Information

1) Increased risk in women with intact uteri who use estrogens alone [69][74]

2) Malignancy in residual endometrial implants have been reported in women treated with estrogen monotherapy following hysterectomy [29][69]

3) Risk appears to be 2- to 12-fold greater with unopposed estrogen use compared with non-users [29][69][74][19][7][38][35][8][11][12][14][15][94]

4) Risk is linked to estrogen dose and duration of use [29][69][74][19][76][7][38][35][8][11][12][14][15][94]

5) Prolonged use (ie, 5 to 10 years) is associated with a 15- to 24-fold increased risk compared with estrogen non-users, which persists for 8 to 15 years after treatment discontinuation [29][69]

6) Most studies indicated no significant increased risk when estrogens are used for less than 1 year [29][69][74][19][76][7][38][35][8][11][12][14][15][94].

7) Periodic bleeding may occur with estrogen and progestin combination therapy [98]

b) Prevention and Management

1) Estrogen therapy with concomitant progestin has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor [29][69][74][130][131][132][133][134][135][136][137]

2) Consider adding medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle to reduce the risk of hyperplasia and carcinoma [69][138].

3) Assess persistent or recurring abnormal genital bleeding in postmenopausal women with directed or random endometrial sampling when indicated to exclude malignancy [29][69][74][76][19]

4) In women with vaginal atrophy, consider low-dose vaginal estrogen formulations instead of oral forms for endometrial hyperplasia prophylaxis [139]

5) Consider long-term gynecologic monitoring in women with intact uteri and a history of 1 or more years of estrogen use, regardless of when treatment was received [140]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Nonsignificant decrease in endometrial cancer risk compared with placebo among women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69]

2) Estrogen replacement (oral, transdermal, vaginal routes): Endometrial cancer recurrence rate: 1% with estrogen replacement vs 14% without estrogen. About half of estrogen-treated patients also received progestin. The disease-free interval was significantly longer among estrogen-treated patients vs untreated patients [141]

3) Estrogen replacement (oral, transdermal, vaginal routes): Risk of endometrial cancer was strongly related to daily, long-term estrogen use, with women using higher estrogen doses experiencing an 8-fold increased risk with 5 or more years of use and a 4-fold increased risk with low-dose therapies compared to no hormonal therapy [139].

4) Multiple indications (breast conditions, endometriosis, estrogen replacement, menstrual problems or irregularities, sexual difficulties): 31% with noncontraceptive estrogens vs 15% among controls. Women who received 1 or more years of estrogen therapy were at increased risk for endometrial carcinoma for at least 10 years after estrogen treatment discontinuation [140].

Endometrial disorder

a) Incidence: Topical emulsion, 15% [35]
b) Adult Clinical Trials

1) Estrogen replacement (topical route, emulsion); 15% vs 8% with placebo [35].

Endometrial hyperplasia

a) Prevention and Management

1) Consider adding progestin to the treatment regimen [29]

b) Postmarketing

1) Has been reported [76].

Endometriosis

a) General Information

1) May exacerbate preexisting endometriosis; malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after hysterectomy [29][74][76][7][38][35][8][92][11][12][36][14][15]

b) Prevention and Management

1) Consider adding progestin to the treatment regimen [29][74][76][7][38][35][8][92][11][12][36][14][15]

Erectile dysfunction

a) Adult Case Studies

1) Gynecomastia and impotence have been reported in 2 men after regular use of an estrogen-containing hair lotion (50 mg estradiol/100 mL alcoholic solution). Although 1 patient had return of libido and regression of the gynecomastia 4 weeks after discontinuing the hair lotion, the other patient had no regression of his gynecomastia. This patients underwent bilateral mastectomy 6 months after discontinuation of the hair product [109].

Fibrocystic breast changes

a) Postmarketing

1) Have been reported [76].

Intermenstrual bleeding - irregular

a) Incidence: Topical gel, 4.1% to 9.6% [76][38]; transdermal system, 0% to 10.6% [29]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.1% to 9.6% vs 1.6% to 2.2% with placebo [76][38]

2) Estrogen replacement (transdermal route): 0% to 10.6% vs 4.5% with placebo [29]

Leukorrhea

a) Incidence: Transdermal system, 1% to 7% [19]
b) General Information

1) Leukorrhea has been reported with estrogen and/or progestin therapy [19][7][13][38][35][8][11][12][36][14][15].

c) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 7% vs 1% with placebo [19]

Normal libido, Change in

a) General Information

1) Changes in libido have been reported with estrogen and/or progestin therapy [76][7][38][35][8][11][12][36][14][15]

Ovarian cancer

a) General Information

1) Risk increases with longer duration of use in current users; no significantly increased risk with 0 to 5 years of use, 24% increased risk with 5 to 9 years of use, 31% increased risk with 10 or more years of use [126].

2) No difference in risk with route of administration or preparation used [126]

3) Mean time to diagnosis in current users is after 9.2 years of estrogen only use, and after 6.9 years of estrogen/progestin combination therapy [126].

4) Mean time to diagnosis in past users is 5.6 years after discontinuation [126].

5) Approximately 95% of cancers were epithelial; greater risk for serous tumors versus mucinous, endometrioid, or clear cell tumors [126]

b) Adult Clinical Studies

1) Hormone replacement therapy (unknown route): Increased risk for ovarian cancer, relative risk with current use was 1.41 (95% CI, 1.32 to 1.50); relative risk with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48). The elevated risk was significant for both estrogen-alone and estrogen plus progestin products according to meta-analysis (17 prospective studies; 12,110 cancer cases) [127][128]

a) UK Million Women Study

1% increased risk with ever use; 20% increased risk with current use; no significant increase in risk with past use [126]

Ovarian cancer incidence rate per 1000 over 5 years: 2.6 for current users vs 2.2 for never users [126]

1 extra ovarian cancer case per 2500 users [126]

Ovarian cancer mortality rate per 1000 over 5 years: 1.6 for current users vs 1.3 for never users [126]

1 extra ovarian cancer death per 3300 users [126]

b) Women's Health Initiative Study

No significant increase in risk for invasive ovarian cancer after 5.6 years of treatment with estrogen/progestin combination therapy [127][128][129][7][13][38][35][8][11][12][36][14][15]

Cases per 10,000 women: 4.2 with estrogen/progestin combination therapy vs 2.7 with placebo [129][7][13][38][35][8][11][12][36][14][15]

Pain of breast

a) Incidence: Topical emulsion, 10% [35]; topical gel, 10.7% [74]; transdermal system, 5% to 34.8% [8][19]; vaginal cream, 7% [15]; vaginal ring, 1% [15]
b) Adult Clinical Studies

1) Estrogen replacement (vaginal route): 1% with estradiol vaginal ring vs 7% with estradiol vaginal cream [15]

2) Estrogen replacement (topical route): 10.7% with estradiol vs 8.2% with placebo [74]; 10% with estradiol emulsion vs 3% with placebo [35]

3) Estrogen replacement (transdermal route): 5% to 34.8% with estradiol patch vs 4% to 8% with placebo [19][8]

Pruritus of genital organs

a) Incidence: Vaginal tablets, 6% [94]
b) Adult Clinical Trials

1) Estrogen replacement (vaginal route): 6% [94]

Sore nipple

a) Incidence: Transdermal spray, 1% to 7% [36]
b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 1% to 7% vs 0% with placebo [36]

Swelling of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [19][76][7][13][38][35][8][11][12][36][14][15].

b) Postmarketing

1) Breast enlargement has been reported [29]

Vaginal bleeding

a) Incidence: Transdermal, 8.7% to 33.3% [8]
b) Estrogen replacement (transdermal route): 8.7% to 33.3% vs 12.9% with placebo [8]

Vaginal discomfort

a) Incidence: Vaginal cream and ring, 5% [15][15]
b) General Information

1) Vaginal discomfort or pain commonly contributed to the discontinuation of treatment with estradiol vaginal ring during clinical studies [15].

c) Adult Clinical Studies

1) Estrogen replacement (vaginal route): 5% [15]

Vaginal ulcer

a) General Information

1) May manifest as vaginal irritation, erythema, abrasion, or spotting [142]

b) Prevention and Management

1) Carefully evaluate if occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to healing tissue [142].

c) Postmarketing

1) Has been reported [142]

Vaginal wall finding

a) Prevention and Management

1) If vaginal ulceration or erosion occurs; consider leaving ring out and not replacing it until healing is complete to prevent adherence of ring to the healing tissue [142].

b) Postmarketing

1) Adherence of ring to vaginal wall, making ring removal difficult, has been reported; in some cases, surgery was necessary [142].

Vaginitis

a) Postmarketing

1) Vaginitis, including vaginal candidiasis, has been reported in postmarketing surveillance [76]

Withdrawal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [66][76][7][38][35][8][19][11][36][14][15]

Estradiol Acetate

Abnormal vaginal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [59].

b) Prevention and Management

1) Patients should inform their healthcare provider of abnormal vaginal bleeding immediately [59].

Breast tenderness

a) Incidence: oral, 0.8% to 6.3%; vaginal, 6.2% to 10.7% [173]
b) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy. The incidence is higher for the vaginal ring preparation (6.2% to 10.7%) than for the oral preparation (0.8% to 6.3%) [170][173].

Candida vaginitis

a) Incidence: 6.2% to 10.7% [173]
b) The incidences of vaginal candidiasis reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 6.2% and 10.7%, respectively [173].

Device adherence, To vaginal wall

a) General Information

1) May make vaginal ring removal difficult [174].

2) Vaginal wall ulceration or erosion have been reported [174].

b) Management

1) Evaluate for vaginal wall ulceration or erosion [174].

2) Consider not replacing ring until healing is complete [174].

c) Postmarketing Reports

1) Cases of ring adherence to the vaginal wall have been reported [174].

Disorder of menstruation

a) Incidence: oral, 2.0% to 3.2%; vaginal, 8.0% to 9.8% [170][173]
b) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy. The incidence is higher for the vaginal ring preparation (8.0% to 9.8%) than for the oral preparation (2.0% to 3.2%) [170][173].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [170].

b) General Information

1) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

2) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low-potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

3) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

4) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

5) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

c) Prevention and Management

1) Postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding should be tested to rule out malignancy [59]

Endometriosis

a) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in

women who have been treated with estrogen-alone therapy after a hysterectomy. The addition of a progestin should be considered [170].

Leukorrhea

a) Leukorrhea has been reported with estrogen and/or progestin therapy [170].

Libido - finding

a) Changes in libido have been reported with the use of estrogen and/or progestin therapy [170].

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][170].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [170].

Pain of uterus

a) Incidence: 1.8% to 4.5% [173]
b) The incidences of uterine pain reported with the use of estradiol acetate vaginal ring 0.05 milligrams/day and 0.10 milligrams/day were 1.8% and 4.5%, respectively [173].

Swelling of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [170].

Estradiol Cypionate

Breast tenderness

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Disorder of menstruation

a) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [55].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women

receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

g) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

h) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

i) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

j) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10

milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].
k) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].
l) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Endometriosis

a) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after a hysterectomy. The addition of a progestin should be considered [55].

Leukorrhea

a) Leukorrhea has been reported with estrogen and/or progestin therapy [55].

Libido - finding

a) Changes in libido have been reported with the use of estrogen and/or progestin therapy [55].

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000,

respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][55].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Swelling of breast

a) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [55].

Withdrawal bleeding

a) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [55].

Estradiol Valerate

Breast cancer

a) General Information

1) Increased risk with estrogen monotherapy or with estrogen and progestin combined therapy [169]

2) Increased risk of invasive breast cancer in postmenopausal women without an uterus who had received unopposed estrogen for 10 years or longer [123].

3) Tumors were larger, more advanced, and more likely node-positive with combination estrogen/progestin therapy than with placebo treatment [169]

4) Risk increases with duration of use [169]

5) Risk may occur earlier when given with progestins [169]

6) Risk returns to baseline 5 years after therapy discontinuation [169]

7) More abnormal mammograms may occur [169]

b) Prevention and Management

1) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [169]

c) Adult Clinical Studies

1) Risk Among Healthy Women

a) Hormone replacement therapy (route unknown): Increases in mammographic density, 32% with estrogen or conjugated equine estrogen (95% CI, 25.7%, 38.6%) vs 3% with controls (95% CI, 0%, 17.2%) (Valdivia & Ortega, 2000)

b) Hormone replacement therapy (unknown route, 50 to 64 years of age): Relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users, 0.9 [154]

1) Women's Health Initiative

a) Conjugated Estrogens Plus Medroxyprogesterone

1) Hormone replacement therapy (oral route): Relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily after an average follow-up of 5.2 years [169]

2) Hormone replacement therapy (oral route): 8 more invasive breast cancer cases per 10,000 women years with conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily [169]

b) Estrogen Monotherapy

1) A non-significant decrease in invasive breast cancer, hazard ratio 0.80 (95% CI, 0.62 to 1.04; p=0.09) with conjugated estrogens 0.625 mg/day monotherapy for a mean of 7.1 years compared with 0.82 (95% CI, 0.65 to 1.04; p=0.1) with placebo-treated women [149]

2) Breast cancers with localized disease, hazard ratio 0.69 (95% CI, 0.51 to 0.95) with conjugated equine estrogens [149]

3) Decreased ductal carcinomas, hazard ratio 0.71 with conjugated equine estrogens (95% CI, 0.52 to 0.99); test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054) [149]

4) Mammographies requiring follow-up after the first year was significantly higher, 9.2% with conjugated equine estrogen group compared with 5.5% with placebo group [149]

5) Cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher, 36.2% with conjugated equine estrogen group compared with 28.1% the placebo group [149]

2) Nurses' Health Study

a) Hormone replacement therapy (unknown route): 32% increased risk with current users of estrogen alone compared with never use, 41% increased risk with estrogen plus progestin compared with postmenopausal women who had never used hormones [153]

b) Hormone replacement therapy (unknown route): 934 invasive breast cancers diagnosed; 226 who never used hormones and 708 current estrogen users (335,296 person-years of follow-up) [123]

c) Hormone replacement therapy (unknown route): Relative risk, current estrogen use 20 years or longer and BMI of less than 25, 1.77 (95% CI, 1.26 to 2.48); current estrogen use 20 years or longer and BMI 25 or greater 1.25 (95% CI, 0.91 to 1.71) [123]

d) Hormone replacement therapy (unknown route): Relative risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers increased with current users of estrogen after 15 years of use, 1.48 (95% CI, 1.05 to 2.07) [123]

e) The relative risk (RR) and 95% CI based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

3) Breast Cancer Detection Demonstration Project

a) Cases of breast cancer identified, 2082 (Study N=46,355) [150][151]

b) Hormone replacement therapy (unknown route): Relative risk, 1.2 current and recent use (previous 4 years) of estrogen only (95% CI, 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin [150][151]

c) Hormone replacement therapy (unknown route): Relative risk increase by 0.01 with estrogen-only use per year vs 0.08 with estrogen-progestin-only use

per year [150][151]

d) Hormone replacement therapy (unknown route): Relative risk, 1.1 with ever using estrogen (95% CI, 1.0-1.3) vs 1.3 with estrogen-progestin (95% CI, 1.0-1.6); increases in relative risk with a BMI of 24.4 kg/m(2) or less, 0.03 with estrogen-only use per year (95% CI, 0.01-0.06) and 0.12 with estrogen-progestin-only use per year (95% CI, 0.02-0.25) [150][151]

2) Risk Among Breast Cancer Survivors

a) Estrogen replacement: The HABITS trial was discontinued early after results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events [124].

b) Estrogen replacement, estrogen monotherapy: Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors [125].

c) Estrogen replacement (oral and intravaginal routes): Rate of recurrence was 50% lower and breast cancer mortality 34% lower with use of hormone replacement therapy (HRT) than with non-use (O'Meara et al, 2001).

d) Estrogen replacement therapy (unknown route) No increase in recurrences or mortality rates; estrogen plus progestogens demonstrated a decrease in recurrence. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users [155].

Breast tenderness

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Disorder of menstruation

a) General Information

1) Breakthrough bleeding, spotting, and dysmenorrhea have been reported with estrogen and/or progestin therapy [57].

Endometrial cancer

a) General Information

1) Increased risk in women with intact uteri who use estrogens alone [169]

2) Malignancy in residual endometrial implants have been reported in women treated with estrogen monotherapy following hysterectomy [169].

3) Risk appears to be 2- to 12-fold greater with unopposed estrogen use compared with non-users [169]

4) Risk is linked to estrogen dose and duration of use [169]

5) Prolonged use (ie, 5 to 10 years) is associated with a 15- to 24-fold increased risk compared with estrogen non-users, which persists for 8 to 15 years after treatment discontinuation [169]

6) Most studies indicated no significant increased risk when estrogens are used for less than 1 year [169].

b) Prevention and Management

1) Estrogen therapy with concomitant progestin has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor [169].

2) Consider adding medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle to reduce the risk of hyperplasia and carcinoma [169][138].

3) Assess persistent or recurring abnormal genital bleeding in postmenopausal women with directed or random endometrial sampling when indicated to exclude malignancy [169]

4) In women with vaginal atrophy, consider low-dose vaginal estrogen formulations instead of oral forms [139]

5) Consider long-term gynecologic monitoring in women with intact uteri and a history of 1 or more years of estrogen use, regardless of when treatment was received [140]

c) Adult Clinical Studies

1) Estrogen replacement (oral, transdermal, vaginal routes): Endometrial cancer recurrence rate: 1% with estrogen replacement vs 14% without estrogen. About half of estrogen-treated patients also received progestin. The disease-free interval was significantly longer among estrogen-treated patients vs untreated patients [141].

2) Estrogen replacement (oral, transdermal, vaginal routes): Risk of endometrial cancer, higher estrogen doses were associated with an 8-fold increased risk with 5

or more years of use compared with no estrogen use; lower estrogen doses were associated with a 4-fold increased risk [139].

Endometriosis

a) General Information

1) Administration of estrogen therapy may exacerbate pre-existing endometriosis. Malignant transformation of residual endometrial implants have been reported in women who have been treated with estrogen-alone therapy after a hysterectomy [57].

b) Prevention

1) The addition of a progestin should be considered [57].

Libido - finding

a) General Information

1) Changes in libido have been reported with the use of estrogen and/or progestin therapy [57].

Ovarian cancer

a) General Information

1) Risk increases with longer duration of use in current users; no significantly increased risk with 0 to 5 years of use, 24% increased risk with 5 to 9 years of use, 31% increased risk with 10 or more years of use [126].

2) No difference in risk with route of administration or preparation used [126]

3) Mean time to diagnosis in current users is after 9.2 years of estrogen only use, and after 6.9 years of estrogen/progestin combination therapy [126].

4) Mean time to diagnosis in past users is 5.6 years after discontinuation [126].

5) Approximately 95% of cancers were epithelial; greater risk for serous tumors vs mucinous, endometrioid, or clear cell tumors [126]

b) Adult Clinical Studies

1) Hormone replacement therapy (unknown route): Increased risk for ovarian cancer, relative risk with current use was 1.41 (95% CI, 1.2 to 150); relative risk with combined current and recent use (discontinued use within 5 years before cancer diagnosis) was 1.37 (95% CI, 1.27 to 1.48). The elevated risk was significant for both estrogen-alone and estrogen plus progestin products according to meta-analysis (17 prospective studies; 12,110 cancer cases) [169]

a) UK Million Women Study

1) 11% increased risk with ever use compared with never use; 20% increased risk with current use compared with never use [126]

2) Ovarian cancer incidence rate per 1000 over 5 years: 2.6 for current users vs 2.2 for never users [126]

3) 1 extra ovarian cancer case per 2500 users [126]

4) Ovarian cancer mortality rate per 1000 patients over 5 years: 1.6 for current users vs 1.3 for never users [126]

5) 1 extra ovarian cancer death per 3300 users [126]

b) Women's Health Initiative Study

1) No significant increase in risk for invasive ovarian cancer after 5.6 years of treatment with estrogen/progestin combination therapy [129]

2) Cases per 10,000 women: 4.2 with estrogen/progestin combination therapy vs 2.7 with placebo [129]

c) Breast Cancer Detection Demonstration Project

1) Short-term estrogen-progestin use did not increase the risk for ovarian cancer [164].

2) Of 44,241 women, 329 developed ovarian cancer during follow-up [164].

3) After adjustment for age, menopause type, and oral contraceptive use, the results were:

Type of Hormone Replacement	Rate Ratio and 95% Confidence Interval (CI)
Ever use of estrogen	1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	1.6; 95% CI, 0.78 to 3.3**

Type of Hormone Replacement	Rate Ratio and 95% Confidence Interval (CI)
Estrogen-progestin use only, 2 or more yrs	0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

4) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% CI, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Pain of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Swelling of breast

a) General Information

1) Breast tenderness, enlargement, and pain have been reported during the use of estrogen and/or progestin therapy [57].

Withdrawal bleeding

a) General Information

1) Changes in vaginal bleeding patterns and abnormal withdrawal bleeding or flow have been reported with estrogen and/or progestin therapy [57].

Respiratory Effects

Estradiol

Asthma

a) General Information

1) Exacerbation of asthma may occur [29]

b) Adult Clinical Trials

1) Hormone replacement therapy (route unknown): 2.29-fold increase in rate of asthma with estrogen alone compared with never use [116]

Multiple leiomyoma of lung

a) Adult Case Study

1) Pulmonary leiomyomatosis manifesting as recurrent pneumothorax has been associated in a single patient with combination hormone replacement therapy consisting of conjugated estrogens 0.625 mg and medroxyprogesterone 10 mg given sequentially. Although the time course of events was somewhat unclear, it appeared that the pulmonary symptoms began with the addition of the progestin, while estrogen monotherapy for an extended period of time prior to this had not produced these effects. The condition resolved gradually over 3 months after discontinuing hormone replacement [117].

Nasopharyngitis

a) Incidence: Topical gel, 4.1% to 10.3% [76][38]; transdermal system, 6.4% to 19.6% [29]

b) Adult Clinical Trials

1) Estrogen replacement (topical route): 4.1% to 10.3% vs 4% to 7.3% with placebo [76][38]

2) Estrogen replacement (transdermal route): 6.4% to 19.6% vs 15.3% with placebo [29]

Pharyngitis

a) Incidence: Transdermal system, 0.5% to 7% [19]

b) Adult Clinical Trials

1) Estrogen replacement (transdermal route): 0.5% to 7% vs 3% with placebo [19]

Pulmonary embolism

a) General Information

1) Increased risk with estrogen monotherapy and with combination estrogen and progestin therapy [29][69][74]

b) Prevention and Management

1) Appropriately manage risk factors for venous thromboembolism (eg, personal or family history, obesity, systemic lupus erythematosus) [29][69][74][76][19]

2) Prescribe estrogen with or without progestins at the lowest effective dose for the shortest duration consistent with treatment goals and risks [29][69]

3) Discontinue (if possible) 4 to 6 weeks before periods of prolonged immobilization or surgeries that increase thromboembolism risk [29][69][74][76]

4) Discontinue immediately if occurs or is suspected [29][69][74][76][19]

c) Adult Clinical Studies

1) Hormone replacement therapy (oral route): Risk of DVT was 47% higher with conjugated estrogen monotherapy versus placebo in a Women's Health Initiative substudy. Increased venous thromboembolism risk occurred during the first 2 years of therapy [69][74][19][76][7][13][38][35][8][11][12][14][15][88]

2) Hormone replacement therapy (oral route): Risk of DVT and pulmonary embolism was 95% and more than 2-fold higher, respectively, compared with placebo among women (mean age, 63) treated with daily conjugated estrogen 0.625 mg/day and medroxyprogesterone acetate 2.5 mg for a mean 5.6 years [29][69][74][19][76][7][13][38][35][8][11][12][14][15][88]

d) Postmarketing

1) Has been reported [66].

Rhinitis

a) Incidence: Transdermal system, 2% to 6% [19]
b) Estrogen replacement (transdermal route): 2% to 6% vs 1% with placebo [19]

Sinusitis

a) Incidence: Topical gel, 3.6% [13]; transdermal system, 4% to 13.1% [29][19]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 3.6% vs 1.4% with placebo [13]

2) Estrogen replacement (transdermal route): 4% to 5% vs 3% with placebo [19]

3) Estrogen replacement (transdermal route): 5.3% to 13.1% vs 10.2% with placebo [29]

Upper respiratory infection

a) Incidence: Topical gel, 1.6% to 5.9% [76][38]; transdermal system, 4.5% to 17% [29][19]; vaginal cream, 6% [15]; vaginal ring, 5% [15]; vaginal tablets, 5% [94]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 1.6% to 5.9% vs 1.6% to 3.6% with placebo [76][38]

2) Estrogen replacement (transdermal route): 4.5% to 10.7% vs 5.7% with placebo [29]

3) Estrogen replacement (transdermal route): 6% to 17% vs 8% with placebo [19]

4) Estrogen replacement (transvaginal route): 5% vaginal ring; 6% with vaginal cream [15]

5) Estrogen replacement (oral route): 5% vs 4% with placebo [94]

Estradiol Acetate

Asthma, acute

a) Estrogen therapy may cause an exacerbation of asthma and should be used with caution in patients with asthma [170].
b) Results from a prospective cohort study indicate postmenopausal treatment with estrogen alone or estrogen plus progestin is associated with an increased rate of newly diagnosed asthma but not chronic obstructive pulmonary disease (COPD). During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate adjusted rate ratio, 2.29; 95% confidence interval (CI), 1.59 to 3.29) compared with those who never used hormones. Women who used estrogen plus progestin had a similarly increased rate of a new diagnosis of definite asthma (multivariate rate ratio, 2.03; 95% CI, 1.42 to 2.90). Rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio, 1.05; 95% CI, 0.80 to 1.37) [116].

Pulmonary embolism

a) The estrogen-plus-progestin substudy of the Women's Health Initiative (WHI) reported an increased risk of pulmonary emboli in postmenopausal women aged 50 to 79 years during 5.6 years of treatment with oral conjugated estrogens 0.625 milligrams (mg) combined with oral medroxyprogesterone acetate 2.5 mg per day relative to placebo. The relative risk of pulmonary embolism in the estrogen-alone substudy of WHI after an average follow-up of 7.1 years was 1.37 (95% confidence interval 0.90 to 2.07) compared with 2.13 (95% confidence interval 1.45 to 3.11) seen in the estrogen-plus-progestin substudy of WHI [88].
b) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and

postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

Estradiol Cypionate

Asthma, acute

a) Estrogen therapy may cause an exacerbation of asthma and should be used with caution in patients with asthma [55].
b) Results from a prospective cohort study indicate postmenopausal treatment with estrogen alone or estrogen plus progestin is associated with an increased rate of newly diagnosed asthma but not chronic obstructive pulmonary disease (COPD). During 546,259 person-years of follow-up, current use of estrogen alone was associated with an increased rate of asthma (multivariate adjusted rate ratio, 2.29; 95% confidence interval (CI), 1.59 to 3.29) compared with those who never used hormones. Women who used estrogen plus progestin had a similarly increased rate of a new diagnosis of definite asthma (multivariate rate ratio, 2.03; 95% CI, 1.42 to 2.90). Rates of newly diagnosed COPD were the same among hormone users and nonusers (multivariate rate ratio, 1.05; 95% CI, 0.80 to 1.37) [116].

Pulmonary embolism

a) The estrogen-plus-progestin substudy of the Women's Health Initiative (WHI) reported an increased risk of pulmonary emboli in postmenopausal women aged 50 to 79 years during 5.6 years of treatment with oral conjugated estrogens 0.625 milligrams (mg) combined with oral medroxyprogesterone acetate 2.5 mg per day relative to placebo. The relative risk of pulmonary embolism in the estrogen-alone substudy of WHI after an average follow-up of 7.1 years was 1.37 (95% confidence interval 0.90 to 2.07) compared with 2.13 (95% confidence interval 1.45 to 3.11) seen in the estrogen-plus-progestin substudy of WHI [88].
b) Results from a population-based, case-control, observational study indicate that conjugated equine estrogen (CEE) but not esterified estrogen is associated with an increased risk of venous thrombosis (VT). Cases (n=586) were perimenopausal and postmenopausal women aged 30 to 89 years who sustained a first deep vein venous thrombosis (DVT) or pulmonary embolism (PE) and controls (n=2268) were matched on age (within the decade), hypertension status, and calendar year of VT first episode. Pharmacy claims data and hospital records were reviewed for all patients. Continual estrogen use was defined as consecutive prescription refills with no more than a 90 day lapse. The study period was 7 years. Of the 586 women who experienced a first VT, 426 (73%) had DVT alone, 68 (12%) had DVT and PE, and 92 (16%) had PE, of which 33 were fatal. Compared with women not currently using hormones, current users of esterified estrogen had no increase in VT risk (odds ratio (OR), 0.92; 95% confidence interval (CI), 0.69 to 1.22). However, women currently taking CEE (121 cases and 289 controls) had an elevated risk (OR, 1.65; 95% CI, 1.24 to 2.19). Current users of CEE also had a higher risk compared to current users of esterified estrogen when the analyses were limited to estrogen users only (OR, 1.78; 95% CI, 1.11 to 2.84). Additionally, concomitant progestin use was associated with increased risk of VT compared with use of estrogen alone (OR, 1.60; 95% CI, 1.13 to 2.26) [89].

Estradiol Valerate

Asthma, acute

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Other

Estradiol

Angioedema

a) General Information

1) May lead to airway obstruction [29]

b) Prevention and Management

1) Do not reuse if patient develops angioedema at anytime during course of treatment [29]

c) Postmarketing

1) Has been reported [29][76].

Death, Overall Mortality

a) General Information

1) Among current users, protective effect is greater for younger patients; age not a risk modifier among former users [104]

b) Adult Clinical Studies

1) Overall mortality rate: 6.9% for current users of estrogen with or without progestin, 17.9% for former users, and 18.3% for never users [104]

Hereditary angioedema, Exacerbation

a) General Information

1) Estrogen therapy may exacerbate symptoms of hereditary angioedema [29][69][74].

Infectious disease

a) Incidence: Topical emulsion, 12% [35]; topical gel, 17.3% [13]
b) General Information

1) Infections included upper respiratory tract infection, the common cold, and eye infection [13]

c) Adult Clinical Trials

1) Estrogen replacement (topical emulsion): 12% vs 7% with placebo [35].

2) Estrogen replacement (topical gel): 17.3% vs 6.8% with placebo [13]

Influenza-like illness

a) Incidence: up to 7.8% [29][13]
b) Adult Clinical Trials

1) Estrogen replacement (topical route): 5.4% vs 1.4% with placebo [13]

2) Estrogen replacement (transdermal route): 0% to 7.8% vs 6.4% with placebo [29]

Mesenchymoma (clinical), Malignant

a) Postmarketing

1) Malignant mesenchymoma has been reported [74]

Pain

a) Incidence: Transdermal system, 0% to 11% [29][19]
b) Estrogen replacement (transdermal route): 0% to 6.2% vs 4.5% with placebo [29]
c) Estrogen replacement (transdermal route): 1% to 11% vs 7% with placebo [19]

Estradiol Acetate

Angioedema

a) General Information

1) Estrogen therapy can exacerbate symptoms of angioedema in women with hereditary angioedema [59].

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year

thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26; 95% confidence interval, 1.00 to 1.59) [170].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of estradiol or conjugated equine estrogens (CEE) increased mammographic density while tibolone and estriol did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included estradiol 2 milligrams (mg), estradiol 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, estradiol 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, estriol 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving estradiol or CEE. No patients receiving tibolone or estriol experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-

progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence

and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [170].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130] [131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of

periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence, and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][170].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Toxic shock syndrome

a) Rarely, cases of toxic shock syndrome have been reported in women using vaginal rings during post-marketing experience [173].

Estradiol Cypionate

Breast cancer

a) Risk Among Healthy Women

1) The overall results of studies are mixed, however, the more recent large-scale and long-term studies identify an increased risk of developing breast cancer with the use of hormone replacement therapy. Estrogen and progestin regimens appear to increase the risk of breast cancer (hazard ratio 1.26, 95% confidence interval 1.00 to 1.59). The risk associated with unopposed estrogen therapy is increased among long-term users (10 years or more) [143][144][145][123].

Final results from the Nurses' Health Study (NHS) reported an increased risk of invasive breast cancer in postmenopausal women without a uterus who had received unopposed estrogen for 10 years or longer. The NHS was an observational, prospective cohort study initially involving a total of 11,508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline. With the expansion of the study population every 2 years to include subsequent postmenopausal women without a uterus, the final follow-up period included 28,835 women. Biennial questionnaires were used to assess estrogen use. The primary outcome was invasive breast cancer. During 335,296 person-years of follow-up, 934 invasive breast cancers were diagnosed, which included 226 among women who never used hormones and 708 among current estrogen users. The relative risk (RR) and 95 confidence intervals (95% CI) based on length of use is reported in the following table:

Length of Estrogen Use	RR	95% CI (p for trend less than 0.001)
less than 5 years	0.96	0.75 to 1.22
5 to 9.9 years	0.90	0.73 to 1.12
10 to 14.9 years	1.06	0.87 to 1.30
15 to 19.9 years	1.18	0.95 to 1.48
20 years or longer	1.42	1.13 to 1.77

When analyses were stratified by body mass index (BMI), the risk of invasive breast cancer appeared to be greater in leaner women, however, the difference did not reach statistical significance (p=0.1). The RR for current estrogen use of 20 years or longer in women with a BMI of less than 25 was 1.77 (95% CI, 1.26 to 2.48) while the RR for current estrogen use of 20 years or longer in women with a BMI of 25 or greater was 1.25 (95% CI, 0.91 to 1.71). Additionally, the risk for estrogen receptor positive (ER+) and progesterone receptor positive (PR+) cancers was increased among current users of estrogen after 15 years of use (RR, 1.48; 95% CI, 1.05 to 2.07). Overall, there did not seem to be a strong dose-response relationship among estrogen use and risk of breast cancer [123].

2) Results from the Women's Health Initiative (WHI) Estrogen-Alone trial indicate treatment with conjugated equine estrogens (CEE) does not increase breast cancer incidence in postmenopausal women without a uterus, however, it was associated with an increased frequency of mammography screening that required short interval follow-up. Women (n=10,739) with similar baseline breast cancer risk were randomized in a double-blind trial to CEE 0.625 milligrams (mg) or placebo daily. After a mean follow-up of 7.1 years, nonsignificant reductions for invasive breast cancer and total breast cancer were observed in women receiving CEE (hazard ratio (HR), 0.80; 95% confidence interval (CI), 0.62 to 1.04; p=0.09 and HR, 0.82; 95% CI, 0.65 to 1.04; p=0.1, respectively) compared with placebo. No effect on in situ disease was evident. Breast cancers with localized disease were diagnosed less frequently in women receiving CEE compared with women receiving placebo (HR, 0.69; 95% CI, 0.51 to 0.95). Advanced stage cancer incidence was comparable between the 2 groups. Compared with placebo, ductal carcinomas were decreased in women receiving CEE (HR, 0.71; 95% CI, 0.52 to 0.99), but the test for interaction by tumor type (ductal versus lobular) was not significant (p=0.054). The interactions between treatment assignment and estimated 5-year breast cancer risk, history of benign breast disease, and number of first-degree relatives with breast cancer were significant (p=0.01, p=0.005, and p=0.01, respectively). The percentage of mammographies requiring follow-up after the first year was significantly higher in the CEE group compared with the placebo group (9.2% versus 5.5%, respectively; p less than 0.001). In addition, the cumulative number of mammograms over the course of the trial that required follow-up each year thereafter was significantly higher in the CEE group compared with the placebo group (36.2% versus 28.1%; p less than 0.001) [149].

3) Results of the Women's Health Initiative substudy involving 16,608 postmenopausal women who received conjugated estrogens 0.625 milligrams (mg) and medroxyprogesterone acetate 2.5 mg daily demonstrated an increased risk of invasive breast cancer in women receiving hormone therapy relative to placebo. After an average follow-up of 5.2 years, the relative risk of invasive breast cancer was 1.26 (95% confidence interval, 1.00 to 1.59) [55].

4) Data from a retrospective cohort study of 46,355 postmenopausal women suggests the risk of developing breast cancer is less with estrogen alone than with estrogen-progestin combined. The data were derived from follow-up (mean=10.2 years) to the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. During follow-up, 2082 cases of breast cancer were identified. Relative risks (RR) were adjusted for age, age at menopause, education, body mass index (BMI), and mammographic screening. The RR for current and recent use (previous 4 years) of estrogen only was 1.2 (95% confidence interval (CI), 1.0-1.4) versus 1.4 (95% CI, 1.1-1.8) for current and recent use of estrogen-progestin. The RR increase by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users. The RR associated with ever using estrogen or estrogen-progestin was 1.1 (95% CI, 1.0-1.3) and 1.3 (95% CI, 1.0-1.6), respectively. Increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users with a BMI of 24.4 kilogram (kg) per meter squared or less were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. Risk in heavier women did not increase in relation to use of either regimen. A limitation of the study includes retrospective collection and problems of recall in the reporting of hormone use, which does not make it a true prospective cohort study [150][151].

5) Results reported from a prospective, longitudinal study involving 210 postmenopausal women with normal baseline mammograms concluded hormone replacement therapy (HRT) with varying regimens of ESTRADIOL or CONJUGATED EQUINE ESTROGENS (CEE) increased mammographic density while tibolone and ESTRIOL did not. Study participants received 1 of 7 oral HRT regimens for a period of one year. The regimens included ESTRADIOL 2 milligrams (mg), ESTRADIOL 2 mg plus sequential medroxyprogesterone acetate (MPA) 5 mg for 10 to 16 days per cycle, ESTRADIOL 2 mg plus continuous MPA 2.5 mg, CEE 0.625 mg, CEE 0.625 mg plus sequential MPA 5 mg, ESTRIOL 2 mg, or tibolone 2.5 mg. Thirty age-matched postmenopausal women served as a control group. Increased mammographic density occurred in 27% to 67% of patients receiving ESTRADIOL or CEE. No patients receiving tibolone or ESTRIOL experienced increases (p less than 0.05 for both). Overall, 32% of patients receiving HRT (95% confidence interval (CI) 25.7%, 38.6%) experienced increases in mammographic density compared to 3% of the controls (95% CI 0%, 17.2%) (Valdivia & Ortega, 2000).

6) A reanalysis of data from 51 epidemiological studies of women with breast cancer (n=52,705) and without breast cancer (n=108,411) identified the risk of developing breast cancer is increased in women using hormone replacement therapy (HRT) and the risk increased with increasing duration of use, especially in women of lower body mass index (BMI). The relative risk (RR) of a breast cancer diagnosis in current users of HRT or in those who discontinued HRT 1 to 4 years earlier, increased by 1.023 (95% confidence interval (CI), 1.011 to 1.036) for each year of use. The RR for women who used HRT for 5 years or longer was 1.35 (95% CI, 1.21 to 1.49). The RR of breast cancer for women who never used HRT increases by 1.028 (95% CI, 1.021 to 1.034) for each year older at menopause. There was no significant increase in the incidence of breast cancer in women who had discontinued HRT for 5 or more years. Additionally, cancers were less advanced in women who ever used HRT compared to those who never used [152].

7) A 16-year cohort analysis of women enrolled in the Nurses' Health Study was conducted. Their results showed the risk of breast cancer to be significantly increased among women who were current users of estrogen alone (Relative Risk (RR) equal 1.32) or estrogen plus progestin (RR equal 1.41) compared with postmenopausal women who had never used hormones. The risk of breast cancer was increased in women taking postmenopausal hormone replacement therapy (HRT) for more than five years, and in women greater than 55 years of age (among women aged 60 to 64, RR equal 1.71. This study supports the conclusions of other research which shows that short term hormone replacement therapy (less than 5 years) seems to have no important effect on the risk for breast cancer. More importantly, the increased mortality related to breast cancer among a subgroup of current, long-term users (greater than 5 years) was offset by a trend toward decreased risk among former users. These findings support a hypothesis that current use of HRT promotes the growth of existing cancers rather than initiating new cancers. Analysis of this cohort a few years from now should provide more reliable data about the risks and benefits of long-term HRT [153].

8) A study of 537 women (aged 50 to 64 years) in the western United States was conducted to determine the risk for breast cancer from use of combined estrogen-progestin hormone replacement therapy (HRT). Compared with non-users of HRT, the relative odds (RO) of breast cancer in estrogen alone or estrogen-progestin users was 0.9. Long-term use of estrogen alone (greater than or equal to 20 years) and of combined estrogen-progestin (less than 8 years) did not contribute to increased risk for breast cancer. The risk of breast cancer was not substantially affected by the type, dose, or regimen of estrogen or progestin, nor by family history of breast cancer, previous benign breast disease, parity, alcohol use, or oral contraceptive use [154].

b) Risk Among Breast Cancer Survivors

1) The HABITS (hormonal replacement therapy after breast cancer - is it safe?) trial was discontinued early after safety results indicated hormone replacement therapy (HRT) after breast cancer was associated with an increased risk of new breast cancer events. The open-label trial randomized 434 women with previous breast cancer to hormone replacement therapy (n=219) or best treatment without hormones (n=215). Of the 434 women, 345 had at least one follow-up report. After a median of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. Further analyses were completed by subgroups defined by receptor status, tamoxifen treatment, and HRT taken before diagnosis. In all subsets, relative hazards for risk of new breast cancer events was above unity, but the confidence intervals were wide due to the small number of events. When the risk was compared by specific type of HRT, method of administration (continuous or sequential), and other preparations to estrogens only, the differences were small and not statistically significant. The authors acknowledge the results might change after the complete assessment of patients' original records, however, the steering committee for the trial judged the data mature enough to strongly indicate exposure to HRT is associated with an unacceptable risk. The women in the trial will be followed for at least 5 years after randomization [124].

2) Estrogen replacement therapy (ERT) relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases in breast cancer survivors. Disease-free survivors (n=277) were prospectively given ERT and controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.6 years and the mean duration of ERT was 3.7 years. ERT was effective in relieving hot flashes in 92%, dyspareunia and vaginal dryness in 89%, and reactive depression, anxiety, and mood change in 88% of women. There were no statistical differences between the ERT and control groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. In addition, there was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (p=0.85), contralateral breast cancers (p=0.99), or systemic metastasis (p=0.13). Overall survival favored the ERT group (p=0.02) [125].

3) Hormone replacement therapy (HRT) after breast cancer was shown to have no adverse impact on recurrence and mortality in a cohort study comprised of 2755 women (aged 35 to 74 years) who were diagnosed with incident invasive breast cancer. Among the 2755 women, 174 users of HRT after diagnosis of breast cancer was identified. Each HRT user was matched to 4 randomly selected nonusers of HRT who were similar in respect to age, disease stage, and year of diagnosis. The women were free of recurrence at the time of HRT initiation or were equivalent in terms of time since diagnosis. The rate of recurrence was 17 per 1000 person-years in patients on HRT after diagnosis versus 30 per 1000 person-years in nonusers (relative risk (RR) 0.50; 95% confidence interval (CI) 0.30 to 0.85). Mortality rates from breast cancer were 5 per 1000 person- years and 15 per 1000 person-years for HRT users and nonusers, respectively (RR 0.34; 95% CI, 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years for HRT users and 30 per 1000 person-years in nonusers (RR 0.48; 95% CI, 0.29 to 0.78). These results were similar for women using any type of HRT (oral, vaginal, oral plus vaginal) and lower relative risks were not associated with increased dosages (O'Meara et al, 2001).

4) In patients with breast cancer, estrogen replacement therapy did not increase recurrences or mortality rates. The addition of progestogens demonstrated a decrease in recurrence. This study involved 76 patients with breast cancer: 50 patients using estrogen replacement for up to 32 years; 8 patients using nonestrogenic hormone replacement for up to 6 years; and 18 patients using no hormone therapy for up to 10 years. Death occurred in 3 of 50 estrogens users, 1 of 8 nonestrogen users, and 6 of 18 no hormone users. The authors suggest patients with early breast cancer be offered hormone replacement therapy after a full discussion of benefits and risks [155].

Endometrial cancer

a) Summary

1) Estrogen replacement therapy increases the risk of endometrial carcinoma in postmenopausal women but does not appear to increase the rate of recurrence and death among endometrial cancer survivors [141]. Unopposed estrogens in women with intact uteri is associated with an increased risk of endometrial cancer; the risk is approximately 2- to 12-fold greater in these women when compared with non-users. The risk appears to be dependent on duration of use and on estrogen dose. Most studies indicated no significant increased risk when estrogens are used for less than one year. The risk increased 15- to 24-fold when therapy continued for five to ten years or more and the risk persisted for at least 8 to 15 years after discontinuation of estrogen therapy. Adding a progestin to

postmenopausal estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer [55].

b) The rate of recurrence and death among endometrial cancer survivors (n=249) did not increase with estrogen replacement therapy with or without the addition of progestins. After receiving similar primary cancer treatment, 130 of the 249 women began estrogen replacement (oral, transdermal, or vaginal), with 49% electing to add medroxyprogesterone 2.5 milligrams to their daily regimen. The study included 75 matched endometrial cancer patients not treated with estrogen. After a mean follow-up of 83 months for estrogen users (n=75) and 69 months for nonusers (n=75), the rate of recurrence was 1% (95% confidence interval (CI) 71.0 to 91.4) and 14% (95% CI 59.1 to 87.7), respectively. The disease-free interval was significantly longer for those receiving estrogen compared to those who did not (p=0.006). The addition of medroxyprogesterone to the regimen did not appear to make a difference in the risk of recurrence or death rate [141].

c) In a large, population-based, case-control study, treatment with estradiol or conjugated estrogens and continuous progestins decreased the relative risk below levels seen in unexposed women. Information was collected from 709 case patients using hormone replacement and 3368 control subjects. Treatment was classified as 1) medium-potency estrogens (conjugated estrogens, estradiol, and other synthetic estrogens) without added progestins; 2) medium-potency estrogens with progestin cyclically combined or added continuously; 3) low- potency estrogens (oral estradiol or vaginal dienoestrol, estriol, or estradiol); or 4) progestins without estrogen. Relative risk for endometrial cancer was strongly related to the daily dose of estrogens. With 5 or more years of use, women using low-dose therapies had a fourfold increased relative risk, and women using higher doses had an eightfold increase [139]. In the same study, the authors recommend vaginal, rather than oral, formulations of low-potency estrogens for women with atrophy as the only indication for treatment. Oral treatment with low-potency estrogen formulations increased the relative risk of endometrial neoplasia [165].

d) Results from the 3-year Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial demonstrated that for endometrial protection from hyperplastic changes in postmenopausal women with a uterus, estrogen and progestin (cyclically or continuously) should be administered concomitantly (n=596). Patients were given a 28-day cycle of 1) placebo; 2) conjugated estrogens (0.625 milligram per day); 3) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (10 milligrams per day) for the first 12 days 4) conjugated estrogens (0.625 milligram per day) plus medroxyprogesterone (2.5 milligrams per day) for the first 12 days; 5) conjugated estrogens (0.625 milligram per day) plus micronized progesterone (200 milligrams per day) for the first 12 days. If women receive conjugated estrogens only, an annual endometrial evaluation should be done with discontinuation of therapy following the diagnosis of endometrial hyperplasia. In these patients hyperplasia usually returns to normal with progestin therapy [166].

e) The addition of a progestin to the estrogen regimen seems to provide a protective effect against endometrial cancer, by assuring more complete sloughing of the endometrium, which in turn prevents the continued proliferation that may result in hyperplastic neoplasia secondary to unopposed estrogen treatment [130][131][132][133][134][135][136][137]. However, combination therapy can result in periodic vaginal bleeding which may be unacceptable to some postmenopausal patients. Recommended therapy in women who have a uterus is the addition of medroxyprogesterone 10 mg or norethindrone 2.5 to 5 mg during the last 10 days of estrogen administration [98], or on a continuous basis throughout the cycle. This reduces the risk of hyperplasia and endometrial carcinoma [138]. Estrogen replacement therapy exerts stimulatory effects on the postmenopausal endometrium, comparable to premenopausal specimens taken in the proliferative phase [167].

f) A large case-control study has suggested that long-term use of estrogens can increase the risk of both localized and widespread endometrial cancer [140]. Women are at an increased risk of developing endometrial carcinoma for at least 10 years after discontinuing estrogens if they had taken estrogen for 1 or more years. It is suggested that all women who have not had hysterectomies and who have used estrogens for 1 year or more should be considered for long-term gynecologic monitoring regardless of when they received estrogens. Endometrial carcinoma was not associated with estrogen use for a period of less than 1 year. In this study, 31% of 425 women with endometrial carcinoma reported having used estrogens, compared to 15% of 792 controls. Histories were obtained in these patients with regard to noncontraceptive estrogens, and whether patients had used estrogens for numerous indications and not just postmenopausal symptoms (regulation of periods, menstrual problems, infertility, breast conditions, endometriosis or sexual difficulties).

Ovarian cancer

a) The use of hormone replacement therapy (HRT) among postmenopausal women was associated with increased risk of fatal and incident ovarian cancer. In a large cohort UK Million Women Study (n=948,576), postmenopausal women who did not have previous cancer or bilateral oophorectomy (ovariotomy) were followed for an average of 5.3 years (over 5 million woman-years) for ovarian cancer incidence,

and an average of 6.9 years (6.5 million woman-years) for death. The mean age was 57.2 +/- 4.6 years at baseline; and at the time of last contact, 50% participants had ever used HRT while 30% were current users. Ever users of HRT experienced an increased risk of ovarian cancer compared with never users (relative risk (RR) 1.11, 95% confidence interval (CI), 1.02 to 1.21; p=0.02). Unlike past users (RR 0.98, 95% CI, 0.88 to 1.11; p=0.7), current users of HRT exhibited significantly higher ovarian cancer risk relative to never users (RR 1.2, 95% CI, 1.09 to 1.32; p=0.0002); and the difference between the current- and past-users were significant (p=0.01 for heterogeneity). It was estimated that current users developed ovarian cancer after 7.7 years of HRT use overall (9.2 years for estrogen-only and 6.9 years for estrogen-progestagen therapy). Past users, on the other hand, were diagnosed with ovarian cancer 5.6 +/- 4.3 years after discontinuing HRT. The relative risk of ovarian cancer also increased with longer duration of HRT among current users (p=0.04 for trend): 1.05 (95% CI, 0.9 to 1.23) for fewer than 5 years of use, 1.24 (95% CI, 1.09 to 1.41) for 5 to 9 years of use, and 1.31 (95% CI, 1.12 to 1.53) for 10 years or more of use; but did not differ significantly by type of preparation used, constituents, or route of administration. While 95% of the malignant ovarian cancers were epithelial, HRT was greater for serous (RR 1.53, 95% CI, 1.31 to 1.79) than for mucinous (RR 0.72, 95% CI, 0.52 to 1), endometroid (RR 1.05, 95% CI, 0.77 to 1.43), or clear cell tumors (RR 0.77, 95% CI, 0.48 to 1.23). Current users of HRT also exhibited higher mortality risk than never users (RR 1.23, 95% CI, 1.09 to 1.38; p=0.0006), but past users did not (RR 0.97, 95% CI, 0.84 to 1.11). Over 5 years, the standardized incidence and mortality rates for ovarian cancer for never users were 2.2 (2.1 to 2.3) and 1.3 (1.2 to 1.4) per 1000, respectively, and 2.6 (2.4 to 2.9) and 1.6 (1.4 to 1.8) per 1000, respectively, for current users; resulting in a projected 1 extra ovarian cancer case in every 2500 users, and 1 extra death from the malignancy in every 3300 users [126].

b) Results of the Women's Health Initiative (WHI) randomized, double-blind, placebo-controlled trial indicate continuous combined estrogen and progestin therapy may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo. Postmenopausal women with a uterus (n=16,608) were randomized to treatment with conjugated estrogens 0.625 milligrams (mg) plus medroxyprogesterone 2.5 mg or placebo. After 5.6 years follow-up, the hazard ratio (HR) for invasive ovarian cancer in women assigned to estrogen plus progestin compared with placebo was 1.58 (95% confidence interval (CI) 0.77 to 3.24), but was not statistically significant. The absolute risk for estrogen plus progestin versus placebo was 4.2 versus 2.7 cases per 10,000 women-years [129][55].

c) Results from a cohort study of former participants in the Breast Cancer Detection Demonstration Project indicate short-term estrogen-progestin use did not increase the risk for ovarian cancer but further study is warranted. Of 44,241 women, 329 developed ovarian cancer during follow-up. After adjustment for age, menopause type, and oral contraceptive use, the results were:

TYPE OF HORMONE REPLACEMENT	RATE RATIO (RR) and 95% CONFIDENCE INTERVAL (CI)
Ever use of estrogen	RR=1.6; 95% CI, 1.2 to 2.0
Estrogen only for 10 to 19 years	RR=1.8; 95% CI, 1.1 to 3.0*
Estrogen only for 20 or more years	RR=3.2; 95% CI, 1.7 to 5.7*
Estrogen-progestin use after estrogen	RR=1.5; 95% CI, 0.91 to 2.4
Estrogen-progestin use only	RR=1.1; 95% CI, 0.64 to 1.7
Estrogen-progestin use only, less than 2 yrs	RR=1.6; 95% CI, 0.78 to 3.3**
Estrogen-progestin use only, 2 or more yrs	RR=0.8; 95% CI, 0.35 to 1.8**

* p value for trend less than 0.001

** p value for trend equal to 0.30

d) A 7% increase in rate ratio (RR) per year of estrogen-only use was observed (95% confidence interval, 2% to 13%). Also observed were significantly elevated RRs with increasing duration of estrogen-only use across all degrees of other ovarian cancer risk factors [164].

Black Box Warning

1) Estradiol

a) Oral (Tablet)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than "synthetic" estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with or without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [62].

b) Transdermal (Gel/Jelly)

1) Endometrial Cancer, Cardiovascular Disorders, Probable Dementia, and Breast Cancer

Estrogen-Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Use adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.
Cardiovascular Disorders and Probable Dementia - Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile.
Cardiovascular Disorders and Probable Dementia - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Do not use estrogen plus progestin therapy for the prevention of cardiovascular disease or dementia. The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus

progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestin products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestin therapy, taking into account her individual risk profile.
Breast Cancer - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [33].

c) Transdermal (Gel/Jelly; Patch, Extended Release)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, and Probable Dementia

Estrogen-Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia [63][64][10][65][66][67].
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens [65][29][67].
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen -alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile [63][68][10][64].
Cardiovascular Disorders and Probable Dementia - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [63][10][64][65][66][67].

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia [63][10][64][65][66][29][67].
Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [63][10][64][65][66][67].
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age and older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [63][10][64][65][66][67].
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [63][10][64][65][66][67].
Breast Cancer - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA, and other combinations and dosage forms of estrogens and progestins [65][67].
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia, and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile [63][68][10][64].
Breast Cancer - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [63][10][64][65][66][67].

d) Transdermal (Spray)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, Probable Dementia, and Unintentional Secondary Exposure to Estrogen

Estrogen Alone Therapy

Endometrial Cancer- There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed and random endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal genital bleeding.
Cardiovascular Disorders and Probable Dementia - Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg] alone, relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women .
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
Cardiovascular Disorders and Probable Dementia - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.
Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo.
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer.
Breast Cancer - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and MPA and other combinations and dosage forms of estrogens and progestins.
Breast Cancer - Estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

Unintentional Secondary Exposure

Breast budding and breast masses in prepubertal females and gynecomastia and breast masses in prepubertal males have been reported following unintentional secondary exposure to estradiol transdermal spray by women using this product. In most cases, the condition resolved with the removal of the estradiol transdermal spray exposure. Women should ensure that children should not come in contact with the site(s) where estradiol transdermal spray is applied. Healthcare providers should advise patients to strictly adhere to recommended instructions for use [69].

e) Vaginal (Cream; Insert, Extended Release)

1) Endometrial Cancer, Cardiovascular Disorders, Breast Cancer, and Probable Dementias

Estrogen Alone Therapy

Endometrial Cancer - There is an increased risk of cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Perform adequate diagnostic measures, including directed or random endometrial sampling when indicated, to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) [0.625 mg]-alone, relative to placebo [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE (0.625 mg)-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [70][71][72][73].

Cardiovascular Disorders and Probable Dementia - Do not use estrogen-alone therapy for the prevention of cardiovascular disease or dementia [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - Only daily oral 0.625 mg CE was studied in the estrogen-alone substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events and dementia to lower CE doses, other routes of administration, or other estrogen-alone products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen-alone therapy, taking into account her individual risk profile [70][71].
Cardiovascular Disorders and Probable Dementia - In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens[72][73].
Cardiovascular Disorders and Probable Dementia - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [70][71][72][73].

Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia - The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism (PE), stroke and myocardial infarction (MI) in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE (0.625 mg) combined with combined medroxyprogesterone acetate (MPA) [2.5 mg], relative to placebo [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - The WHIMS estrogen plus progestin ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE (0.625 mg) combined with MPA (2.5 mg), relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [70][71][72][73].
Cardiovascular Disorders and Probable Dementia - Do not use estrogen and progestin therapy for the prevention of cardiovascular disease or dementia [70][71][72][73].
Breast Cancer - The WHI estrogen plus progestin substudy also demonstrated an increased risk of invasive breast cancer [70][71][16][72][73].
Breast Cancer - Only daily oral 0.625 mg CE and 2.5 mg MPA were studied in the estrogen plus progestin substudy of the WHI. Therefore, the relevance of the WHI findings regarding adverse cardiovascular events, dementia, and breast cancer to lower CE plus other MPA doses, other routes of administration, or other estrogen plus progestogen products is not known. Without such data, it is not possible to definitively exclude these risks or determine the extent of these risks for other products. Discuss with your patient the benefits and risks of estrogen plus progestogen therapy, taking into account her individual risk profile [70][71].
Breast Cancer - Prescribe estrogens with or without progestins at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [70][71][72][73].

2) Estradiol Acetate

a) Oral (Tablet)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with or without progestins should not be used for the preventions of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and DVT in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE) 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg relative to placebo.

The WHI Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral CE plus MPA relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral CE with MPA, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [61].

b) Vaginal (Insert, Extended Release)

1) Estrogen Alone Therapy

Endometrial Cancer

There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens. Adding a progestin to estrogen therapy has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

Cardiovascular Disorders and Probable Dementia

Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia.
The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risk of stroke and DVT in postmenopausal women (50 to 79 years of age) during 7.1 years of treatment with daily oral conjugated estrogens (CE) 0.625 mg-alone, relative to placebo.
The WHI Memory Study (WHIMS) estrogen-alone ancillary study of the WHI reported an increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 5.2 years of treatment with daily CE 0.625 mg-alone, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women.
In the absence of comparable data, these risks should be assumed to be similar for other doses of CE and other dosage forms of estrogens.
Estrogens with or without progestins should be described at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [59].

2) Estrogen Plus Progestin Therapy

Cardiovascular Disorders and Probable Dementia

Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia.
The WHI estrogen plus progestin substudy reported increased risks of DVT, pulmonary embolism, stroke and myocardial infarction in postmenopausal women (50 to 79 years of age) during 5.6 years of treatment with daily oral CE 0.625 mg combined with medroxyprogesterone acetate (MPA) 2.5 mg, relative to placebo.
The WHIMS estrogen plus progestin ancillary study of the WHI reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with daily CE 0.625 mg combined with MPA 2.5 mg, relative to placebo. It is unknown whether this finding applies to younger postmenopausal women [59].

3) Estradiol Cypionate

a) Intramuscular (Oil)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is currently no evidence that the use of "natural" estrogens results in a different endometrial risk profile than "synthetic" estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens with and without progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen-alone therapy.

Other doses of conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [55].

4) Estradiol Valerate

a) Intramuscular (Oil)

1) Estrogens Increase the Risk of Endometrial Cancer

Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses.

2) Cardiovascular and Other Risks

Estrogens and progestins should not be used for the prevention of cardiovascular disease.

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo.

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy.

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman [58].

REMS

No results available

Drug Interactions (single)

Drug-Drug Combinations

Abametapir

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Avoid use of CYP3A4 substrates within 2 weeks after application of abametapir. If this is not feasible, avoid use of abametapir[230].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid use of CYP3A4 substrates within 2 weeks after application of abametapir. If this is not feasible, avoid use of abametapir[230].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by abametapir

Amifampridine

1) Interaction Effect: increased risk of seizures
2) Summary: Concomitant use of amifampridine and this drug may increase the risk of seizures. Consider this risk if these agents are to be used concomitantly[364].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of amifampridine and this drug may increase the risk of seizures. Consider this risk if these agents are to be used concomitantly[364].
7) Probable Mechanism: unknown

Amiodarone

1) Interaction Effect: increased hormonal contraceptive exposure
2) Summary: The concomitant use of hormonal contraceptives (CYP3A4 substrates) and amiodarone, a CYP3A4 inhibitor and substrate[445], may increase the exposure of the hormonal contraceptive. If amiodarone is used concomitantly with hormonal contraceptives, monitor for adverse effects related to the hormonal contraceptive.
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: If hormonal contraceptives (CYP3A4 substrates) are used concomitantly with amiodarone, a CYP3A4 inhibitor and substrate[445], the oral contraceptive exposure may be increased. If amiodarone is used concomitantly with hormonal contraceptives, monitor for adverse effects related to the hormonal contraceptive.

7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism of the hormonal contraceptive by amiodarone

Amitriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily.

Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Amoxapine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

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mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Amoxicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Amoxicillin may alter intestinal flora, possibly leading to lower estrogen reabsorption and decreased oral combination contraceptive efficacy[354]. Concomitant use has been associated with unintended pregnancies and menstrual changes [356][357] [358]. However, systemic exposure to ethinyl estradiol/etonogestrel was not different when the vaginal ring was used with or without a 10-day course of amoxicillin during a randomized, crossover study (n=15) [355]. Furthermore, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins.. The OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If a 1% to 3% contraceptive failure rate is unacceptable, recommend an additional form of contraception [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of amoxicillin and combination contraceptives may result in decreased contraceptive efficacy[354]; however, significant differences in contraceptive failure rates were not demonstrated during a study of oral contraceptives with or without antibiotics [183] and no significant difference in exposure was observed with the use of the vaginal ring with or without amoxicillin [355]. If a typical failure rate of 1% to 3% is a concern for the patient, consider additional or alternative forms of birth control.
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) Systemic exposure of ethinyl estradiol/etonogestrel with use of the vaginal ring contraceptive was not affected by concomitant use of amoxicillin in a randomized, 2-way crossover study in healthy women volunteers (n=15). Following synchronization of menstrual cycles by 21 to 28 days and a 7-day ring-free period, volunteers received the vaginal ring for 21 days with or without amoxicillin 875 mg orally twice daily for 10 days (mean age, 29.9 +/- 5.8 years). After a 7-day ring-free washout period, subjects crossed over to the opposite treatment arm. With administration of the vaginal ring alone, the mean AUC of ethinyl estradiol, measured at 12 hours, day 9 to 10, day 10, and day 21, was 0.328 +/- 0.092 nanograms x hr/mL, 0.266 +/- 0.0874 nanograms x hr/mL, 5.86 +/- 1.77 nanograms x hr/mL, and 11.7 +/- 3.86 nanograms x hr/mL, respectively. With administration of the ring plus amoxicillin, the mean AUC of ethinyl estradiol was 0.328 +/- 0.0757 nanograms x hr/mL, 0.252 +/- 0.0935 nanograms x hr/mL, 5.49 +/- 1.67 nanograms x hr/mL, and 11.3 +/- 3.57 nanograms x hr/mL, respectively. The AUC interaction/control ratio (ring with amoxicillin to ring alone) also showed absence of drug interaction. At 12 hours, day 9 to 10, day 10, and day 21, the interaction/control ratio was 1.01 (90% CI, 0.87 to 1.18), 0.96 (90% CI, 0.84 to 1.09), 0.95 (90% CI, 0.85 to 1.06), and 0.98 (90% CI, 0.88 to 1.09), respectively. The etonogestrel plasma concentrations and interaction/control ratio demonstrated similar findings at all time points [355].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial

difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Ampicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. Another study showed concurrent ampicillin administration did not to diminish the effectiveness of the oral contraceptive studied [184].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) In a study of 11 regularly menstruating women, ages 21 to 39, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times/day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [184].

Amprenavir

1) Interaction Effect: decreased serum concentrations of amprenavir and loss of contraceptive efficacy
2) Summary: A loss of virologic response and possible resistance to amprenavir may occur when hormonal contraceptives (containing ethinyl estradiol/norethindrone) are used concomitantly. Alternate methods of non-hormonal contraception are recommended[231]. Significant changes (increase and decrease) in the mean AUCs of the estrogen and progestin may occur with concomitant administration of protease inhibitors [232]. Concomitant administration of ethinyl estradiol/norethindrone 0.035 mg/1 mg for one cycle and amprenavir 1200 mg twice daily for 28 days in 10 patients resulted in a decrease in AUC by 22% and a decrease minimum plasma concentration (Cmin) by 20% [233].

3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Those taking amprenavir should be instructed not to use hormonal contraceptives because some oral contraceptives (containing ethinyl estradiol/norethindrone) have been found to decrease the concentration of amprenavir. Likewise, concomitant use of oral contraceptives with protease inhibitors may result in increases or decreases of estrogen and progestin serum drug levels.
7) Probable Mechanism: induction of contraceptive metabolism

Apalutamide

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as apalutamide, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of apalutamide [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as apalutamide, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of apalutamide[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by apalutamide
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Aprepitant

1) Interaction Effect: reduced efficacy of contraceptives
2) Summary: Concomitant use of aprepitant or fosaprepitant with hormonal contraceptives may result in decreased contraceptive efficacy. Studies have demonstrated a significant decrease in the AUC and minimum concentration of ethinyl estradiol and norethindrone with concomitant administration. Patients should be advised to use an alternative or back-up method of contraception during therapy and for 1 month after the last dose[342].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving aprepitant or fosaprepitant, alternative or back-up methods of contraception should be used during treatment and for 1 month after the last dose[342].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral aprepitant 100 mg was given once daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the ethinyl estradiol AUC decreased by 43%, and the norethindrone AUC decreased by 8%. In a separate study, a daily dose of a combination contraceptive containing ethinyl estradiol and norethindrone was administered for 21 days. On day 8, oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg were administered. On days 9 and 10, oral aprepitant 80 mg/day and dexamethasone 8 mg/day were given. On day 11, oral dexamethasone 8 mg was administered alone. The AUC of ethinyl estradiol decreased 19% and there was no change in the norethindrone AUC on day 10. The minimum concentration of ethinyl estradiol decreased as much as 64% and norethindrone decreased up to 60% during days 9 through 21 [342].

Armodafinil

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as armodafinil, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of armodafinil [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as armodafinil, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of armodafinil[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by armodafinil
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Artemether

1) Interaction Effect: reduced hormonal contraceptive plasma concentrations
2) Summary: Artemether is an inducer of CYP3A4 isozymes, and both artemether and lumefantrine are primarily metabolized by CYP3A4. Although not formally studied, concomitant use of artemether/lumefantrine and a hormonal contraceptive may reduce the effectiveness of the hormonal contraceptive. Therefore, patients should be advised to use an additional non-hormonal contraceptive when artemether/lumefantrine and a hormonal contraceptive are coadministered[331].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of artemether/lumefantrine and a hormonal contraceptive may decrease the hormonal contraceptive plasma concentrations. Therefore, advise patients to use an additional non-hormonal method of birth control when artemether/lumefantrine and a hormonal contraceptive are coadministered[331].
7) Probable Mechanism: induction of hormonal contraceptive metabolism by artemether

Atazanavir

1) Interaction Effect: an increase in exposure to the combination contraceptive
2) Summary: Concomitant use of atazanavir (with/without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive has resulted in a substantial increase in progesterone exposure and both increases and decreases in ethinyl estradiol exposure[307] In a study in healthy HIV-negative women (n=20), coadministration of atazanavir/ritonavir and an oral contraceptive containing ethinyl estradiol and norgestimate resulted in increased exposure of norgestimate and decreased exposure of ethinyl estradiol; however, the reduction in ethinyl estradiol levels was not expected to decrease contraceptive efficacy. Results of this study indicate that an oral contraceptive containing at least 30 mcg of ethinyl estradiol would be sufficient to maintain adequate exposure of ethinyl estradiol [308]. Use caution when prescribing oral contraceptives in patients receiving atazanavir. A combination oral contraceptive with the appropriate dose of ethinyl estradiol (at least 35 mcg with concomitant atazanavir plus ritonavir and no more than 30 mcg with concomitant atazanavir) is recommended. An alternate method of contraception is recommended when the patient is using other hormonal contraceptives (eg, patch, vaginal ring, injection), oral contraceptives that contain progestins other than norethindrone or norgestimate, or oral contraceptives that contain less than 25 mcg of ethinyl estradiol, as studies have not been conducted [307].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable

6) Clinical Management: Use caution when coadministering atazanavir (with or without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive as concomitant use has resulted in substantial increases in progesterone exposure and both reductions and elevations in ethinyl estradiol exposure[307][308]. If an oral contraceptive is administered with atazanavir plus ritonavir, the oral contraceptive should contain at least 35 mcg of ethinyl estradiol. If administered with atazanavir alone, the oral contraceptive should contain no more than 30 mcg of ethinyl estradiol. An alternative method of contraception is recommended if atazanavir (with or without ritonavir) is being considered for a patient who is using other hormonal contraceptives (eg, patch, vaginal ring, or injection), oral contraceptives that contain progestins other than norethindrone or norgestimate, or oral contraceptives that contain less than 25 mcg of ethinyl estradiol, as studies have not been conducted in these cases [307].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant use of atazanavir (with or without ritonavir) and a combination ethinyl estradiol/norgestimate or norethindrone oral contraceptive has resulted in substantial increases in progesterone exposure. Long-term effects of increases in progestational agent bioavailability are not known and could result in an increased risk of insulin resistance, dyslipidemia, and acne. Concomitant use of atazanavir 300 mg plus ritonavir 100 mg once daily with an ethinyl estradiol/norgestimate oral contraceptive resulted in decreased ethinyl estradiol and increased norgestimate exposure. Coadministration of atazanavir 400 mg once daily with an ethinyl estradiol/norethindrone contraceptive resulted in increased exposure to both ethinyl estradiol and norethindrone. No studies have been conducted on the concomitant use of atazanavir (with or without ritonavir) with other hormonal contraceptives (eg, patch, vaginal ring, or injection), with oral contraceptives that contain progestins other than norethindrone or norgestimate, or with oral contraceptives that contain less than a 25-mcg dose of ethinyl estradiol [307].

b) In a pharmacokinetic study in healthy HIV-negative women (n=20; mean age 28 years), coadministration of atazanavir/ritonavir and an oral contraceptive containing ethinyl estradiol (EE) and norgestimate (NGM) resulted in increased exposure of norgestimate and decreased exposure of ethinyl estradiol; however the reduction in ethinyl estradiol levels was not expected to decrease contraceptive efficacy. In this open-label, three-period study, participants received in the lead-in period a full 28-day cycle of Ortho Tri-CyClen(R) (EE 0.035 mg plus NGM 0.18/0.215/0.25 mg). This was followed by period 1 in which participants received a second cycle of daily Ortho Tri-CyClen(R) (treatment A). Participants with satisfactory safety assessments began a third cycle on day 29 of Ortho Tri-Cyclen LO(R) (EE 0.025 mg plus NGM 0.18/0.215/0.25 mg) coadministered with atazanavir 300 mg/ritonavir 100 mg once daily for 14 days (treatment B). A dose normalization was performed to account for the different EE doses in the 2 treatments and to estimate the magnitude of reduction in EE exposures. Coadministration of atazanavir/ritonavir plus dose-normalized EE/NGM resulted in geometric mean reductions in EE of 16%, 19%, and 37% for Cmax, AUC, and Cmin, respectively. For NGM exposure, Cmax, AUC, and Cmin were increased by 68%, 85%, and 102%, respectively. Results of this study indicate that an oral contraceptive containing at least 30 mcg of EE would be sufficient to maintain adequate exposure of EE. Since the contraceptive efficacy of Ortho Tri-Cyclen(R) is primarily dependent on progestin, the contraceptive efficacy was not expected to be compromised [308].

Bacampicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186][443]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of bacampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183]. Another study indicated that alternative contraceptive methods are not required during combined therapy, as ampicillin had no significant effect on plasma levels of oral contraceptives [437].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) Concomitant ampicillin and oral contraceptive therapy has been reported to result in menstrual irregularity and unplanned pregnancy, as well as reduced urinary excretion of endogenous estrogens [438][439][440][441][442].

c) Ampicillin had no significant effect on plasma levels of ethinyl estradiol, levonorgestrel, follicle-stimulating hormone, or progesterone when given in combination with oral contraceptives. The authors indicate that alternative contraceptive methods are not required during combined therapy [437].

d) The interaction between oral contraceptives and ampicillin may be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [443].

e) In a study of 11 regularly menstruating women, ages 21 to 39 years, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times a day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [444].

Belzutifan

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of belzutifan and a hormonal contraceptive may decrease plasma concentrations of the contraceptive leading to contraceptive failure or an increase in breakthrough bleeding. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with belzutifan and for 1 week after the last dose[382].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of belzutifan and a hormonal contraceptive may decrease plasma concentrations of the contraceptive leading to contraceptive failure or an increase in breakthrough bleeding. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with belzutifan and for 1 week after the last dose[382].
7) Probable Mechanism: induction of CYP450-mediated hormonal contraceptive metabolism by belzutifan

Betamethasone

1) Interaction Effect: increased corticosteroid effects
2) Summary: Combination oral contraceptives have been demonstrated to alter the pharmacokinetics of hydrocortisone and prednisone, thereby potentially enhancing therapeutic effect. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease 2- to 5-fold[297][298][299].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients should be monitored for increased corticosteroid effects; the betamethasone dose may need to be reduced.
7) Probable Mechanism: inhibition of corticosteroid metabolism by the combination contraceptive

Bexarotene

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Bexarotene can potentially increase the rate of metabolism and reduce plasma concentrations of other substrates metabolized by CYP3A4, including hormonal contraceptives. If concomitant use cannot be avoided, two reliable forms of contraception are strongly recommended, one of which should be non-hormonal[359].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: During administration of bexarotene, the use of hormonal contraceptives is not recommended. If concurrent administration cannot be avoided, it is strongly recommended that one of the two reliable forms of contraception be non-hormonal.
7) Probable Mechanism: induction of metabolic enzymes by bexarotene

Bosentan

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of bosentan (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when coadministered. Coadministration of bosentan and a combination oral hormonal contraceptive decreased mean norethindrone levels and ethinyl estradiol levels as much as 56% and 66% in individual patients. Do not use a hormonal contraceptive as the sole means of contraception[276] Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use a non-hormonal contraceptive back-up method during coadministration and for 28 days after discontinuing a CYP3A4 inducer [250].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of bosentan (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may not be reliable when coadministered. Do not use a hormonal contraceptive as the sole means of contraception[276]. Use a non-hormonal back-up contraceptive method during coadministration and for 28 days after discontinuing a CYP3A4 inducer [250].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Coadministration of bosentan and a combination oral hormonal contraceptive decreased mean norethindrone levels by 14% and ethinyl estradiol levels by 31% in a study. However, decreases in exposure were as high as 56% and 66%, in individual patients [276].

Bupropion

1) Interaction Effect: increased risk of seizures
2) Summary: BuPROPion is associated with a dose-related risk of seizures and when used concomitantly with other seizure threshold-lowering agents there is an increased risk. Use extreme caution when coadministering bupropion with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial buPROPion dose and increase the dose gradually. If a patient experiences a seizure, discontinue buPROPion and do not reinitiate[424][425].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: BuPROPion is associated with a dose-related risk of seizures and when used concomitantly with other seizure threshold-lowering agents there is an increased risk. Use extreme caution when coadministering buPROPion with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial buPROPion dose and increase the dose gradually. If a patient experiences a seizure, discontinue buPROPion and do not

reinitiate[424][425].
7) Probable Mechanism: additive lowering of the seizure threshold

Carbamazepine

1) Interaction Effect: a decrease in plasma concentrations of hormonal contraceptives and contraceptive failure and breakthrough bleeding
2) Summary: Carbamazepine is a strong CYP3A4 inducer and concomitant use with hormonal contraceptives may significantly decrease exposure and contraceptive efficacy. Coadministration of carbamazepine and oral ethinyl estradiol/norethindrone significantly decreased AUC and increased clearance of the contraceptive in a randomized study[179]. Concomitant use of a CYP3A4 inducer disproportionally increased unplanned pregnancy rate with oral and implanted contraceptives, but not with intrauterine devices or intravaginal rings [177]. Because breakthrough bleeding and significantly increased pregnancy rates have been reported with coadministration, consider an alternative to carbamazepine, or employ alternative or backup contraceptive methods [175] during coadministration and for at least 28 days after discontinuation of carbamazepine [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of carbamazepine (a strong CYP3A4 inducer) with hormonal contraceptives (oral and subdermal implant) has resulted in breakthrough bleeding and pregnancies. Consider an alternative to carbamazepine, or employ alternative or backup contraceptive methods[175] during coadministration and for at least 28 days after discontinuation of carbamazepine [176].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a study in healthy women (N=10 evaluable; 18 to 45 years) using an etonogestrel implant for 13 to 34 months, 3 weeks of coadministered carbamazepine titrated up to 300 mg twice daily resulted in a significant median 61% decrease in etonogestrel levels from 158 picogram (pg)/mL (range, 127.9 to 347.3 pg/mL) to 50.8 pg/mL (range 39.4 to 202.3 pg/mL). In 8 women, the etonogestrel level was below the threshold for ovulatory suppression (less than 90 pg/mL) after carbamazepine coadministration. There was no significant change in the number of ovarian follicle-like structures or endometrial thickness. No pregnancies were reported during the study period [178].

c) A randomized, open-label, five-group study concluded that carbamazepine significantly decreased the mean AUC and Cmax values of oral contraceptives containing ethinyl estradiol and norethindrone. In two, 28-day cycles, five groups of female subjects received oral doses of ethinyl estradiol and norethindrone (Ortho-Novum 1/35(R)) alone in the first cycle and then in combination with topiramate or carbamazepine during the second cycle. When carbamazepine 600 mg/day was coadministered with ethinyl estradiol and norethindrone, a significant 42% and 58% decrease was observed in the mean AUC of both oral contraceptives, respectively, as was the mean Cmax by 19.2%. However, oral clearance significantly increased in both contraceptives by 127% and 69%, respectively. Coadministration of topiramate at daily doses for nonobese (50 mg, 100 mg, and 200 mg) and obese (200 mg) women resulted in a nonsignificant change in the AUC of ethinyl estradiol by -12%, +5%, -11% and -9%, respectively, when compared with the oral contraceptive alone. Norethindrone results were similar with plasma levels and AUC not significantly changed [179].

d) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme inducing anticonvulsant; however, if unplanned pregnancy is a special concern, a moderate dose formulation (50 mcg ethinyl estradiol) should be

considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme inducing anticonvulsants are discontinued in women receiving moderate or high-dose contraceptives [180].

e) Carbamazepine reduced the AUC of ethinyl estradiol by 6% to 60% in 4 women taking carbamazepine 300 to 600 mg daily within 8 to 12 weeks of initiation of therapy. Norgestrel AUCs were also significantly reduced to 29% to 57% of baseline. The authors suggest that breakthrough bleeding can be controlled for most women with use of oral contraceptives containing 80 to 100 mcg ethinyl estradiol [181].

f) Accidental pregnancy occurred in a 20-year-old epileptic who was using phenytoin 400 mg daily plus carbamazepine 400 mg daily. The plasma concentration of levonorgestrel in this patient was very low (107 to 120 picograms (pg)/mL) when compared with controls (325 +/- 135 pg/mL). Carbamazepine appears to decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsant therapy [182].

Carbenicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of carbenicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefaclor

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major

4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefaclor and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefadroxil

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefadroxil and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefdinir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that

cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefdinir and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefditoren

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, multiple doses of cefditoren had no effect on the pharmacokinetics of ethinyl estradiol [416]. Additionally, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. In addition, cefditoren given in multiple doses had no effect on the pharmacokinetics of ethinyl estradiol (the estrogenic component in most contraceptive combinations) [416].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics; however, multiple doses of cefditoren had no effect on the pharmacokinetics of ethinyl estradiol[416] Additionally, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics

for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefixime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives, which could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefixime and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefpodoxime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefpodoxime and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].

7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefprozil

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefprozil and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Ceftazidime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Similar to other antibiotics, ceftazidime may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[330]. Patients should be advised to use an additional form of birth control if these agents are used concomitantly.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceftazidime and a combination oral estrogen/progesterone-containing contraceptive may result in decreased contraceptive effectiveness[330]. Counsel patients to use an additional form of birth control if these agents are used concomitantly.

7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption

Ceftibuten

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceftibuten and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cefuroxime

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of cefuroxime and combination contraceptives may result in decreased contraceptive efficacy . The mechanism of interaction is thought that cephalosporins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives[344] resulting in unintended pregnancies and menstrual changes [185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cefuroxime and combination contraceptives may result in decreased contraceptive efficacy[344]; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including cephalosporins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up

survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cenobamate

1) Interaction Effect: reduced hormonal contraceptive plasma concentrations and reduced contraceptive efficacy
2) Summary: Because of a potential for reduced efficacy, women should use additional or alternative non-hormonal birth control when used concomitantly with cenobamate (a CYP3A4 inducer)[290]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cenobamate and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive. Women should use additional or alternative non-hormonal birth control while taking cenobamate[290].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Ceritinib

1) Interaction Effect: increased exposure of CYP3A substrate
2) Summary: Concomitant use of ceritinib (a strong CYP3A inhibitor) and a CYP3A substrate may increase exposure of the substrate. Coadministration with midazolam (a sensitive CYP3A substrate) has resulted in an increase in the midazolam AUC by 5.4-fold and Cmax by 1.8-fold. Avoid use of sensitive CYP3A substrates and if other CYP3A substrates are coadministered, consider dose reductions of the CYP3A substrate[422].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ceritinib (a strong CYP3A inhibitor) and a CYP3A substrate may increase exposure of the substrate. Avoid use of sensitive CYP3A substrates and if other CYP3A substrates are coadministered, consider dose reductions of the CYP3A substrate[422].
7) Probable Mechanism: inhibition of CYP3A-mediated metabolism of drug by ceritinib
8) Literature Reports

a) Coadministration of a single dose of midazolam (a sensitive CYP3A substrate) following 3 weeks of ceritinib 750 mg daily under fasted conditions increased the midazolam AUC by 5.4-fold and Cmax by 1.8-fold compared to midazolam administered alone [422]

Clavulanic Acid

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Ticarcillin/clavulanic acid may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[345]. Concomitant use has been associated with unintended pregnancies and menstrual changes [346] [347] However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure

rate is unacceptable to the patient, an additional form of contraception should be recommended [183]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ticarcillin/clavulanic acid and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Clobazam

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Administration of clobazam, a CYP3A4 inducer, with hormonal contraceptives, which are CYP3A4 substrates, may decrease plasma concentrations of the contraceptives. During concurrent use and for 28 days following use of clobazam and hormonal contraceptives, effective additional non-hormonal forms of birth control should be used throughout clobazam therapy[281].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Administration of clobazam with hormonal contraceptives may decrease plasma concentrations of the contraceptive. During concurrent use and for 28 days following use of clobazam and hormonal contraceptives, effective use of additional non-hormonal forms of birth control is recommended[281].
7) Probable Mechanism: induction of CYP3A4-mediated hormonal contraceptive metabolism by clobazam

Clomipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients

taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Cloxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cloxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral

contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Colesevelam

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concurrent use of an oral contraceptive containing ethinyl estradiol/norethindrone and colesevelam was associated with decreased bioavailability of the oral contraceptive. If co-treatment with colesevelam and an oral contraceptive containing ethinyl estradiol/norethindrone is necessary, patients should take the contraceptive at least 4 hours prior to colesevelam[198].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: If concomitant use of colesevelam and an oral contraceptive containing ethinyl estradiol and norethindrone is necessary, patients should usually take the contraceptive at least 4 hours prior to colesevelam[198].
7) Probable Mechanism: reduced absorption of contraceptive by nonspecific binding with colesevelam
8) Literature Reports

a) Concurrent administration of colesevelam in participants receiving an oral contraceptive containing ethinyl estradiol and norethindrone significantly reduced the exposure of the contraceptive. Coadministration of colesevelam 3.75 g with ethinyl estradiol 0.035 mg/norethindrone 1 mg resulted in reductions of 24% in both ethinyl estradiol AUC and Cmax, and a 1% and 20% reduction in norethindrone AUC and Cmax, respectively. When the combination contraceptive was administered 1 hour prior to colesevelam, the AUC and Cmax were changed by -18% and -1%, respectively, for ethinyl estradiol, and by 5% and -3%, respectively, for norethindrone. Administration of the combination contraceptive 4 hours prior to colesevelam, led to a -12% change in ethinyl estradiol AUC, and changes of 6% and 7% in norethindrone AUC and Cmax, respectively [198].

Conivaptan

1) Interaction Effect: increased exposure of CYP3A substrate
2) Summary: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. Conivaptan increased the AUC of CYP3A substrates midazolam, simvastatin, and amlodipine. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[386].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of conivaptan (strong CYP3A inhibitor) with drugs eliminated primarily by CYP3A-mediated metabolism, as this may result in increased exposure of the CYP3A substrate. The CYP3A substrate may be initiated no sooner than 1 week after completion of conivaptan therapy[386].
7) Probable Mechanism: inhibition of CYP3A-mediated substrate metabolism by conivaptan
8) Literature Reports

a) The strong CYP3A inhibitor conivaptan 40 mg/day IV increased the AUC of midazolam, a CYP3A substrate, by approximately 100% with a 1-mg IV dose and by 200% with a 2-mg oral dose [386].

b) Conivaptan 30 mg/day IV tripled the AUC of simvastatin, a CYP3A substrate [386].

c) Conivaptan 40 mg orally twice daily doubled the AUC and half-life of amlodipine, a

CYP3A substrate [386].

Cyclacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of cyclacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Cyclosporine

1) Interaction Effect: an increased risk of cycloSPORINE toxicity (renal dysfunction, cholestasis, paresthesias)
2) Summary: Concurrent use of cycloSPORINE and combination contraceptives has resulted in higher cycloSPORINE concentrations[335] according to several case reports [336][337]. These reports have demonstrated that androgens, estrogens, and progestins increase cycloSPORINE concentrations, probably through reduced hepatic cycloSPORINE metabolism [338][339][336].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: When possible, this combination should be avoided. If cycloSPORINE and combination oral contraceptives are used concurrently, cycloSPORINE serum levels and the patients clinical response should be monitored carefully.
7) Probable Mechanism: decreased cycloSPORINE metabolism
8) Literature Reports

a) Concomitant administration of cycloSPORINE and an oral contraceptive doubled plasma cycloSPORINE concentrations compared with baseline in a 32-year-old woman. The oral contraceptive contained levonorgestrel 150 mcg and ethinyl estradiol 30 mcg. The level declined after the preparation was discontinued, but the same sequence occurred on rechallenge [333].

b) Norethindrone was associated with increased cycloSPORINE levels in a 15-year-old female renal transplant patient. The cycloSPORINE level decreased after norethindrone was discontinued [334].

Dabrafenib

1) Interaction Effect: decreased plasma concentrations and loss of efficacy of the hormonal contraceptive
2) Summary: Concomitant use of dabrafenib and hormonal contraceptives could decrease the plasma concentrations of the contraceptives and render them ineffective. Because dabrafenib can cause fetal harm, advise patient to use nonhormonal forms of

contraception during dabrafenib therapy and for 4 weeks after treatment. If concomitant use is unavoidable, monitor for loss of efficacy of the hormones[363].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of dabrafenib and hormonal contraceptives could decrease the plasma concentrations of the contraceptives and render them ineffective. Because dabrafenib can cause fetal harm, advise patient to use nonhormonal forms of contraception during dabrafenib therapy and for 4 weeks after treatment. If concomitant use is unavoidable, monitor for loss of efficacy of the hormones[363].
7) Probable Mechanism: altered metabolism of contraceptives by dabrafenib

Darunavir

1) Interaction Effect: reduced exposure to hormonal contraceptives and reduced hormonal contraceptive efficacy
2) Summary: Coadministration of darunavir/ritonavir with estrogen-based contraceptives led to significantly decreased plasma concentrations of ethinyl estradiol and norethindrone in 1 study[236]. Consider supplementary or non-hormonal contraception options for women of childbearing potential during darunavir therapy, as no data are available to provide guidance on coadministration of darunavir with oral or other hormonal contraceptives [235].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Consider supplementary or non-hormonal contraception options for women of childbearing potential during darunavir therapy, as no data are available to provide guidance on coadministration of darunavir with oral or other hormonal contraceptives[235].
7) Probable Mechanism: unknown
8) Literature Reports

a) An open-label, randomized, crossover study in 19 healthy, HIV-negative females aged 18 to 43 years (median, 34 years) revealed that coadministration of ethinyl estradiol/norethindrone with darunavir/ritonavir resulted in significantly lower exposure and mean plasma concentrations of ethinyl estradiol and norethindrone. Compared to administration of ethinyl estradiol and norethindrone alone, coadministration with darunavir/ritonavir led to decreases in ethinyl estradiol Cmin, Cmax, and AUC of 62%, 32%, and 44%, respectively. Similarly, norethindrone Cmin, Cmax, and AUC decreased by 30%, 10%, and 14%, respectively. There were no significant changes in darunavir or ritonavir pharmacokinetic parameters [236].

Dehydroepiandrosterone

1) Interaction Effect: increased risk of estrogenic adverse effects
2) Summary: Combining dehydroepiandrosterone (DHEA) with estrogen may result in symptoms of estrogen excess. DHEA has increased endogenous estrogen levels in postmenopausal women[283]. Pre- and post-menopausal women have effective enzymatic systems for the biotransformation of DHEA to C-19 and C-18 sex steroids [283], suggesting that increased estrogen levels may occur in all women regardless of menopausal status.
3) Severity: minor
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dehydroepiandrosterone (DHEA) and estrogen is not recommended. Monitor for symptoms and adverse effects of estrogen excess in those patients who elect to combine therapies. Such symptoms include (but are not limited to) nausea, headache, intolerance to contact lenses, insomnia, chorea, cholasma, colitis, acute breakthrough or withdrawal bleeding, changes in menstrual flow, leukorrhea, and pancreatitis.
7) Probable Mechanism: additive estrogenic effect since dehydroepiandrosterone is enzymatically converted into C-19 and C-18 sex steroids
8) Literature Reports

a) Estrone and estradiol levels increased to two-times the basal value following four weeks of dehydroepiandrosterone (DHEA) 400 milligrams (mg) four times daily for 28 days in six postmenopausal women in a double-blind, placebo-controlled, crossover study. Subjects received DHEA or placebo for 28 days, followed by a 2-week washout period, then crossed over to the other treatment (DHEA or placebo). Estrone increased from 58.7 +/- 11.0 to 167.4 +/- 66.6 picomole/liter (pmol/L) and estradiol increased from 36.7 +/- 3.7 to 121.1 +/- 25.7 pmol/L. This corresponds to a maximal percent change of 214 +/- 67 percent and 181 +/- 29 percent for estrone and estradiol, respectively [282].

Desipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical

importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased

clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Dexamethasone

1) Interaction Effect: decreased plasma levels of hormonal contraceptive and prolonged dexamethasone effect
2) Summary: Concomitant use of dexamethasone and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of dexamethasone[176]. Combination contraceptives have altered the pharmacokinetics of hydrocortisone and prednisone, potentially enhancing the therapeutic effect. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease 2- to 5-fold [291][292][293]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dexamethasone and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of dexamethasone[176]. Combination contraceptives have altered the pharmacokinetics of hydrocortisone and prednisone, potentially enhancing the therapeutic effect [291][292][293].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism; decreased dexamethasone clearance
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Diazepam

1) Interaction Effect: diazepam toxicity (CNS depression, hypotension)
2) Summary: Combination contraceptives may decrease the metabolism of diazepam, alprazolam, triazolam and chlordiazepoxide. Combination contraceptives may increase the effect of diazepam on psychomotor performance[252][253][254]. Therefore, diazepam dosage reduction may be necessary in patients receiving both diazepam and oral contraceptive steroids. Patients should be monitored for the possibility of increased clinical effects although a direct relation between diazepam's plasma concentration and its clinical effectiveness has not clearly been established [251].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent hormonal contraceptives and diazepam for an increased response to the benzodiazepine.
7) Probable Mechanism: inhibition of oxidative diazepam metabolism by the contraceptive
8) Literature Reports

a) The long term use of low-dose (less than 50 mcg) estrogen-containing oral contraceptives has been found to impair diazepam clearance and significantly increase the elimination half-life of diazepam. Eight healthy women receiving low-dose estrogen-containing contraceptives for more than 3 months and a control group of 8 patients not taking oral contraceptives received a single dose of diazepam 10 mg given by intravenous infusion over 15 to 30 seconds. Venous blood samples were drawn periodically for up to 7 days following infusion. No difference was observed in diazepam clearance or protein binding between the two groups. However, apparent elimination half-life of diazepam was significantly increased in the contraceptive patients compared with the control patients (69 +/- 9 hours vs 47 +/- 4 hours; p less than 0.05). Total metabolic clearance was also significantly reduced with diazepam plus contraceptives compared with diazepam alone (0.27 +/- 0.02 mL/minute/kg vs 0.45 +/- 0.04 mL/minute/kg; p less than 0.001) [251]. Although these results refer only to intravenous

administration of diazepam, it is likely that experience with oral administration of diazepam would be similar since diazepam is rapidly absorbed and 100% bioavailable.

b) Although the mechanism of the diazepam/estrogen-containing oral contraceptive interaction is not clear, it may be related to inhibition of the cytochrome P450 system-mediated diazepam metabolism by the estrogen. This would subsequently reduce the oxidation of diazepam in the liver [251].

Dicloxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of dicloxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Dicumarol

1) Interaction Effect: decreased anticoagulant effectiveness
2) Summary: Concomitant combination contraceptive and dicumarol therapy may result in diminished or enhanced dicumarol activity. Combination contraceptives may increase Factor VII, IX, X and XII while decreasing Factor III[190][191].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: In patients receiving oral anticoagulant therapy, the prothrombin time ratio or INR should be closely monitored with the addition or withdrawal of treatment with combination contraceptives, and should be reassessed periodically during concurrent therapy. Adjustments of the dicumarol dose may be necessary in order to maintain the desired level of anticoagulation.
7) Probable Mechanism: unknown

Donepezil

1) Interaction Effect: reduced seizure threshold
2) Summary: Seizure threshold lowering effects have been associated with donepezil[385]. Use extreme caution when prescribing donepezil with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Seizure threshold lowering effects have been associated with donepezil[385]. Use extreme caution when prescribing donepezil with drugs that lower seizure threshold (eg, antipsychotics, antidepressants, theophylline, systemic

corticosteroids). Begin treatment with a low initial dose and increase dose gradually.
7) Probable Mechanism: unknown

Dothiepin

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily.

Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Doxepin

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120

mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Doxycycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of doxycycline and oral combination contraceptives (OC) may reduce contraceptive efficacy because tetracyclines alter intestinal flora which, in turn, may alter enterohepatic circulation of the contraceptive[204]. In a review of 163 cases of OC failure in reliable pill takers, 23% were attributed to concurrent use of antibiotics; 4% included a concurrent tetracycline [361]. Absence of interaction was shown in a study (N=15) of concurrent use of ethinyl estradiol/etonogestrel vaginal ring contraceptive and doxycycline [355]. A retrospective review (N=356) showed no difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines. Failure rate did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to a patient, an additional form of contraception is recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of doxycycline and combination oral contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Absence of interaction was also shown in a study (N=15) of concurrent use of ethinyl estradiol/etonogestrel vaginal ring combination contraceptive and doxycycline [355]. A retrospective review (N=356) showed no difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception is recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) Systemic exposure of ethinyl estradiol/etonogestrel with use of the vaginal ring contraceptive was not affected by concomitant use of doxycycline in a randomized, 2-way crossover study in healthy volunteers (n=15). Following synchronization of menstrual cycles by 21 to 28 days and a 7-day ring-free period, volunteers received the vaginal ring for 21 days with or without doxycycline 200 mg orally on day 1 then, 100 mg daily for 10 days. After a 7-day ring-free washout period, subjects crossed over to the opposite treatment arm. With administration of the vaginal ring alone, the mean AUC of ethinyl estradiol, measured at 24 hours, day 9 to 10, day 10, and day 21, was 0.638 nanograms x hr/mL, 0.538 nanograms x hr/mL, 5.51 nanograms x hr/mL, and 11.2 nanograms x hr/mL, respectively. With administration of the ring plus doxycycline, the mean AUC of ethinyl estradiol was 0.6 nanograms x hr/mL, 0.512 nanograms x hr/mL, 5.35 nanograms x hr/mL, and 10.9 nanograms x hr/mL, respectively. The AUC interaction/control ratio (ring with doxycycline to ring alone) also showed absence of drug interaction. At 24 hours, day 9 to 10, day 10, and day 21, the interaction/control ratio was 0.95, 0.92, 0.95, and 0.95, respectively. The etonogestrel plasma concentrations and interaction/control ratio demonstrated similar findings at all time points [355].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure

rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

c) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low-dose estrogen oral contraceptives for a total period of 71 women-years. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

d) The effect of doxycycline on serum levels of estradiol and norethindrone was studied in 24 women taking oral contraceptives. The subjects had been taking an oral contraceptive containing 1 mg norethindrone and 35 mcg ethinyl estradiol for at least 2 months prior to the study. Administration of doxycycline 100 mg daily for 7 days starting on day 14 of the 28-day cycle had no significant effect on the average serum levels of estradiol and norethindrone, however, there was substantial variability. Progesterone levels indicated that ovulation had not occurred in any of these subjects [360]. Although no significant effect was observed in this study, antibiotics may have an effect in patients with unusually low oral contraceptive hormone levels.

e) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

f) The interaction between oral contraceptives and tetracyclines has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

Efavirenz

1) Interaction Effect: loss of contraceptive efficacy
2) Summary: Coadministered efavirenz may result in increased or reduced serum concentrations of hormonal contraceptives[391]. In healthy women, coadministration of efavirenz and an oral contraceptive (ethinyl estradiol/norgestimate) did not increase ethinyl estradiol exposure; however, exposure to the progestin components (norgestimate and levonorgestrel) was significantly decreased [390]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Contraceptive failure with etonogestrel in patients receiving efavirenz has been reported. A reliable method of barrier contraception is indicated when efavirenz and a hormonal contraceptive are coadministered. Continue adequate contraceptive measures for 12 weeks upon discontinuation of efavirenz [389].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Based on clinical studies, decreased progestin levels may be expected if efavirenz is coadministered with hormonal contraceptives including oral contraceptives, implants, and injections. Advise patients to use a reliable method of barrier contraception when efavirenz and a hormonal contraceptive are coadministered. Continue adequate contraceptive measures for 12 weeks upon discontinuation of efavirenz[389].
7) Probable Mechanism: altered metabolism of the hormonal contraceptive
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to

all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a pharmacokinetic study in healthy HIV-negative women (n=28; mean age 26 years), coadministration of efavirenz (600 mg daily) and an oral contraceptive containing ethinyl estradiol (EE) and norgestimate (NGM) resulted in similar exposure for ethinyl estradiol to that seen when given alone; however, exposure to the progestin components (norgestimate and levonorgestrel) was significantly decreased. In this open-label, three-period, four-treatment study, participants received in period 1 (treatment A) Ortho Tri-Cyclen LO(R) (EE 0.025 mg plus NGM 0.18 mg on days 1 to 7 (phase 1); EE 0.025 mg plus NGM 0.215 mg on days 8 to 14 (phase 2); and EE 0.025 mg plus NGM 0.25 mg on days 15 to 21 (phase 3)). This was followed by period 2 (days 29 to 56) where participants with acceptable baseline safety assessments received a full cycle of Ortho-CyClen(R) (EE 0.035 mg plus NGM 0.25 mg (phases 1 to 3; treatment B)). Participants with satisfactory safety assessments began a second cycle of Ortho-CyClen(R) (days 57 to 77; period 3) coadministered with efavirenz 600 mg/day for 14 days (days 57 to 70; treatment C). Ethinyl estradiol pharmacokinetic parameters (Cmax, AUC, and Cmin) were not significantly different when efavirenz was given concurrently. However, norgestimate exposure was significantly decreased in the presence of efavirenz. The adjusted geometric means for Cmax, AUC, and Cmin were reduced by 46% (90% confidence interval (CI), 39% to 52%), 64% (90% CI, 62% to 67%), and 82% (90% CI, 79% to 85%), respectively. Post-hoc analysis also showed similar results with levonorgestrel exposure (adjusted geometric means for Cmax, AUC, and Cmin reduced by 80% to 86% in the presence of efavirenz) [390].

Elagolix

1) Interaction Effect: increased estrogen exposure, reduced progestin efficacy, and reduced elagolix efficacy
2) Summary: Concomitant use of elagolix 200 mg twice daily with an estrogen-containing contraceptive is not recommended as it may increase estrogen exposure and increase the risk of thromboembolic and vascular adverse events. Estrogen-containing contraceptives are also expected to decrease the efficacy of elagolix. Additionally, coadministration of elagolix and progestin-containing oral contraceptives may reduce contraceptive efficacy. In a study, coadministration of a single-dose of a combined oral contraceptive containing ethinyl estradiol and levonorgestrel following administration of elagolix 200 mg twice daily increased the ethinyl estradiol AUC by 2.18-fold and Cmax by 1.36-fold, and decreased the levonorgestrel AUC and Cmax by 27% and 3%, respectively. Progestin-containing intrauterine contraceptive systems have not been studied. Use effective non-hormonal contraception during treatment with elagolix and for 28 days after discontinuing therapy[247].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of elagolix 200 mg twice daily with an estrogen-containing contraceptive is not recommended as it may increase estrogen exposure and increase the risk of thromboembolic and vascular adverse events. Estrogen-containing contraceptives are also expected to decrease the efficacy of elagolix. Additionally, coadministration of elagolix and progestin-containing oral contraceptives may reduce contraceptive efficacy; progestin-containing intrauterine contraceptive systems have not been studied. Use effective non-hormonal contraception during treatment with elagolix and for 28 days after discontinuing therapy[247].
7) Probable Mechanism: unknown
8) Literature Reports

a) Coadministration of a single-dose of combined oral contraceptive (COC) (containing ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg) following administration of elagolix 200 mg twice daily for 15 days in 20 subjects increased the ethinyl estradiol AUC by 2.18-fold and Cmax by 1.36-fold compared to the COC alone. Additionally, levonorgestrel AUC and Cmax were decreased by 27% and 3%, respectively [247].

b) Coadministration of a combined oral contraceptive (COC) (containing ethinyl estradiol 35 mcg/triphasic norgestimate 0.18/0.215/0.25 mg) once daily together with elagolix 150 mg once daily in 21 subjects increased the ethinyl estradiol AUC by 1.3-fold and Cmax by 1.15-fold compared to the COC alone. Additionally, norelgestromin AUC and Cmax were decreased by 15% and 13%, and norgestrel by 8% and 11%, respectively [247].

Elvitegravir

1) Interaction Effect: altered contraceptive effectiveness and risk of side effects
2) Summary: Caution is advised when using elvitegravir as the combination product elvitegravir/cobicistat/emtricitabine/tenofovir in combination with hormonal contraceptives as this has resulted in a rise in norgestimate concentrations and a decrease in ethinyl estradiol concentrations. Increased progestin concentrations may lead to an increased risk for insulin resistance, dyslipidemia, acne, or venous thrombosis. Coadministration with other hormonal contraceptives (ie, patches, rings, injectable contraceptives) has not been studied and thus nonhormonal alternatives may be considered. If concomitant use is indicated, consider the potential risks and benefits, especially in women with additional risk factors for progestin-related adverse events[228].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: In combined use with elvitegravir, as part of the combination product elvitegravir/cobicistat/emtricitabine/tenofovir, norgestimate concentration was increased and ethinyl estradiol concentration was decreased. Increased progestin concentrations may lead to an increased risk for insulin resistance, dyslipidemia, acne, or venous thrombosis. If concomitant use of elvitegravir and a hormonal contraceptive is indicated, consider the potential risks and benefits, especially in women with additional risk factors for these events. Coadministration with other hormonal contraceptives (ie, patches, rings, injectable contraceptives) has not been studied and thus nonhormonal alternatives may be considered[228].
7) Probable Mechanism: unknown
8) Literature Reports

a) Administration of elvitegravir/cobicistat/emtricitabine/tenofovir with ethinyl estradiol and norgestimate resulted in a more than 2-fold increase in AUC, Cmax, and Cmin of norgestimate and a 25% and 44% reduction in ethinyl estradiol AUC and Cmin, respectively [229].

Encorafenib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of encorafenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Avoid concomitant use. Advise women of reproductive potential to use an effective non-hormonal method of contraception during treatment with encorafenib and for 2 weeks after the final dose[383].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use of encorafenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Avoid concomitant use. Advise women of reproductive potential to use an effective non-hormonal method of contraception during treatment with encorafenib and for 2 weeks after the final dose[383].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism

Enzalutamide

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of enzalutamide (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding[176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of enzalutamide [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of enzalutamide (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of enzalutamide[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted

etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Eslicarbazepine Acetate

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as eslicarbazepine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of eslicarbazepine [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as eslicarbazepine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of eslicarbazepine[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by eslicarbazepine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Etravirine

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as etravirine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of etravirine [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as etravirine, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of etravirine[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by etravirine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted

etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Fedratinib

1) Interaction Effect: increased exposure of substrate
2) Summary: Concomitant use of fedratinib (an inhibitor of CYP3A4, CYP2C19, and CYP2D6) with a substrate of CYP3A4, 2C19, or 2D6 may increase substrate concentrations and the risk of adverse reactions of those drugs. In single-dose pharmacokinetic studies, fedratinib increased midazolam (CYP3A4 substrate) AUC by 4-fold, omeprazole (CYP2C19 substrate) AUC by 3-fold, and metoprolol (CYP2D6 substrate) AUC by 2-fold. If coadministration is necessary, monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates[381].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of fedratinib (a CYP3A4, CYP2C19, and CYP2D6 inhibitor) with a substrate of CYP3A4, 2C19, or 2D6 may increase substrate concentrations and the risk of adverse reactions of those drugs. If coadministration is necessary, monitor for adverse reactions and adjust the dose of drugs that are CYP3A4, CYP2C19, or CYP2D6 substrates[381].
7) Probable Mechanism: inhibition of CYP-mediated substrate metabolism by fedratinib
8) Literature Reports

a) Coadministration of a single dose of midazolam 2 mg (CYP3A4 substrate) with fedratinib increased midazolam AUC by 4-fold [381].

b) Coadministration of a single dose of omeprazole 20 mg (CYP2C19 substrate) with fedratinib increased omeprazole AUC by 3-fold [381].

c) Coadministration of a single dose of metoprolol 100 mg (CYP2D6 substrate) with fedratinib increased metoprolol AUC by 2-fold [381].

Fexinidazole

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Avoid concomitant use of fexinidazole (a CYP3A4 inhibitor) with CYP3A4 substrates as there is an increased risk for adverse reactions associated with increased concentrations of these drugs[393].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of fexinidazole (a CYP3A4 inhibitor) with CYP3A4 substrates as there is an increased risk for adverse reactions associated with increased concentrations of these drugs[393].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by fexinidazole

Fosamprenavir

1) Interaction Effect: altered hormonal levels and an increased risk of liver enzyme elevations
2) Summary: Fosamprenavir is the prodrug of amprenavir. Reduced exposure to amprenavir and altered hormonal levels occurred when combined oral contraceptives (containing ethinyl estradiol/norethindrone) were used concomitantly with amprenavir. Coadministration of ethinyl estradiol/norethindrone and fosamprenavir/ritonavir has resulted in significant decreases in ethinyl estradiol and norethindrone levels and may also result in hepatic transaminase elevations. Therefore, patients receiving oral contraceptives should be instructed to use alternative methods of non-hormonal contraception[332].
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concomitant administration of amprenavir, the active metabolite of fosamprenavir, and oral contraceptives (containing ethinyl estradiol/norethindrone) has resulted in decreased amprenavir concentrations and altered hormonal levels. Additionally, coadministration of fosamprenavir with ritonavir, and oral contraceptives led to altered hormonal levels and may result in hepatic transaminase elevations. Alternative methods of non-hormonal contraception are recommended in patients receiving fosamprenavir with or without ritonavir[332].
7) Probable Mechanism: unknown
8) Literature Reports

a) Concomitant administration of ethinyl estradiol 0.035 mg/norethindrone 0.5 mg once daily for 21 days and fosamprenavir 700 mg/ritonavir 100 mg twice daily for 21 days in 25 patients resulted in decreases (90% confidence interval) of 34% (30% to 37% decrease), 38% (32% to 44% decrease), and 26% (20% to 32% decrease) in norethindrone AUC, Cmax, and Cmin, respectively. The corresponding decreases in ethinyl estradiol were 37% (30% to 42% decrease), 28% (21% to 35% decrease), and

minimal or no change, respectively. No change was noted in amprenavir pharmacokinetics [332].

b) Concomitant administration of ethinyl estradiol 0.035 mg/norethindrone 1 mg for one cycle and amprenavir 1200 mg twice daily for 28 days in 10 patients resulted in a decrease in AUC (90% confidence interval (CI)) by 22% (8% to 35% decrease) and a decrease minimum plasma concentration (Cmin) (90% CI) by 20% (41% decrease to a 8% increase) of amprenavir. No change was noted in the Cmax of amprenavir. No change was noted in the Cmax or AUC of ethinyl estradiol, but the Cmin increased 32% (3% decrease to 79% increase). No change was noted in the Cmax of norethindrone, but the AUC increased 18% (1% to 38% increase) and the Cmin increased 45% (13% to 88% increase) [332].

Fosaprepitant

1) Interaction Effect: reduced efficacy of contraceptives
2) Summary: Concomitant use of aprepitant or fosaprepitant with hormonal contraceptives may result in decreased contraceptive efficacy. Studies have demonstrated a significant decrease in the AUC and minimum concentration of ethinyl estradiol and norethindrone with concomitant administration. Patients should be advised to use an alternative or back-up method of contraception during therapy and for 1 month after the last dose[342].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving aprepitant or fosaprepitant, alternative or back-up methods of contraception should be used during treatment and for 1 month after the last dose[342].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral aprepitant 100 mg was given once daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the ethinyl estradiol AUC decreased by 43%, and the norethindrone AUC decreased by 8%. In a separate study, a daily dose of a combination contraceptive containing ethinyl estradiol and norethindrone was administered for 21 days. On day 8, oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg were administered. On days 9 and 10, oral aprepitant 80 mg/day and dexamethasone 8 mg/day were given. On day 11, oral dexamethasone 8 mg was administered alone. The AUC of ethinyl estradiol decreased 19% and there was no change in the norethindrone AUC on day 10. The minimum concentration of ethinyl estradiol decreased as much as 64% and norethindrone decreased up to 60% during days 9 through 21 [342].

Fosnetupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Coadministration of netupitant, a moderate inhibitor of CYP3A4, with a CYP3A4 substrate may increase the plasma concentration of the CYP3A4 substrate. The mean AUC and Cmax of the CYP3A4 substrate erythromycin was increased following the coadministration of netupitant in a pharmacokinetic study. Increases in the AUC of dexamethasone, a CYP3A4 probe substrate, remained for up to 8 days following a single dose of netupitant. The concomitant use of CYP3A4 substrates with netupitant should be avoided for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of CYP3A4 substrates with netupitant (a moderate inhibitor of CYP3A4) for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant
8) Literature Reports

a) In one study where the duration of CYP3A4 inhibition was assessed using dexamethasone as a CYP3A4 probe substrate, the mean AUC of dexamethasone increased by 1.6-fold on day 1, 2.4-fold on day 4, 1.5-fold on day 6, and 1.2-fold on day 8 after a single dose of the combination netupitant 300 mg/palonosetron 0.5 mg was coadministered to participants on day 1. The participants had been treated with a dexamethasone regimen of 12 mg on day 1 followed by 8 mg on days 2, 3, 4, 6, 8, and 10 [304].

b) A pharmacokinetic study demonstrated that when erythromycin 500 mg was coadministered with netupitant 300 mg, the mean AUC of erythromycin increased by 56% and the Cmax increased by 92% [304].

Fosphenytoin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. Oral contraceptives have also been reported to

increase or decrease phenytoin levels [268]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception [264]. One study found that the use of phenytoin and/or phenobarbital increased the frequency of pregnancy 25-fold in patients taking oral contraceptives [265]. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme-inducing anticonvulsant; however, if unplanned pregnancy is a particular concern, a moderate dose formulation (ethinyl estradiol 50 mcg) should be considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme-inducing anticonvulsants are discontinued in women receiving moderate or high-dose contraceptive steroids to reduce the risk of vascular disease [264].

c) Contraception by levonorgestrel subdermal capsules is not reliable in patients on anticonvulsant therapy. In addition to levonorgestrel therapy, 2 patients took phenytoin, 3 took phenytoin plus carbamazepine, 2 used carbamazepine only, 1 used clonazepam, and 1 used phenytoin plus sodium valproate. At 3 to 12 months, the mean plasma levonorgestrel concentration was significantly lower in the 6 patients with epilepsy using phenytoin alone or in combination with other anticonvulsants (203 +/- 128 picograms/milliliter [pg/mL]) than in controls using levonorgestrel implants only (325 +/- 135 pg/mL). Two of the 9 patients with epilepsy became pregnant; 1 was taking phenytoin 250 mg daily and the second phenytoin 400 mg daily and carbamazepine 400 mg daily [266]. A 26-year-old woman receiving phenytoin 300 mg/day became pregnant after 9 months of implant use. It appears that phenytoin, and probably carbamazepine, decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction [267]. Phenytoin also induces sex hormone binding globulin (SHBG) and thereby decreases the amounts of biologically active levonorgestrel. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsants.

Ginseng

1) Interaction Effect: additive estrogenic effects
2) Summary: Case reports suggest estrogen-like activity of ginseng[378][379][380]. The exact type of ginseng (i.e. Panax, Siberian, American, etc) was not reported. Concomitant use of ginseng with conjugated estrogens may result in symptoms of estrogen excess or interference. Avoid concomitant use if possible until further information characterizing

this interaction is available.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Since estrogenic effects have been noted with topical and oral estrogen, either dosage form should be treated with the same caution when coadministered with ginseng. If estrogenic symptoms such as mastalgia and breakthrough menstrual bleeding occur, decreased the ginseng dosage. Because of the apparent estrogen-like effect, avoid ginseng in patients with breast cancer, undiagnosed abnormal genital bleeding, active thrombophlebitis or thromboembolic disorders, or if the woman is pregnant.
7) Probable Mechanism: saponin glycoside constituents of ginseng may stimulate liver RNA and protein synthesis mimicking the effect of ovarian steroids
8) Literature Reports

a) A 72-year-old woman ingested one tablet daily of a Swiss-Austrian geriatric formula which contained 200 mg of ginseng (Geriatric Pharmaton, Bernardgass, Austria). This resulted in vaginal bleeding and what was described as a "moderate estrogen effect" [374].

b) A 70-year-old woman experienced swollen tender breasts with diffuse nodularity after 3 weeks of "regular" ingestion of ginseng powder. The breast symptoms resolved upon discontinuation of the ginseng powder, although a time period is not provided. With two subsequent rechallenges, the symptoms reappeared. Neither dose nor time period were provided in the case report. Serum prolactin levels were measured both during ginseng powder use as well as when the patient was not using the powder; these levels were reported as normal although exact levels were not provided [375].

c) Five women aged 25 to 40 who had been taking ginseng for varying periods reported to their doctor the development of breast symptoms, including nipple enlargement, and an increased sexual responsiveness [376].

d) A 62-year-old woman (14 years post-menopausal) had a vaginal smear exhibiting a strong estrogenic effect with a maturation index of 0/65/35 (parabasal/intermediate/superficial cells) which was attributed to her intake of "Rumanian ginseng in an unspecified dose. The ginseng product was analyzed and was shown not to contain any estrogen, nor was the woman taking any estrogen product. Within 3 weeks of discontinuing the ginseng use, the vaginal smear displayed a maturation index of 9/95/5. Within 2 weeks of ginseng rechallenge, the vaginal smear maturation index was 0/90/10. Throughout periods of ginseng use and abstinence, the serum concentrations of estrone, estradiol, and estriol remained essentially unchanged within the normal range (0.32 nanomoles/liter (nmol/L), 0.03 nmol/L and less than 0.01 nmol/L, respectively). The authors theorize the saponin content of ginseng interacts with estrogen receptor proteins in a manner similar to ovarian steroids [377].

Griseofulvin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Griseofulvin may decrease the effectiveness of hormonal contraceptives and produce contraceptive failure, breakthrough bleeding[176][417][418], or irregular menstruation [417][418]. The mechanism of action is thought to be an enhanced hepatic metabolism of contraceptive steroids by griseofulvin [419][420][421]. Limited data suggest that the effects of this interaction may be more prevalent with combination contraceptives that contain a lower dose of estrogen [420]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation griseofulvin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Griseofulvin may decrease the effectiveness of hormonal contraceptives and produce contraceptive failure, breakthrough bleeding[176][417][418], or irregular menstruation [417][418]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of griseofulvin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) A case report described pregnancy occurring in a 25-year-old woman receiving griseofulvin and oral contraceptives concurrently. The woman, who had been taking the oral contraceptive (OC), Triphasil(R), for 4 years with no menstrual irregularities, was treated with ultramicrocrystalline griseofulvin 330 mg twice daily while continuing to use oral contraception. Two month after initiation of griseofulvin, her nails were greatly improved but she reported transient headaches. Two months later, the patient was found to be pregnant. Her last menstrual period had occurred 2 months after initiation of griseofulvin. The patient claimed to have taken her OC regularly and did not take any other medications during this period. It was postulated the pregnancy probably resulted from failure of the oral contraceptive due to an interaction between the oral contraceptive and griseofulvin [419].

b) A case report described oligomenorrhea and irregular menses in a 32-year-old woman receiving concomitant griseofulvin and oral contraceptive therapy with norethindrone 0.5 and 1 mg plus ethinyl estradiol 0.035 mg (Ortho Novum 7/7/7(R)). The woman, who

had two normal pregnancies and subsequent deliveries from 1981 to 1984 and who had been taking the oral contraceptive for the preceding four months with no abnormalities in menstruation, was diagnosed with tinea unguium. She was treated with griseofulvin 250 mg daily for 14 days, then increased to 500 mg daily for the remainder of the 6-month regimen. No other drugs were given. Following griseofulvin therapy initiation, the woman presented with oligomenorrhea and irregular menses. As a result, the patient's gynecologist changed her oral contraceptive to norgestrel 0.5 mg plus ethinyl estradiol 0.05 mg (Ovral-28(R)), providing a 57% increase in the estrogen component. Six months following the oral contraceptive change, the patient reported regular menses with normal menstrual flow [420].

c) The Safety of Medicines in the United Kingdom committee and the Netherlands Centre for Monitoring of Adverse Reactions to Drugs received 22 reports of a possible oral contraceptive (OC) and griseofulvin interaction. Among the 22 women using long-term OC who began receiving griseofulvin 0.5 to 1 g/day, 15 women (mean age, 26 years; range, 17 to 42 years; mean griseofulvin dose, 550 mg/day) reported transient intermenstrual bleeding and 5 women (mean age, 33.4 years; range, 17 to 44 years; mean griseofulvin dose, 880 mg/day) reported amenorrhea in the first and second cycles following griseofulvin initiation. In 7 of the intermenstrual bleeding cases and one of the amenorrhea cases, the women were using OCs with less than 50 mcg estrogen. Of the 20 women reporting menstrual irregularities, 14 women received no other drugs during the time of griseofulvin treatment and 3 women used drugs not known to interfere with OCs (ie, miconazole ointment, grass pollen vaccine, tetanus vaccine). In the 3 remaining patients, details of concurrent drug administration were not reported. In 2 patients with intermenstrual bleeding and 2 with amenorrhea, the original reaction recurred upon rechallenge with griseofulvin. Two unintended pregnancies were also reported among the 22 cases. In one case, the patient had been using a high-dose OC for 15 months and griseofulvin 500 mg/day for 2.5 months. One month after starting griseofulvin, she received a 1-week course of cotrimoxazole and became pregnant in that time period. In the second case, conception occurred when a patient was taking an unspecified OC, griseofulvin, and a combination of sulfonamides [421].

Guar Gum

1) Interaction Effect: reduced contraceptive effectiveness
2) Summary: Women receiving oral contraceptives have been advised to take additional contraceptive precautions during guar gum therapy, due to potential effects on oral contraceptive absorption[201]. Clinical studies evaluating this interaction are lacking.
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Advise patients to use additional contraceptive methods while taking guar gum with oral contraceptives.
7) Probable Mechanism: reduced contraceptive absorption

Hydrocortisone

1) Interaction Effect: prolonged hydrocortisone effect
2) Summary: Combination oral contraceptives have been demonstrated to increase the antiinflammatory effect of hydrocortisone and prednisone. The half-lives of these steroids may increase by 2 to 3 times[456][457][458].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Monitor closely for increased corticosteroid effects and adjust hydrocortisone dose as needed.
7) Probable Mechanism: unknown

Imipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150

mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Insulin

1) Interaction Effect: may decrease blood glucose lowering effect of insulin
2) Summary: Concurrent use of estrogens and insulin may decrease the blood glucose lowering effect of insulin. Dose adjustments and increase frequency of glucose monitoring may be required[404][405].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of estrogens and insulin may decrease the blood glucose lowering effect of insulin. Dose adjustments and increase frequency of glucose monitoring may be required[404][405].
7) Probable Mechanism: unknown

Insulin Lispro, Recombinant

1) Interaction Effect: may decrease blood glucose lowering effect of insulin lispro
2) Summary: Concurrent use of estrogens and insulin lispro may decrease the blood glucose lowering effect of insulin lispro. Dose adjustments and increase frequency of glucose monitoring may be required[394][395][396].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent use of estrogens and insulin lispro may decrease the blood glucose lowering effect of insulin lispro. Dose adjustments and increase frequency of glucose monitoring may be required[394][395][396].
7) Probable Mechanism: unknown

Isotretinoin

1) Interaction Effect: decreased effectiveness of hormonal contraceptives
2) Summary: When coadministered with isotretinoin, pharmacokinetic and pharmacodynamic changes to estrogens and progestins are small but highly variable and unpredictable. Pregnancy has been reported in women who have used combined oral contraceptives, as well as topical/injectable/implantable/insertable hormonal birth control products. Such reports have occurred more frequently in those using a single form of contraception. Micro-dosed progestin-only pills elevate the risk of contraceptive failure during concomitant treatment with isotretinoin. During isotretinoin therapy, female patients of child bearing potential must use 2 forms of contraception simultaneously, one form should include: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, or topical/injectable/implantable/insertable hormonal birth control products[367][368][369].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Advise patients to use 2 forms of contraception simultaneously during isotretinoin therapy, unless patient has agreed to absolute abstinence or has had a hysterectomy. One form should include one of the following: tubal ligation, partner's vasectomy, intrauterine devices, birth control pills, or topical/injectable/implantable/insertable hormonal birth control products. Micro-dosed progesterone preparations (minipills than do not contain an estrogen) may be inadequate. Counsel patients about contraception and behaviors that increase the risk of pregnancy[367][368][369].
7) Probable Mechanism: unknown
8) Literature Reports

a) Isotretinoin did not interact with oral contraceptives in a study. Nine women taking isotretinoin 0.5 mg/kg for severe pustular acne received oral contraceptives (brand unknown) for at least three months prior to starting isotretinoin therapy. Plasma concentrations of ethinyl estradiol and levonorgestrel in the control cycle and in two cycles after starting isotretinoin were similar as determined by radioimmunoassay [370].

b) Pharmacokinetic and pharmacodynamic changes were inconsistent and relatively small when isotretinoin was given with a combination ethinyl estradiol/norethindrone product. In a single-center, open-label drug interaction study, 26 healthy women completed a study in which they were given ethinyl estradiol/norethindrone oral contraceptive (OC) triphasic tablets (35 micrograms and 0.5/0.75/1 milligrams, respectively) daily. At the start of the third month and after the possibility of pregnancy was ruled out, participants were also given isotretinoin 1 milligrams/kilogram/day in two divided doses to complete 16 to 20 weeks of isotretinoin treatment for severe, recalcitrant nodular acne. Ethinyl estradiol and norethindrone plasma concentrations were slightly reduced (9% and 11%, respectively) during the OC plus isotretinoin phase compared with the OC alone phase; patient variability was high, however. Follicle stimulating hormone concentration declined 44% (p=0.03) when isotretinoin was added to the regimen, again with a high degree of variability; serum progesterone and luteinizing hormone levels were unchanged. No pregnancies were reported [371].

Ivosidenib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of ivosidenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Advise women of reproductive potential to use an effective non-hormonal method of contraception[329].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use of ivosidenib (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly. Advise women of reproductive potential to use an effective non-hormonal method of contraception[329].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism

Lamotrigine

1) Interaction Effect: decreased lamotrigine plasma concentrations
2) Summary: The concomitant use of combined hormonal contraceptives and lamotrigine has resulted in significant decreases in plasma lamotrigine levels[237]. A sudden change

in a patient's clinical condition and altered plasma levels of lamotrigine may occur with the use, or changes in the use, of oral contraceptives [239][241][240]. There have been reports of decreased lamotrigine concentrations following introduction of oral contraceptives and reports of increased lamotrigine concentrations following withdrawal of oral contraceptives in women taking lamotrigine. Dosage adjustments may be necessary to maintain clinical response when starting or discontinuing oral contraceptives during lamotrigine therapy [238].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Estrogen-containing oral contraceptives have been shown to significantly decrease lamotrigine plasma concentrations during concomitant use. Carefully monitor and adjust lamotrigine doses in women who choose estrogen-containing hormonal contraception[237][238].
7) Probable Mechanism: induction of lamotrigine glucuronidation by combination contraceptive
8) Literature Reports

a) Evidence from a double-blind, placebo-controlled trial involving 7 women with epilepsy suggests that oral contraceptives induce the metabolism of lamotrigine. All patients were treated with lamotrigine monotherapy and taking combination oral contraceptives at study enrollment. They were then allocated in a crossover fashion to receive either placebo or contraceptive (ethinyl estradiol 35 mcg/norgestimate 250 mcg) over 4 periods (21 days of treatment followed by a 7-day pause). Steady-state blood samples were collected as trough levels (just prior to the next dose) and urine samples were collected between the evening and morning doses. Mean lamotrigine plasma concentrations increased by 84% (95% CI, 45% to 134%) after placebo for 21 days compared with oral contraceptive treatment for 21 days. Urine excretion of lamotrigine metabolites, measured as the N-2-glucuronide/lamotrigine ratio, was decreased by 31% (95% CI, -20% to 61%) when placebo was taken instead of oral contraceptive. Seizures occurred in 3 patients during oral contraceptive therapy while no seizures occurred during placebo therapy. The mechanism of the interaction is likely the induction of glucuronidation pathways involved in the metabolism of lamotrigine and ethinyl estradiol [239].

b) Several cases in which oral contraceptives changed the plasma levels of lamotrigine as well as the patient's clinical condition have been reported. Five patients who were seizure-free (1 with epilepsy, 2 with complex partial seizures, and 2 with absence epilepsy) had decreased lamotrigine serum concentrations after oral contraceptives were initiated. Two other patients, 1 with simple partial seizures and 1 with complex partial seizures, had discontinued their oral contraceptives. Plasma levels of lamotrigine in these 2 patients had increased significantly as well. Oral contraceptives reduce the plasma levels of lamotrigine 41% to 64% (mean, 49%). As a result, seizure control deteriorated when oral contraceptives were added, or side effects occurred when oral contraceptives were discontinued. These effects were independent of whether the oral contraceptives contained desogestrel, ethinyl estradiol, or norethindrone. The author concludes that there is a need for careful monitoring and adjustment of the lamotrigine doses in women with epilepsy who use combination contraceptives [240].

c) Lamotrigine plasma levels are reduced by greater than 50% during oral contraceptive coadministration. A retrospective study evaluated 52 women, 22 who used oral contraceptives and 30 who did not. The mean lamotrigine dose was 349 mg/day among women taking oral contraceptives and 327 mg/day among those who did not. Mean plasma level of lamotrigine was 13 mcmol/L in patients on oral contraceptives and 28 mcmol/L in patients without oral contraceptives (p less than 0.0001). Oral contraceptives markedly decrease plasma concentrations of lamotrigine [241].

d) In a study of 16 female volunteers, estrogen-containing oral contraceptive (ethinyl estradiol 30 mcg/levonorgestrel 150 mcg) increased the apparent clearance of lamotrigine 300 mg/day by approximately 2-fold with a mean decrease in AUC of 52% and in Cmax of 39%. Trough serum lamotrigine concentrations gradually increased and were approximately 2-fold higher at the end of the week of inactive treatment ("pill-free" week) compared with trough serum lamotrigine concentrations at the end of the active hormone cycle. This increase occurred in women not taking a drug that increased the clearance of lamotrigine (carbamazepine, phenytoin, phenobarbital, primidone, or rifampin). Dosage adjustment of lamotrigine will be necessary in women taking estrogen-containing oral contraceptives [238].

Lesinurad

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Coadministration of lesinurad and hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may result in decreased effectiveness of the contraceptive. Additional methods of contraception are recommended[326].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of lesinurad and hormonal contraceptives, including oral, injectable, transdermal, and implantable forms, may result in decreased effectiveness of the contraceptive. Additional methods of contraception are recommended[326].

7) Probable Mechanism: interference with metabolism of hormonal contraceptive by lesinurad

Levothyroxine

1) Interaction Effect: decrease in serum-free thyroxine concentration
2) Summary: Estrogens, including those in oral combined hormonal contraceptives and in hormone-replacement therapy, may raise serum concentrations of thyroxine-binding globulin, necessitating an increase in the dose of replacement thyroid hormone therapy[249][272][273].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Estrogens, including those in oral combined hormonal contraceptives and in hormone-replacement therapy, may raise serum concentrations of thyroxine-binding globulin, necessitating an increase in the dose of replacement thyroid hormone therapy[249][272][273].
7) Probable Mechanism: estrogen-induced increases in serum thyroxine-binding globulin concentration
8) Literature Reports

a) Women with hypothyroidism who are treated with thyroxine, who then receive estrogen, may experience a decrease in the concentration of serum-free thyroxine, thereby increasing serum thyrotropin concentrations and increasing the need for thyroxine. Thirty-six women were evaluated for the effects of estrogen administration on pituitary-thyroid function. Twenty-five of these women were receiving thyroxine therapy for chronic hypothyroidism, 18 of these patients received thyroid replacement therapy and 7 received thyroxine for thyrotropin suppression for thyroid cancer. In women with normal thyroid function, serum-free thyroxine and thyrotropin concentrations did not change. The mean serum thyroxine concentration increased 30% and serum thyroxine-binding globulin level increased 54%. In women with hypothyroidism, the serum-free thyroxine concentration decreased 18% and the serum thyrotropin concentration increased 256%. Thyrotropin levels increased to greater than 7 mcU/mL in seven women receiving thyroid replacement therapy and to greater than 1mcU/mL in three women in the thyrotropin-suppression group, necessitating increases in thyroxine doses [274].

Licorice

1) Interaction Effect: increased risk of fluid retention and elevated blood pressure
2) Summary: Elevated blood pressure and fluid retention has been associated with concomitant use of licorice and oral contraceptives in case reports[350][351], which may be related to estrogen and/or progesterone. The glycyrrhetinic acid component of licorice is metabolized to 3-monoglucuronyl-glycyrrhetinic acid (3MGA), which inhibits 11-beta-hydroxysteroid dehydrogenase and reduces cortisol breakdown, resulting in a hypermineralocorticoid effect [352][353].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Caution is advised if licorice is taken with estrogen. If the patient develops fluid retention and increased blood pressure, discontinue licorice.
7) Probable Mechanism: increased mineralocorticoid effect
8) Literature Reports

a) A 21-year-old female developed headache and hypertension (190/120 mmHg), associated with licorice consumption (100 grams daily) along with an oral contraceptive. She was advised to discontinue eating licorice. Blood pressure remained elevated with treatment combining atenolol, lisinopril, hydrochlorothiazide, and amlodipine. Drug treatment was discontinued, and 2 weeks later blood pressure was 180/110 mmHg, potassium 2.6 mmol/L (normal 3.8 to 5.0 mmol/L), bicarbonate 35.9 mmol/L (normal 23 to 29 mmol/L). Plasma aldosterone was 160 picomoles/liter (pmol/L) (normal 320 to 2000 pmol/L). The patient then admitted to replacing her licorice intake with two packets of Stimerolol Sugar Free(R) chewing gum per day. This chewing gum contains 585 mg licorice in each 15 gram packet, which equals 8% to 12% glycyrrhizinic acid. Her glycyrrhizinic acid intake was calculated to be 120 mg daily. Within 3 weeks of discontinuing the gum, her blood pressure and potassium level normalized [348].

b) A 35-year-old woman taking an oral contraceptive and chlorothiazide experienced hypokalemia (2.2 mmol/L). Her blood pressure was 140/80 mmHg. Chlorothiazide was stopped and potassium chloride 600 mg three times daily was started. After one week, potassium remained abnormal at 2.0 mmol/L, after 2 weeks it decreased further to 1.5 mmol/L. Intravenous potassium supplementation was started. Although she denied licorice use, it was discovered that she used BenBits Cool Mint(R) chewing gum (Leaf, United Kingdom), 3 packets daily. This product contained 160 mg licorice in each 16 gram packet, of which 10% was glycyrrhizinic acid. After 2 days of intravenous potassium and 15 days of oral potassium, and within 3 weeks of discontinuing the chewing gum, edema disappeared, blood pressure decreased to 110/80 mmHg and potassium increased to 4.2 mmol/L. The authors attributed the hypokalemia to the licorice intake [348].

c) In a study of 4 groups of 6 healthy volunteers administered varying doses of licorice root, the group administered 814 mg of glycyrrhizin experienced a decrease in serum

potassium from 4.25 millimoles/liter (mmol/L) to 3.53 mmol/L (p equals 0.014) after one week. Two of the subjects were taking oral contraceptives concomitantly; all others were taking no other medications. One of the subjects taking an oral contraceptive developed headache, peripheral edema, borderline arterial hypertension (144/91 mmHg), and hypokalemia (2.6 mmol/L) and discontinued treatment. Kaliuresis was noted as well, though not statistically significant. After one week, plasma renin activity significantly decreased in groups taking 380 mg and 814 mg glycyrrhizin (p equals 0.025 and p equals 0.045, respectively). Plasma aldosterone decreased significantly in the group taking 814 mg glycyrrhizin (p equals 0.04). This indicates that volume expansion occurred; however, renal sodium retention was not found to be significant [349].

Lixisenatide

1) Interaction Effect: decreased absorption of oral contraceptives
2) Summary: Concomitant use of lixisenatide with oral contraceptives may decrease absorption of the oral contraceptive. When a single dose of the oral contraceptive, ethinylestradiol/levonorgestrel was administered 1 hour after lixisenatide, ethinylestradiol and levonorgestrel Cmax decreased by approximately half; however, when a single dose of ethinylestradiol/levonorgestrel was administered either 1 hour before or 11 hours after lixisenatide, the Cmax and other absorption parameters of ethinylestradiol and levonorgestrel were not affected. If these agents are coadministered, instruct patients to take oral contraceptives at least 1 hour before lixisenatide or at least 11 hours after lixisenatide administration[384].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lixisenatide with oral contraceptives may result in decreased absorption of the oral contraceptive. If these agents are coadministered, instruct patients to take oral contraceptives at least 1 hour before lixisenatide or at least 11 hours after lixisenatide administration[384].
7) Probable Mechanism: delayed gastric emptying
8) Literature Reports

a) In a drug interaction study, administration of a single dose of the oral contraceptive, ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg one hour or 4 hours after lixisenatide 10 mcg decreased ethinylestradiol Cmax by 52% and 39%, respectively, and levonorgestrel Cmax by 46% and 20%, respectively. The median Tmax of the oral contraceptive was also delayed by 1 to 3 hours. However, the overall exposure (AUC) and mean t(1/2) of ethinylestradiol and levonorgestrel were not affected. When a single dose of ethinylestradiol 0.03 mg/levonorgestrel 0.15 mg was administered either 1 hour before or 11 hours after lixisenatide 10 mcg, the Cmax, AUC, t(1/2), and Tmax of ethinylestradiol and levonorgestrel did not change [384].

Lofepramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving

only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Lomitapide

1) Interaction Effect: increased exposure of lomitapide
2) Summary: The concomitant use of lomitapide (a CYP3A4 substrate) with oral contraceptives (weak CYP3A4 inhibitors) may cause increased exposure to lomitapide. When the combined oral contraceptive ethinylestradiol/norgestimate was coadministered with lomitapide, the systemic exposure of lomitapide increased by 30%. If concurrent use is required, the maximum lomitapide dosage is 40 mg daily. When initiating an oral contraceptive in a patient already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 40 mg daily[275].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: The concomitant use of lomitapide (a CYP3A4 substrate) with oral contraceptives (weak CYP3A4 inhibitors) may cause increased exposure to lomitapide. If concurrent use is required, the maximum lomitapide dosage is 40 mg daily. When initiating an oral contraceptive in a patient already taking lomitapide 10 mg/day or more, decrease the lomitapide dose by 50%. Then carefully titrate based on response and tolerability to a maximum of 40 mg daily[275].
7) Probable Mechanism: inhibition of CYP3A4-mediated lomitapide metabolism
8) Literature Reports

a) The concomitant administration of the combined oral contraceptive, ethinylestradiol 0.035 mg and norgestimate 0.25 mg daily, with a single 20-mg dose of lomitapide was shown to increase the AUC of lomitapide by 30% and Cmax by 40% compared with lomitapide administered alone [275].

Lonapegsomatropin-tcgd

1) Interaction Effect: reduced lonapegsomatropin-tcgd efficacy
2) Summary: Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to lonapegsomatropin-tcgd. Patients receiving oral estrogen replacement may require higher lonapegsomatropin-tcgd dosages[312].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Patients receiving oral estrogen replacement may require higher lonapegsomatropin-tcgd dosages. Oral estrogens may reduce the serum insulin-like growth factor-1 (IGF-1) response to lonapegsomatropin-tcgd.[312].
7) Probable Mechanism: an unknown mechanism

Lorazepam

1) Interaction Effect: decreased lorazepam effectiveness
2) Summary: Combination contraceptives may increase benzodiazepine metabolism by glucuronidation of lorazepam[412][413][414]. Women taking combination contraceptives may require a higher dose of lorazepam [415].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and lorazepam therapy for a reduced response to the benzodiazepine.
7) Probable Mechanism: increased hepatic metabolism of lorazepam
8) Literature Reports

a) Some data indicate that oral contraceptives can enhance the metabolism and reduce serum levels of lorazepam, which undergoes glucuronide conjugation [407][408]. In seven healthy women receiving oral contraceptives containing norethindrone 1 mg and ethinyl estradiol 50 mcg for at least six months, the administration of intravenous lorazepam 2 mg resulted in a 55% decrease in the half-life and a 50% increase in the volume of distribution of lorazepam. The total clearance of lorazepam was increased 3.7-fold as compared with that of eight healthy control females [409].

b) The half-life resulting from intravenous lorazepam 2 mg was reduced (from 13.4 hours to 4.8 hours) and the clearance was higher (302 mL/minute vs 78 mL/minute) in eight women while receiving oral contraceptives compared with nine women who were not taking oral contraceptives [410].

c) Another report indicates that the metabolic clearance of lorazepam (and oxazepam) was not significantly affected by concurrent oral contraceptive therapy (50 mcg or less of estrogen) [411]. The differences observed in these reports might be explained by differences in patient sample size or characteristics; the number of patients (controls and lorazepam-treated patients) was greater in the Abernethy report.

Lorlatinib

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of a CYP3A4 inducer, such as lorlatinib, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure[197]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of lorlatinib [197].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of a CYP3A4 inducer, such as lorlatinib, and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and lead to breakthrough bleeding and/or contraceptive failure. If coadministration is required, use an alternative non-hormonal method of contraception or a back-up method during coadministration and for at least 28 days after discontinuation of lorlatinib[197].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism of hormonal contraceptives by lorlatinib
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not

significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Lumacaftor

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of lumacaftor/ivacaftor with hormonal contraceptives increased menstrual abnormality events and may decrease the exposure of the hormonal contraceptive; lumacaftor is a strong CYP3A inducer. Avoid concomitant use unless the potential benefit outweighs the potential risk, and do not rely on a hormonal contraceptive alone as an effective method of contraception[432]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of a CYP3A inducer [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of lumacaftor/ivacaftor with hormonal contraceptives increased menstrual abnormality events and may decrease the exposure of the hormonal contraceptive. Avoid concomitant use unless the potential benefit outweighs the potential risk, and do not rely on a hormonal contraceptive alone as an effective method of contraception[432]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of a CYP3A inducer [176].
7) Probable Mechanism: induction of CYP3A-mediated metabolism by lumacaftor
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mavacamten

1) Interaction Effect: decreased exposure of hormonal contraceptive
2) Summary: Concomitant administration of mavacamten, a CYP3A4 inducer, and progestin and/or ethinyl estradiol, CYP3A4 substrates, may decrease exposures of progestin and ethinyl estradiol, which may lead to contraceptive failure or an increase in breakthrough bleeding. Patients should use a contraceptive method that is not affected by CYP450 enzyme induction (eg, intrauterine system) or add nonhormonal contraception (eg, condoms) during treatment with mavacamten and for 4 months after the last mavacamten dose[246].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant administration of mavacamten, a CYP3A4 inducer, and progestin and/or ethinyl estradiol, CYP3A4 substrates, may decrease exposures of progestin and ethinyl estradiol, which may lead to contraceptive failure or an increase in breakthrough bleeding. Patients should use a contraceptive method that is not affected by CYP450 enzyme induction (eg, intrauterine system) or add nonhormonal contraception (eg, condoms) during treatment with mavacamten and for 4 months after the last mavacamten dose[246].
7) Probable Mechanism: induction of CYP3A4 mediated metabolism of hormonal contraceptive by mavacamten
8) Literature Reports

a) Concomitant use of a 16-day course of the CYP3A4 inducer mavacamten (25 mg on days 1 and 2, followed by 15 mg for 14 days) with midazolam, a CYP3A4 substrate, resulted in a 13% decrease in midazolam AUC(inf) and a 7% decrease in Cmax, in healthy CYP2C19 normal metabolizers. Following coadministration of mavacamten once daily in patients with hypertrophic cardiomyopathy, midazolam AUC(inf) is predicted to decrease by 21% to 64% and Cmax is predicted to decrease by 13% to 48%, depending on the dose of mavacamten and CYP2C19 phenotype [246].

Minocycline

1) Interaction Effect: decreased contraceptive efficacy
2) Summary: Concomitant use of minocycline and combination oral contraceptives (OC) may result in decreased OC efficacy[277] Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% [183]. Despite these findings, minocycline-related changes in plasma levels of estradiol, progestinic hormone, follicle stimulating hormone, and luteinizing hormone, breakthrough bleeding, and contraceptive failure were not ruled out based on the results of a multicenter study. Thus, if concomitant use is required, an additional form of birth control during therapy is recommended [277].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of minocycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy[277]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. Evidence from a large retrospective chart review showed there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]; additionally, it is recommended to advise patients to use an additional form of birth control during concomitant treatment with minocycline and combination contraceptives [277].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) In a multicenter study, hormone levels over 1 menstrual cycle were evaluated in women administered low-dose contraceptives concomitantly with minocycline hydrochloride extended-release formulation (1 mg/kg once daily) and in those who received low-dose contraceptives alone. Minocycline-related changes in plasma levels of estradiol, progestinic hormone, follicle stimulating hormone, and luteinizing hormone, as well as breakthrough bleeding and contraceptive failure cannot be ruled out based on the results of this study. Therefore, women are advised to use an additional form of birth control during concomitant treatment with minocycline [277].

b) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

c) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use). The patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

d) In a retrospective cohort study using chart reviews and surveys, the oral contraceptive failure rate for combined use with oral antibiotics was 1.6 pregnancies per 100 woman-years of exposure, compared with a failure rate of 0.96 in the control group. Five pregnancies resulted in the antibiotic-exposed group, and all of these women had been using oral contraceptives for at least 6 months at the time of pregnancy and had been taking antibiotics for at least 3 months. Three of the five pregnancies occurred in women taking minocycline, while the other two pregnancies occurred in women receiving a cephalosporin [278].

e) The interaction between oral contraceptives and tetracycline has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

f) During a four-year period documenting 163 cases of contraceptive failure in reliable pill takers, 37 cases of pill failures (23%) were attributed to the concomitant use of antibiotics. Tetracyclines, including minocycline, were featured in 6 of these 37 cases [279].

Mitapivat

1) Interaction Effect: decreased hormonal contraceptive exposure
2) Summary: Coadministration of mitapivat (CYP3A inducer) and a sensitive CYP3A substrate, such as hormonal contraceptives, decreases the exposure of hormonal contraceptives. If coadministration is required, use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment[280].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of mitapivat (CYP3A inducer) and a sensitive CYP3A substrate, such as hormonal contraceptives, decreases the exposure of hormonal contraceptives. If coadministration is required, use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment[280].
7) Probable Mechanism: induction of CYP3A-mediated metabolism by mitapivat

Mitotane

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of mitotane (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding[176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of mitotane [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of mitotane (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness or increase breakthrough bleeding. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of mitotane[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mobocertinib

1) Interaction Effect: decreased plasma concentrations of the hormonal contraceptive, which may result in reduced contraceptive efficacy
2) Summary: Coadministration of mobocertinib with hormonal contraceptives may decrease plasma concentrations of the contraceptive, which may lead to reduced

contraceptive efficacy. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with mobocertinib and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mobocertinib and for 1 week after the last dose of mobocertinib[343].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Coadministration of mobocertinib with hormonal contraceptives may decrease plasma concentrations of the contraceptive, which may lead to reduced contraceptive efficacy. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with mobocertinib and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with mobocertinib and for 1 week after the last dose of mobocertinib[343].
7) Probable Mechanism: induction of the metabolism of the hormonal contraceptive by mobocertinib

Modafinil

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Use of modafinil (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly and for 1 month after discontinuation of modafinil[234]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives and for 1 month after discontinuation of modafinil treatment [234].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Use of modafinil (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness when used concomitantly and for 1 month after discontinuation of modafinil. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives and for 1 month after discontinuation of modafinil treatment[234].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Mycophenolate Mofetil

1) Interaction Effect: decreased contraceptive exposure and effectiveness
2) Summary: Coadministration of mycophenolate mofetil with combined oral contraceptives resulted in a significant decrease in exposure to levonorgestrel. Decreased exposure could result in reduced effectiveness of the combination contraceptive. Use additional barrier contraceptive methods when coadministration is required[431].
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of combination oral contraceptives and mycophenolate mofetil may decrease exposure to the progestin component and result in reduced oral contraceptive effectiveness. Use additional barrier contraceptive methods when coadministration is required[431].
7) Probable Mechanism: unknown
8) Literature Reports

a) .In a study involving 18 women with psoriasis, coadministration of mycophenolate mofetil (1 g twice daily) and combined oral contraceptives containing ethinyl estradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg and 0.2 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.1 mg) over 3 consecutive menstrual cycles resulted in a significant decrease in levonorgestrel AUC by approximately 15%. The mean AUC was similar for ethinyl estradiol and 3-keto desogestrel. There was large interpatient

variability (%CV in the range of 60% to 70%) in the data, especially for ethinyl estradiol. The mean serum levels of luteinizing hormone, follicle-stimulating hormone, and progesterone were not significantly affected [431].

Mycophenolic Acid

1) Interaction Effect: decreased contraceptive efficacy
2) Summary: Concomitant use of mycophenolic acid or mycophenolic sodium and oral contraceptives may result in reduced oral contraceptive effectiveness. In a drug interaction study, mean levonorgestrel AUC was decreased by 15% when coadministered with mycophenolic mofetil, the prodrug of mycophenolic acid. Use of additional barrier contraceptive methods is required when coadministered with hormonal contraceptives (such as birth control pills, transdermal patch, vaginal ring, injection, and implant)[426].
3) Severity: major
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Concomitant use of mycophenolic acid or mycophenolic sodium and oral contraceptives may result in reduced oral contraceptive effectiveness. Use of additional barrier contraceptive methods is required when coadministered with hormonal contraceptives (such as birth control pills, transdermal patch, vaginal ring, injection, and implant)[426].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a study involving 18 women with psoriasis, coadministration of mycophenolate mofetil (1 g twice daily), the prodrug of mycophenolic acid, and combined oral contraceptives containing ethinyl estradiol (0.02 mg to 0.04 mg) and levonorgestrel (0.05 mg and 0.02 mg), desogestrel (0.15 mg) or gestodene (0.05 mg to 0.1 mg) resulted in a significant decrease in levonorgestrel AUC by approximately 15%. The mean AUC was similar for ethinyl estradiol and 3-keto desogestrel. There was a large interpatient variability (%CV in the range of 60% to 70%) in the data, especially for ethinyl estradiol. The mean serum levels of luteinizing hormone, follicle-stimulating hormone, and progesterone were not significantly affected [427].

Nafcillin

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nafcillin, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nafcillin [249] [250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nafcillin, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nafcillin[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by nafcillin
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Nelfinavir

1) Interaction Effect: contraceptive failure
2) Summary: Coadministration of protease inhibitors, such as nelfinavir, and combination contraceptives may cause significant changes (increase and decrease) in the mean AUC of the estrogen and progestin[310]. Coadministered nelfinavir may decrease serum concentrations of contraceptives, which could cause a reduction in their effectiveness.

Patients should be instructed to use alternate or additional contraceptive measures when taking nelfinavir [311].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Patients receiving concurrent combination oral contraceptives and nelfinavir should be counseled to use alternative or additional contraceptive measures.
7) Probable Mechanism: increased estrogen and progestin metabolism
8) Literature Reports

a) Nelfinavir 750 mg every eight hours for seven days has been shown to decrease the AUC of norethindrone (0.4 mg daily for 15 days) by 18%. When ethinyl estradiol 35 mcg daily for 15 days was administered to 12 patients on the same nelfinavir regimen, the AUC and Cmax of ethinyl estradiol were decreased by 47% and 28%, respectively [309].

Netupitant

1) Interaction Effect: increased exposure of CYP3A4 substrate
2) Summary: Coadministration of netupitant, a moderate inhibitor of CYP3A4, with a CYP3A4 substrate may increase the plasma concentration of the CYP3A4 substrate. The mean AUC and Cmax of the CYP3A4 substrate erythromycin was increased following the coadministration of netupitant in a pharmacokinetic study. Increases in the AUC of dexamethasone, a CYP3A4 probe substrate, remained for up to 8 days following a single dose of netupitant. The concomitant use of CYP3A4 substrates with netupitant should be avoided for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
3) Severity: major
4) Onset: rapid
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of CYP3A4 substrates with netupitant (a moderate inhibitor of CYP3A4) for 1 week. If a CYP3A4 substrate must be administered within 1 week of netupitant, consider reducing the dose of the CYP3A4 substrate[304].
7) Probable Mechanism: inhibition of CYP3A4-mediated metabolism by netupitant
8) Literature Reports

a) In one study where the duration of CYP3A4 inhibition was assessed using dexamethasone as a CYP3A4 probe substrate, the mean AUC of dexamethasone increased by 1.6-fold on day 1, 2.4-fold on day 4, 1.5-fold on day 6, and 1.2-fold on day 8 after a single dose of the combination netupitant 300 mg/palonosetron 0.5 mg was coadministered to participants on day 1. The participants had been treated with a dexamethasone regimen of 12 mg on day 1 followed by 8 mg on days 2, 3, 4, 6, 8, and 10 [304].

b) A pharmacokinetic study demonstrated that when erythromycin 500 mg was coadministered with netupitant 300 mg, the mean AUC of erythromycin increased by 56% and the Cmax increased by 92% [304].

Nevirapine

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nevirapine, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding[249][250].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nevirapine [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as nevirapine, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of nevirapine[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by nevirapine
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were

administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Nortriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless,

and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Octreotide

1) Interaction Effect: decreased bioavailability and decreased efficacy of combined oral contraceptives or increased breakthrough bleeding
2) Summary: Concomitant use of octreotide and combined oral contraceptives (COCs) may decrease bioavailability and decrease efficacy of COCs or increase breakthrough bleeding. In a single-dose study, coadministration of levonorgestrel 0.3 mg and octreotide 40 mg orally significantly decreased levonorgestrel AUC and Cmax by 24% and 38%, respectively; coadministration of ethinyl estradiol 0.06 mg and octreotide 40 mg orally did not significantly change ethinyl estradiol AUC or Cmax. If concomitant use is required, an alternative non-hormonal method of contraception or a back-up method should be used[406].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of octreotide and combined oral contraceptives (COCs) may decrease bioavailability and decrease efficacy of COCs or increase breakthrough bleeding. If concomitant use is required, an alternative non-hormonal method of contraception or a back-up method should be used[406].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a single-dose study, coadministration of levonorgestrel 0.3 mg and octreotide 40 mg orally significantly decreased levonorgestrel AUC by 24% (mean ratio, 0.76; 90% CI, 0.67 to 0.86) and Cmax by 38% (mean ratio, 0.62; 90% CI, 0.54 to 0.71). Coadministration of ethinyl estradiol 0.06 mg and octreotide 40 mg orally did not significantly change ethinyl estradiol AUC (mean ratio, 0.94; 90% CI, 0.86 to 1.03) or Cmax (mean ratio, 0.92; 90% CI, 0.83 to 1.01) [406].

Oxacillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxacillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183]
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years

or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) A case of potential oral contraceptive failure was reported in an 18-year-old female receiving concurrent oxacillin (500 mg every 6 hours for six weeks) and a combination oral contraceptive agent (norethindrone 1 mg/0.035 mg estradiol) [398].

Oxcarbazepine

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of oxcarbazepine (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and may diminish effectiveness. In 2 studies, oxcarbazepine decreased the AUC of ethinyl estradiol by 48% and 52% and of levonorgestrel by 32% and 52%[455][176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration [455] and for at least 28 days after discontinuation of oxcarbazepine [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of oxcarbazepine (a CYP3A4 inducer) and a hormonal contraceptive may decrease plasma concentrations of the hormonal contraceptive and may diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration[455][176] and for at least 28 days after discontinuation of oxcarbazepine [176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Coadministration of oxcarbazepine with an oral contraceptive containing ethinyl estradiol and levonorgestrel has resulted in an mean decrease in AUC of ethinyl estradiol by 48% and 52% and of levonorgestrel by 32% and 52% in 2 studies [455].

b) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Oxytetracycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of oxytetracycline and oral combination contraceptives (OC) may reduce contraceptive efficacy. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives[204]. Isolated cases of contraceptive failure with oxytetracycline have been reported [206]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of oxytetracycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Evidence

from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) In a study of 24 women taking the oral contraceptive Ortho-Novum 1/35, serum concentrations of ethinyl estradiol, norethindrone, and endogenous progesterone measured on days 18 to 20 of the menstrual cycle were not significantly different on the same days the following cycle during which doxycycline 100 mg twice daily was coadministered [203].

d) The interaction between oral contraceptives and tetracyclines has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

e) A 20-year-old woman taking an oral contraceptive containing ethinyl estradiol 30 mcg and D-norgestrol 150 mcg became pregnant after receiving tetracycline 500 mg every 6 hours for 3 days followed by 250 mg every 6 hours for 2 days [205].

Penicillin G

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin G and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral

contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Penicillin G Procaine

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin G and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Penicillin V

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when combined oral contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins;

and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of penicillin V and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Phenobarbital

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as phenobarbital, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of phenobarbital [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as phenobarbital, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased contraceptive efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of phenobarbital[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by phenobarbital
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Phenylbutazone

1) Interaction Effect: reduced contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with drugs that increase the metabolism of contraceptive steroids,

such as phenylbutazone. This could result in unintended pregnancy or breakthrough bleeding[341].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with medications, such as phenylbutazone, that increase the metabolism of contraceptive steroids.
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) No alterations were found in phenylbutazone serum concentrations when a single-dose of phenylbutazone was coadministered with low-estrogen combination contraceptives. Seven volunteers using oral contraceptives containing norethindrone 1 mg plus ethinyl estradiol 30 mcg received one dose of phenylbutazone 400 mg. Phenylbutazone serum levels were not affected (the same study reported that oral contraceptives lowered aspirin concentrations) [340]. Although phenylbutazone has been demonstrated to interact with oral contraceptives in animal studies, no interaction has been reported in humans.

Phenytoin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. Oral contraceptives have also been reported to increase or decrease phenytoin levels [268]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of phenytoin and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive[176]. Breakthrough bleeding, spotting, and pregnancy have been reported in women taking phenytoin concurrently with hormonal contraceptives [263]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of phenytoin [176].
7) Probable Mechanism: increased metabolism of contraceptive steroids
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) Concomitant administration of oral contraceptives with enzyme-inducing anticonvulsant agents, primarily phenobarbital, phenytoin, carbamazepine, or primidone, has been reported to result in an increased failure rate of contraception [264]. One study found that the use of phenytoin and/or phenobarbital increased the frequency of pregnancy 25-fold in patients taking oral contraceptives [265]. The benzodiazepines and valproic acid have not been associated with increased failure rates in women receiving oral contraceptives. Increasing the dose of ethinyl estradiol or mestranol in oral contraceptives may diminish breakthrough bleeding and decrease the risk of conception. However, higher doses of estrogens may also increase the risk of vascular side effects, primarily in patients where enzyme induction does not occur. It is recommended that low doses of estrogen and progestin be given initially in patients receiving an enzyme-inducing anticonvulsant; however, if unplanned pregnancy is a particular concern, a moderate dose formulation (ethinyl estradiol 50 mcg) should be considered. If breakthrough bleeding occurs with low-dose contraception, progressive increases in the dose of mestranol or its equivalent (up to 80 mcg) should be considered. If spotting occurs, it is suggested that the contraceptive not be discontinued, but rather that a traditional method of barrier contraception be initiated during the remainder of that cycle. Switching to a lower dose oral contraceptive is recommended if enzyme-inducing

anticonvulsants are discontinued in women receiving moderate or high-dose contraceptive steroids to reduce the risk of vascular disease [264].

c) Contraception by levonorgestrel subdermal capsules is not reliable in patients on anticonvulsant therapy. In addition to levonorgestrel therapy, 2 patients took phenytoin, 3 took phenytoin plus carbamazepine, 2 used carbamazepine only, 1 used clonazepam, and 1 used phenytoin plus sodium valproate. At 3 to 12 months, the mean plasma levonorgestrel concentration was significantly lower in the 6 patients with epilepsy using phenytoin alone or in combination with other anticonvulsants (203 +/- 128 picograms/milliliter [pg/mL]) than in controls using levonorgestrel implants only (325 +/- 135 pg/mL). Two of the 9 patients with epilepsy became pregnant; 1 was taking phenytoin 250 mg daily and the second phenytoin 400 mg daily and carbamazepine 400 mg daily [266]. A 26-year-old woman receiving phenytoin 300 mg/day became pregnant after 9 months of implant use. It appears that phenytoin, and probably carbamazepine, decrease plasma levonorgestrel concentrations by enhancing the hepatic metabolism of the steroid via enzyme induction [267]. Phenytoin also induces sex hormone binding globulin (SHBG) and thereby decreases the amounts of biologically active levonorgestrel. Levonorgestrel should not be relied upon as the sole means of contraception in patients on anticonvulsants.

Pitolisant

1) Interaction Effect: reduced effectiveness of hormonal contraceptive
2) Summary: Avoid concomitant use of pitolisant with oral contraceptives, as pitolisant may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential should use an alternative method of non-hormonal contraception during treatment and for at least 21 days after discontinuation[365].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Avoid concomitant use of pitolisant with oral contraceptives, as pitolisant may reduce the effectiveness of hormonal contraceptives. Women of childbearing potential should use an alternative method of non-hormonal contraception during treatment and for at least 21 days after discontinuation[365].
7) Probable Mechanism: induction of contraceptive metabolism

Pixantrone

1) Interaction Effect: increased exposure of CYP1A2 substrates
2) Summary: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[399].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concurrent administration of pixantrone (a CYP1A2 inhibitor) and a CYP1A2 substrate may increase the exposure of the CYP1A2 substrate. If concomitant administration is required, use caution and monitor the patient closely[399].
7) Probable Mechanism: inhibition of CYP1A2-mediated metabolism by pixantrone

Prednisolone

1) Interaction Effect: an increased risk of corticosteroid side effects (neuropsychiatric reactions, fluid and electrolyte disturbances, hypertension, hyperglycemia)
2) Summary: Combination contraceptives may decrease prednisoLONE clearance significantly[470][471][472][473].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor closely for increased corticosteroid effects and adjust prednisoLONE dose as required.
7) Probable Mechanism: may decrease hepatic metabolism
8) Literature Reports

a) Chronic contraceptive and steroid use results in a marked decrease in prednisoLONE clearance. Six females using chronic oral contraceptives received prednisoLONE 0.53 (high dose) and 0.14 mg/kg (low dose) intravenously. Six females (controls) received only prednisoLONE. A significant decrease in clearance occurred for each of the prednisoLONE doses in women receiving oral contraceptives as compared with the control values (p less than 0.01). There is a significant decrease in unbound prednisoLONE clearance for women taking oral contraceptives compared with 0 control subjects at both doses (p less than 0.01). The results presented in this study demonstrate that an approximate 3.5-fold increase in prednisoLONE dose resulted in an increase, observed in each subject, in clearance by a factor of 1.96 +/- 0.52 for the control subjects and by a factor of 1.44 +/- 0.33 for the oral contraceptives group. Dose-dependent prednisoLONE kinetics and marked decreases in prednisoLONE clearance in women taking oral contraceptives results from concomitant synthetic estrogen dosing. Women taking oral contraceptives who are currently undergoing prednisoLONE therapy should be monitored carefully. The author expects lower doses of prednisoLONE to yield clinical efficacy in these patients [468].

b) The clearance of free prednisoLONE is reduced in women taking oral contraceptives compared to women who do not. The study evaluated eight female subjects who used

oral combination contraceptives and eight female control subjects who did not. Each subject received prednisoLONE phosphate equivalent to 0.1 mg/kg intravenous of prednisoLONE and 1.0 mg/kg of prednisoLONE. Free prednisoLONE clearance was reduced approximately 30% in oral contraceptive users compared with control subjects (p less than 0.001). Pre-dose plasma cortisol concentrations were elevated two-fold (p less than 0.001) in oral contraceptive users compared with control subjects. The authors conclude that inhibition of prednisoLONE clearance by cortisol may be the mechanism for circadian variations in free prednisoLONE clearance. This mechanism could contribute the inhibition of prednisoLONE clearance by oral contraceptives. This study demonstrated that there is a reduction in the dose dependency of free prednisoLONE clearance in oral contraceptive users compared to control subjects [469].

Prednisone

1) Interaction Effect: decreased plasma levels of hormonal contraceptive; increased risk of corticosteroid side effects (neuropsychiatric reactions, fluid and electrolyte disturbances, hypertension, hyperglycemia)
2) Summary: Concomitant use of predniSONE and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness[176].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of predniSONE [176]. Hormonal contraceptives have been demonstrated to alter the pharmacokinetics of hydrocortisone and predniSONE, thereby potentially enhancing therapeutic effect [255]. The half-lives of these steroids increase by 2 to 3 times and their clearance may decrease by 2- to 5-fold [258][259][260]. Combination oral contraceptives may also decrease prednisolone clearance by 20% to 80% [261][262].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of predniSONE and hormonal contraceptives may decrease plasma concentrations of the hormonal contraceptive and potentially diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of predniSONE[176]. Hormonal contraceptives have also altered the pharmacokinetics of hydrocortisone and predniSONE, potentially enhancing therapeutic effect [255].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism; decreased predniSONE metabolism
8) Literature Reports

a) Concomitant oral contraceptive and prednisolone therapy can result in reduced corticosteroid elimination [256][257]. In a study by [256], the plasma clearance of prednisolone was decreased by approximately 50% with a corresponding rise in the AUC for free prednisolone. It is not known if this effect is due to the estrogen component alone. Studies using progestogen oral contraceptives have not been performed.

b) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Primidone

1) Interaction Effect: decreased efficacy of hormonal contraceptive
2) Summary: Concomitant use of a hormonal contraceptive with a CYP3A inducer, such as primidone, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding[249][250]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of primidone [249][250].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of a hormonal contraceptive with a CYP3A

inducer, such as primidone, may reduce the plasma concentration of the estrogen and/or progestin component of the contraceptive and lead to decreased efficacy or an increase in breakthrough bleeding. Use an alternative non-hormonal method of contraception or a back-up method when coadministration is required and for 28 days after discontinuation of primidone[249][250].
7) Probable Mechanism: induction of CYP3A4-mediated metabolism by primidone
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Protriptyline

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Red Clover

1) Interaction Effect: altered estrogenic effects or increased side effects
2) Summary: Red clover isoflavones have affinity for estradiol-alpha and -beta receptors and may act as both agonists and antagonists[300][301]. Red clover may enhance the estrogenic effects of estrogens [302][303].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Caution is advised if red clover is taken with estrogens. Monitor the patient for symptoms of estrogen excess or loss of efficacy.
7) Probable Mechanism: red clover extract may act as an estrogen agonist or antagonist, and may have antiprogestin effects

Rifabutin

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Coadministered rifabutin may induce hormonal contraceptive metabolism, resulting in reduced contraceptive efficacy[195]. During an crossover study, rifabutin altered the disposition of an oral contraceptive and resulted in a higher incidence of spotting compared with controls [196]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifabutin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of rifabutin and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifabutin[176].
7) Probable Mechanism: induction of CYP450-mediated hormonal contraceptive metabolism by rifabutin
8) Literature Reports

a) In 22 healthy women maintained on hormonal combination contraceptives (ethinyl estradiol/norethindrone), the administration of rifabutin resulted in a decrease of AUC and Cmax of both contraceptive components [192].

b) An open-label, randomized, three-way crossover study of healthy females (n=28) was undertaken to determine the impact of concomitant rifabutin and rifampin therapy on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone (Ortho-Novum 1/35(R)). Twenty-two women completed all three phases of the study. All women received the oral contraceptive for 21 days for the first cycle, which served as the control. They were then randomized to one of two sequences to receive concomitant rifampin or rifabutin 300 mg daily for 10 days. When evaluating the

pharmacokinetics of ethinyl estradiol, women receiving rifabutin had a decreased Cmax (333.4 picograms (pg)/mL vs. 416.1 pg/mL) and a decreased AUC (2192.6 pg/hr/mL vs. 3362 pg/hr/mL) when compared with controls. Similarly, the Cmax of norethindrone was 15.37 nanograms (ng)/mL in the rifabutin group and 22.61 ng/mL in control, and the AUC of norethindrone was 86.19 ng/hr/mL during the rifabutin phase and 159.09 ng/hr/mL during control. The incidence of spotting was 3.7% during the control cycle and increased to 21.7% during rifabutin therapy. However, there was no clear evidence of ovulation in this study [193].

c) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

d) The effects of rifampin and rifabutin on an oral contraceptive were examined in a randomized, 2-period, crossover trial involving 12 females. All subjects were on a stable contraceptive regimen that contained ethinyl estradiol 35 mcg and norethindrone 1 mg (Ortho-Novum(R) 1/35). Each participant was randomized to receive 14 days of therapy with rifampin 600 mg daily or rifabutin 300 mg daily on days 7 through 21 of their menstrual cycle. Rifabutin decreased the mean trough ethinyl estradiol concentration (Cmin) by 50%, but the mean Cmax was not significant. Mean norethindrone Cmin values decreased by 32%, while Cmax did not significantly change. Luteinizing hormone and follicle stimulating hormone levels were not statistically altered by rifabutin. All subjects remained anovulatory after rifabutin therapy as indicated by undetectable progesterone levels [194].

Rifampin

1) Interaction Effect: decreased plasma levels of hormonal contraceptive
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with drugs that increase the metabolism of contraceptive steroids, such as rifampin. This could result in unintended pregnancy or breakthrough bleeding[448][227].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Rifampin may alter intestinal flora, which alters the enterohepatic circulation of oral contraceptives. Concomitant use has been associated with unintended pregnancies and menstrual changes [449]. An alternative method of contraception should be used [450] during coadministration and for at least 28 days after discontinuation of rifampin [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of rifampin and a hormonal contraceptive may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of rifampin[176].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) An open-label, randomized, three-way crossover study was conducted on 28 healthy females to determine the impact of concomitant rifabutin and rifampin therapy on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norethindrone

(Ortho-Novum 1/35(R)). Twenty-two women completed all three phases of the study. All women received the oral contraceptive for 21 days for the first cycle, which served as the control. They were then randomized to one of two sequences to receive concomitant rifampin or rifabutin 300 mg daily for 10 days. When evaluating the pharmacokinetics of ethinyl estradiol, women receiving rifampin had a decreased Cmax (243.1 picograms (pg)/mL vs. 416.1 pg/mL) and a decreased AUC (1220.7 pg/hr/mL vs. 3362 pg/hr/mL) when compared with controls. Similarly, the Cmax of norethindrone was 16.5 nanograms (ng)/mL in the rifampin group and 22.61 ng/mL in control, and the AUC of norethindrone was 65.08 ng/hr/mL during the rifampin phase and 159.09 ng/hr/mL during control. The incidence of spotting was 3.7% during the control cycle and increased to 36.4% during rifampin therapy. However, there was no clear evidence of ovulation in this study [446].

c) The effects of rifampin and rifabutin on an oral contraceptive were examined in a randomized, 2-period crossover trial involving 12 females. All subjects were on a stable contraceptive regimen that contained ethinyl estradiol 35 mcg and norethindrone 1 mg (Ortho-Novum(R) 1/35). Each participant was randomized to receive 14 days of therapy with rifampin 600 mg daily or rifabutin 300 mg daily on days 7 through 21 of their menstrual cycle. Rifampin decreased the mean trough ethinyl estradiol concentration (Cmin) by 79% and decreased the mean Cmax by 43%. Mean norethindrone Cmin values decreased by 89%, while Cmax did not significantly change. Luteinizing hormone levels were not statistically altered by rifampin, while follicle stimulating hormone values increased by 69%. Despite these profound pharmacokinetic alterations, all subjects remained anovulatory after rifampin therapy as indicated by undetectable progesterone levels [447].

Rifapentine

1) Interaction Effect: loss of hormonal contraceptive efficacy
2) Summary: Systemic concentrations of the estrogen or progestin component of a combination hormonal contraceptive may be reduced with concomitant use of a metabolic enzyme inducer of CYP3A[249] such as rifapentine, and thus reduce the effectiveness of hormonal contraceptives. Changing to non-hormonal methods of birth control is advised in patients using oral, transdermal patch, or other systemic hormonal contraceptives [435]. Continue back-up contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability [249]. Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Systemic concentrations of the estrogen or progestin component of a combination hormonal contraceptive may be reduced with concomitant use of a metabolic enzyme inducer of CYP3A[249] such as rifapentine, and thus reduce the effectiveness of hormonal contraceptives. Changing to non-hormonal methods of birth control is advised in patients using oral, transdermal patch, or other systemic hormonal contraceptives [435]. Continue back-up contraception for 28 days after discontinuing the enzyme inducer to maintain contraceptive reliability [249].
7) Probable Mechanism: induction of metabolism of hormonal contraceptives
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

Ritonavir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of ritonavir and combination hormonal contraceptives may decrease efficacy of the contraceptive. The AUC of a single 50 mcg dose of ethinyl estradiol declined by 40% on average when given concomitantly with ritonavir 500 mg twice daily. Cmax of ethinyl estradiol also decreased by 32%[187]. In a study, the AUC of ethinyl estradiol decreased from 1670 pg/mL/hr to 993 pg/mL/hr when coadministered with ritonavir [188]. If concomitant use is necessary, alternate methods of contraception should be considered [187].
3) Severity: major
4) Onset: delayed

5) Substantiation: probable
6) Clinical Management: Concomitant use of ritonavir and combination hormonal contraceptives may decrease efficacy of the contraceptive. Alternative methods of contraception should be considered[187].
7) Probable Mechanism: decreased plasma ethinyl estradiol levels
8) Literature Reports

a) Twenty-three female study participants received a single oral dose of an oral contraceptive containing ethinyl estradiol 50 mcg and ethynodiol diacetate 1 mg on study days 1 and 29. From days 15 through 30, ritonavir was administered twice daily. Cmax of ethinyl estradiol was 104 picograms (pg)/mL when administered alone, and decreased to 70.7 pg/mL in the presence of ritonavir. Likewise, the AUC of ethinyl estradiol decreased from 1670 pg/mL/hr to 993 pg/mL/hr when coadministered with ritonavir. These results are consistent with an increase in ethinyl estradiol clearance from hepatic enzyme induction of glucuronidation and/or cytochrome P450 hydroxylation caused by ritonavir [188].

b) Ritonavir is an inhibitor of CYP3A4, which is involved in the metabolism of both estrogens and levonorgestrel. As such, inhibition of metabolism may result in increase plasma concentrations of estrogen and/or levonorgestrel and risk of related side effects [189].

c) The AUC of a single 50 mcg dose of ethinyl estradiol declined by 40% on average when given concomitantly with ritonavir 500 mg twice daily. Cmax of ethinyl estradiol also decreased by 32% [187].

Rufinamide

1) Interaction Effect: reduced efficacy of combination contraceptives
2) Summary: Concomitant use of rufinamide with hormonal contraceptives may result in decreased contraceptive efficacy. One study demonstrated a decrease in the AUC and Cmax of ethinyl estradiol and norethindrone when rufinamide was administered concurrently. Patients should be advised to use an alternative or backup method of contraception during rufinamide therapy[474] and for 28 days after discontinuation of rufinamide [250].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Due to the potential for reduced efficacy of hormonal contraceptives in patients receiving rufinamide, alternative or backup methods of contraception should be used during treatment with rufinamide[474] and for 28 days after discontinuation of rufinamide [250].
7) Probable Mechanism: unknown
8) Literature Reports

a) When oral rufinamide 800 mg was given twice daily for 14 days with an oral contraceptive containing ethinyl estradiol 35 mcg and norethindrone 1 mg, the mean ethinyl estradiol AUC and Cmax decreased by 22% and 18%, respectively, and the mean norethindrone AUC and Cmax decreased by 14% and 18%, respectively [474].

Secobarbital

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant combination contraceptive and chronic barbiturate therapy may lead to an increased metabolism of contraceptive steroids, thus decreasing their effectiveness as a contraceptive[451][452][453]. This may result in unintended pregnancy or breakthrough bleeding [454].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients taking secobarbital chronically should use alternative methods of birth control along with the hormonal contraceptive.
7) Probable Mechanism: induction of estrogen metabolism

Selegiline

1) Interaction Effect: an increase in selegiline oral bioavailability and an increased risk of selegiline adverse reactions
2) Summary: During a randomized study to determine the dose relationship of selegiline and its main metabolite, desmethylselegiline, female subjects who were receiving oral contraceptives had a Cmax and AUC that was 10- to 20-fold higher than subjects not receiving oral contraceptives. The marked elevation in the bioavailability of selegiline may result in a loss of selective inhibition of monoamine oxidase (MAO) type B, which would predispose the patient to hypertensive reactions after the intake of amines[328].
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: The concomitant use of selegiline and a combination contraceptive should be avoided. Alternately, the selegiline dose should be reduced to minimize the risks of selegiline adverse effects, including hypertensive reactions.
7) Probable Mechanism: inhibition of selegiline first-pass metabolism to desmethylselegiline
8) Literature Reports

a) Eight healthy females, four using oral contraceptives, entered an open, four-period randomized study to characterize the dose relationship of selegiline and desmethylselegiline pharmacokinetics. Subjects ingested a single dose of 5 mg, 10 mg, 20 mg, or 40 mg of selegiline, with a washout period of at least two weeks between treatment phases. Although researchers were not looking for differences in the pharmacokinetics of selegiline between oral contraceptive users and non-users, there was a 20-fold increase in selegiline AUC in oral contraceptive users as compared with non-users. The median Cmax was more than 10 times higher in the group taking oral steroids. Desmethylselegiline AUC values were also higher in contraceptive users, although the increase was smaller in magnitude and did not reach statistical significance. The difference in the metabolic ratio between the two groups suggests that oral contraceptives inhibit the N-demethylation of selegiline to desmethylselegiline. The increase in selegiline bioavailability in oral contraceptive users may lead to loss of selective inhibition of monoamine oxidase type B, predisposing the patient to hypertensive reactions [327].

Somapacitan-beco

1) Interaction Effect: decreased somapacitan-beco efficacy
2) Summary: Treatment with somapacitan-beco and oral estrogens may decrease the serum IGF-1 response to somapacitan-beco. Patients receiving oral estrogen replacement may require higher somapacitan-beco dosages. If coadministration with oral estrogens is required, increase initial dose to somapacitan-beco 2 mg subQ once weekly[207].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Treatment with somapacitan-beco and oral estrogens may decrease the serum IGF-1 response to somapacitan-beco. Patients receiving oral estrogen replacement may require higher somapacitan-beco dosages. If coadministration with oral estrogens is required, increase initial dose to somapacitan-beco 2 mg subQ once weekly[207].
7) Probable Mechanism: decreased serum IGF-1 response to somapacitan-beco

Somatropin

1) Interaction Effect: decreased somatropin efficacy
2) Summary: Treatment with somatropin and oral estrogens may decrease the serum IGF-1 response to somatropin. Patients receiving oral estrogen may require higher somatropin dosages[366].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Treatment with somatropin and oral estrogens may decrease the serum IGF-1 response to somatropin. Patients receiving oral estrogen may require higher somatropin dosages[366].
7) Probable Mechanism: decreased serum IGF-1 response to somatropin

St John's Wort

1) Interaction Effect: decrease in estrogen plasma concentrations and in contraceptive effectiveness
2) Summary: Pregnancy and breakthrough bleeding have been reported when St. John's wort was taken concurrently with hormonal contraceptives[217][218][219][220][221]. St. John's wort significantly increased the metabolism of norethindrone in a clinical trial [222], likely through induction of CYP3A4 and p-glycoprotein metabolism [223][224] [225]. The effect of St. John's wort on transdermal and injectable contraceptives is unknown, though caution is advised [226].Concomitant use of a CYP3A4 inducer disproportionally increased the rate of unplanned pregnancy with oral and implanted contraceptives; therefore, consider intrauterine or intravaginal routes if coadministration is required [177]. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use an alternate nonhormonal contraceptive method [227] during coadministration and for at least 28 days after discontinuation of St. John's wort [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Concomitant use of St. John's wort and hormonal contraceptives may decrease plasma concentrations of the contraceptive and diminish effectiveness. If coadministration is required, use an alternative method of contraception during coadministration and for at least 28 days after discontinuation of St. John's wort[176].
7) Probable Mechanism: induction of CYP3A4-mediated hormone metabolism and induction of intestinal P-glycoprotein drug transporter by St. John's wort
8) Literature Reports

a) Concomitant use of a CYP3A4 inducer with oral or implantable contraceptive products containing levonorgestrel (684 events) or etonogestrel/desogestrel (864 events) was associated with a disproportionately higher rate of unintended pregnancy compared to all other event types reported to the FDA Adverse Event Reporting System (FAERS) between 1971 and 2020 [levonorgestrel (14,504 total events); etonogestrel/desogestrel (9348 total events)]. When compared between CYP3A4 inducer exposure vs no exposure, cases of unintended pregnancy made up a significantly higher proportion of

total events when levonorgestrel was administered orally (32.8% vs 10.5%) or as an implant (51.9% vs 11.9%), and a similar association was identified with implanted etonogestrel products (42.5% vs 13.1%). However, when contraceptives were administered as an intrauterine device (levonorgestrel, 10.3% vs 11.5%) or intravaginal ring (etonogestrel, 10.9% vs 8.7%), no significant associations were identified. Oral desogestrel (pro-drug of etonogestrel) in combination with ethynyl estradiol also was not significantly affected (11.8% vs 17.4%). Intrauterine and vaginal ring products may be preferred in lieu of oral and implantable contraceptive products in women concomitantly receiving CYP3A4 inducers [177].

b) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with ethinyl estradiol in 4 studies resulted in no change in ethinyl estradiol AUC with products containing hyperforin dosages of 0.4 mg/day, and a decrease in ethinyl estradiol AUC of 10% to 34% with hyperforin dosages of 2.4 to 33 mg/day [210].

c) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with norethindrone in 2 studies resulted in a 11% to 12% decrease in norethindrone AUC with products containing hyperforin dosages of 27 to 33 mg/day [210].

d) In a systematic review of studies of pharmacokinetic interactions involving St John's Wort, concomitant use with desogestrel in 2 studies resulted in a 42% decrease in the AUC of ketodesogestrel, the active desogestrel metabolite with products containing hyperforin dosages of 4.8 to 7.5 mg/day and no change in AUC with 0.4 mg/day [210].

e) There have been 8 reports of breakthrough bleeding and 1 case of changed menstrual bleeding by women 23 to 31 years of age who were taking St. John's wort and oral contraceptives. Most of the women had been taking oral contraceptives for a long time. The time between coadministration of St. John's wort and onset of problems was approximately 1 week for most patients. Induction of CYP3A4, which metabolizes steroids, is suggested to be the cause [211].

f) Three case reports detail women taking ethinyloestradiol and desogestrel combination contraceptives who experienced breakthrough bleeding while taking hypericum. The author cites the possible mechanism of this interaction as a CYP3A4 induction by St. John's wort, causing increased metabolism and consequent lowering of ethinyloestradiol concentrations [212].

g) St. John's wort caused breakthrough bleeding in 7 of 12 women taking oral contraceptives. Twelve healthy female subjects received a combination oral contraceptive (ethinyl estradiol/norethindrone) for three months. During months 2 and 3, St. John's wort 300 mg was administered 3 times daily. Follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone, ethinyl estradiol, and norethindrone concentrations as well as CYP3A enzyme activity were assessed in months 1 and 3. FSH, LH and progesterone concentrations on days 11 through 16 were not altered by St. John's wort. St. John's wort significantly increased the oral clearance of norethindrone from 8.2 to 9.5 L/hr . Seven of 12 subjects experienced breakthrough bleeding during month 3, compared with 2 of twelve in month 1. The authors conclude that long-term St. John's wort administration alters the efficacy and disposition of combination oral contraceptives due to the ability of St. John's wort to induce intestinal wall CYP3A [213].

h) Two women experienced unintended pregnancy within 5 months of starting St. John's wort. Both had used oral contraceptives for more than 8 years [214].

i) A 36-year-old female experienced an unplanned pregnancy associated with the concomitant use of St. John's wort and an oral hormonal contraceptive (ethinyl estradiol/dienogest (Valette(R))). She had self-medicated with St. John's wort extract (Helarium(R) 425, Bionorica) up to 1700 mg daily for approximately 3 months before conception. She was on no other medications [215].

j) Seven reports of pregnancy have been received by the United Kingdom since February 2000 associated with concomitant use of St. John's wort and oral contraceptives [216].

Succinylcholine

1) Interaction Effect: prolongation of neuromuscular blockade
2) Summary: The chronic use of oral contraceptives has been reported to reduced plasma cholinesterase activity by approximately 20%[387]. Plasma cholinesterase rapidly hydrolyzes succinylcholine to succinylmonocholine, which possesses insignificant muscle relaxant properties. By reducing the activity of plasma cholinesterase, the neuromuscular blocking effect of succinylcholine may be enhanced [388]. The enhanced response to succinylcholine may be more pronounced in patients who have a pathologically depressed cholinesterase activity.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Patients receiving chronic combination contraceptive therapy should be monitored for prolongation of neuromuscular blockade when administered succinylcholine. The enhanced response to succinylcholine may be more pronounced in patients who have a pathologically depressed cholinesterase activity.
7) Probable Mechanism: inhibition of plasma cholinesterase activity

Sugammadex

1) Interaction Effect: decreased contraceptive serum concentration and efficacy
2) Summary: Concomitant use of sugammadex and hormonal contraceptives may result in decreased contraceptive serum concentrations and efficacy due to binding of progestogen by sugammadex. An additional, nonhormonal contraceptive method or backup method of contraception (such as condoms and spermicides) is recommended for 7 days after sugammadex administration in patients who are on non-oral hormonal contraceptives or in patients who took an oral contraceptive on the same day as the sugammadex administration[248].
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of sugammadex and hormonal contraceptives may result in decreased contraceptive serum concentrations and efficacy due to binding of progestogen by sugammadex. An additional, nonhormonal contraceptive method or backup method of contraception (such as condoms and spermicides) is recommended for 7 days after sugammadex administration in patients who are on non-oral hormonal contraceptives or in patients who took an oral contraceptive on the same day as the sugammadex administration[248].
7) Probable Mechanism: binding of progestogen by sugammadex

Sultamicillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Contraceptive effectiveness may be reduced when hormonal contraceptives are coadministered with antibiotics. The mechanism of interaction is thought that penicillins may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives. This could result in unintended pregnancies and menstrual changes[185][186]. However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]. Another study showed concurrent ampicillin administration did not to diminish the effectiveness of the oral contraceptive studied [184].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ampicillin and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) In a study of 11 regularly menstruating women, ages 21 to 39, concurrent ampicillin administration appeared not to diminish the effectiveness of the oral contraceptive studied. Demulen(R) (1 mg ethynodiol diacetate and 50 mcg ethinyl estradiol) was given to each subject for 2 consecutive menstrual cycles, 21 days on and 7 days off. Ampicillin 250 mg or placebo was given 4 times/day from day 1 through day 16 of each study cycle. Two subjects experienced breakthrough bleeding while taking ampicillin. One subject reported spotting with Demulen(R)/placebo combination, but not with Demulen(R)/ampicillin. There was no difference in quantity of menstrual flow between the two study cycles. One subject reported mid-cycle abdominal pain while on Demulen(R)/ampicillin. All cycles appeared to be anovulatory with no significant difference in follicle-stimulating hormone, luteinizing hormone, and steroid hormone

levels in patients on Demulen(R)/ampicillin compared with patients on Demulen(R)/placebo [184].

Tacrine

1) Interaction Effect: an increased risk of tacrine adverse effects
2) Summary: Hormone replacement therapy (HRT) with estradiol valerate and levonorgestrel significantly increased tacrine concentrations in ten healthy female volunteers. HRT reduces the metabolic conversion of tacrine to its main metabolite, 1-hydroxytacrine, by inhibiting cytochrome P450 1A2 enzymes during the first-pass phase, which may increase the likelihood of enhanced tacrine efficacy and adverse effects[430].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients for enhanced tacrine adverse effects during long-term treatment in conjunction with estradiol. Smaller doses of tacrine may be appropriate.
7) Probable Mechanism: inhibition of cytochrome P450 1A2-mediated conversion of tacrine to 1-hydroxytacrine
8) Literature Reports

a) Ten healthy female volunteers participated in a randomized, double-blind crossover study which evaluated the effects of hormone replacement therapy (HRT) on the pharmacokinetics of tacrine. Each subject received HRT with estradiol valerate 2 mg and levonorgestrel 0.25 mg or matching placebo once daily for ten days. One hour after the last dose of HRT on day 10, a single dose of tacrine 40 mg was administered. HRT increased the area under the concentration-time curve (AUC) of tacrine by 60% and increased the mean maximum concentration (Cmax) by 46%. The mean apparent oral clearance of tacrine was reduced by 31% in the presence of HRT. No significant pharmacokinetic effects were seen on 1-hydroxytacrine during the HRT phase, indicating that HRT reduces the 1-hdyroxylation of tacrine by cytochrome P450 1A2. While this drug interaction may enhance the efficacy of tacrine in the treatment of Alzheimer's disease, the incidence and severity of adverse effects may also increase, which could contribute to decreased patient compliance [429].

Tazemetostat

1) Interaction Effect: decreased plasma levels of hormonal contraceptives
2) Summary: Concomitant use of tazemetostat and with CYP3A substrates, including hormonal contraceptives, may result in decreased concentrations and reduced efficacy of CYP3A substrates. Coadministration of tazemetostat with midazolam (a sensitive CYP3A substrate) decreased midazolam AUC by 40% and Cmax by 21%. Tazemetostat may render some hormonal contraceptives ineffective. Advise females of reproductive potential using tazemetostat to use effective non-hormonal contraception during treatment and for 6 months after the final dose[362].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tazemetostat with CYP3A substrates, including hormonal contraceptives, may result in decreased concentrations and reduced efficacy of CYP3A substrates. Tazemetostat may render some hormonal contraceptives ineffective. Advise females of reproductive potential using tazemetostat to use effective non-hormonal contraception during treatment and for 6 months after the final dose[362].
7) Probable Mechanism: increased CYP3A4-mediated contraceptive metabolism
8) Literature Reports

a) Concomitant use of tazemetostat 800 mg twice daily with oral midazolam (a sensitive CYP3A substrate) in patients decreased midazolam AUC(0 to12) by 40% and Cmax by 21% [362].

Telaprevir

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Administration of telaprevir with ethinyl estradiol may significantly decrease plasma concentrations of ethinyl estradiol. Norethindrone concentrations were minimally effected. In a drug interaction study, concurrent administration of ethinyl estradiol and telaprevir led to significant decreases in ethinyl estradiol Cmax, AUC, and Cmin[306]. During concurrent use of telaprevir and combination contraceptives, 2 effective non-hormonal forms of birth control should be used throughout telaprevir therapy and until approximately 2 weeks following the discontinuation of telaprevir, at which time hormonal contraceptives may be used as 1 of the 2 contraceptive measures required during ribavirin and peginterferon alfa therapy; however, specific contraceptive prescribing guidelines should be followed. Patients who are using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency [305].
3) Severity: major
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Administration of telaprevir with ethinyl estradiol may significantly decrease plasma concentrations of ethinyl estradiol. During concurrent use of telaprevir and combination contraceptives, 2 effective non-hormonal forms of birth control should be used throughout telaprevir therapy and until approximately 2 weeks following the discontinuation of telaprevir, at which time hormonal contraceptives may be

used as 1 of the 2 contraceptive measures required during ribavirin and peginterferon alfa therapy; however, specific contraceptive prescribing guidelines should be followed. Patients who are using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency[305].
7) Probable Mechanism: unknown
8) Literature Reports

a) In a pharmacokinetic study (n=24), the concomitant administration of telaprevir 750 mg every 8 hours with an oral contraceptive containing ethinyl estradiol 0.035 mg and norethindrone 0.5 mg daily resulted in a 26% to 33% reduction in ethinyl estradiol exposure. Female volunteers 18 and 45 years old who were taking ethinyl estradiol 0.035 mg/norethindrone 0.5 mg for at least 3 months were enrolled. During the study, study participants received this combination contraceptive regimen for 21 days followed by a 7-day washout period, then ethinyl estradiol 0.035 mg/norethindrone 0.05 mg plus telaprevir for 21 days followed by telaprevir alone for 7 days. The mean Cmax, AUC at steady state, and Cmin for ethinyl estradiol decreased by 26%, 28% and 33%, respectively, after the administration of telaprevir. The least-squares mean ratios for ethinyl estradiol were all outside the no-effect boundaries of 0.8 to 1.25 (0.74 (90% confidence interval (CI); 0.68 to 0.80), 0.67 (90% CI; 0.63 to 0.71), and 0.72 (90% CI 0.69 to 0.75) for Cmax, Cmin, and AUC at steady state, respectively). Norethindrone and telaprevir exposures were found not to be significantly affected by the coadministration of both agents [306].

b) In 2 drug interaction studies (n=23 and n=24), administration of telaprevir 750 mg every 8 hours for 21 days concurrently with ethinyl estradiol 0.035 mg and norethindrone 0.5 mg daily for 21 days did not significantly change norethindrone concentrations. The norethindrone ratio estimate (norethindrone with telaprevir to norethindrone without) was 1 (90% confidence interval (CI), 0.93 to 1.07) for Cmax, 0.99 (90% CI, 0.93 to 1.05) for AUC and 1 (90% CI, 0.93 to 1.08) for Cmin for one study (n=23). In the second study (n=24), the ratio estimates were 0.85 (90% CI, 0.81 to 0.89), 0.89 (90% CI, 0.86 to 0.93), and 0.94 (0.87 to 1), respectively [305].

Temazepam

1) Interaction Effect: decreased temazepam effectiveness
2) Summary: Combination contraceptives may stimulate the glucuronide conjugation of temazepam[296] and increase the clearance of temazepam [294]. More studies are needed to confirm this interaction and determine any clinical effects. Monitoring a patient receiving concurrent combination contraceptives and temazepam for a reduced response to the benzodiazepine should be considered.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of temazepam and combination oral contraceptives may increase temazepam clearance[294]. Consider monitoring patients receiving concurrent combination contraceptives and temazepam for a reduced response to temazepam.
7) Probable Mechanism: increased temazepam clearance
8) Literature Reports

a) Concomitant oral contraceptive and temazepam therapy has been reported to alter the metabolism of temazepam. In one study, low-dose estrogen oral contraceptives significantly decreased the AUC and increased the elimination rate of temazepam following single-dose therapy (30 mg). Based on these data, normal therapeutic doses of temazepam may be less effective in women using oral contraceptives [295].

Tetracycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Concomitant use of tetracycline and combination oral contraceptives may result in decreased contraceptive efficacy[269]. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives [204]. Although there was no increased risk of contraceptive failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tetracycline and combination oral contraceptives may result in decreased contraceptive efficacy[269]; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3%

contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) The interaction between oral contraceptives and tetracycline has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

d) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

e) In a pharmacokinetic study, oral administration of tetracycline 500 mg four times daily for 3 days prior to and 7 days during use of the norelgestromin and ethinyl estradiol combination transdermal did not significantly affect the pharmacokinetics of norelgestromin or ethinyl estradiol [271].

Theophylline

1) Interaction Effect: theophylline toxicity (nausea, vomiting, palpitations, seizures)
2) Summary: Combination hormonal contraceptives containing some synthetic estrogens (ethinyl estradiol) may inhibit the metabolism of theophylline[401]. Combination contraceptives have been reported to decrease theophylline clearance by 34% and increase the half-life by 33% (7.9 vs 5.4 hr) [402]. The distribution of theophylline has not been reported to change. A longer dosing interval may be possible while on combination contraceptives [403].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: During initiation of concurrent therapy, monitor theophylline serum levels and for signs of theophylline toxicity such as nausea, tremors, headache, or rapid, irregular heartbeat. Careful monitoring is also necessary when the combination contraceptive is stopped.
7) Probable Mechanism: decreased theophylline metabolism
8) Literature Reports

a) Low-dose oral contraceptives do not appear to influence single-dose (intravenous) theophylline pharmacokinetics in adolescents [400]. No differences were found in theophylline distribution volume, elimination half-life, or total body clearance between

control subjects (n=10) and subjects who received 3 to 9 months of low-dose oral contraceptives (n=10).

Ticarcillin

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Ticarcillin/clavulanic acid may alter intestinal flora, which may lead to lower reabsorption of estrogen and decreased effectiveness of combination oral estrogen/progesterone contraceptives[345]. Concomitant use has been associated with unintended pregnancies and menstrual changes [346][347] However, in a large retrospective chart review, there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183]
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of ticarcillin/clavulanic acid and combination contraceptives may result in decreased contraceptive efficacy; however, evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended[183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including penicillins; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

Tigecycline

1) Interaction Effect: decreased contraceptive effectiveness
2) Summary: Tigecycline, a tetracycline derivative, used concomitantly with oral contraceptive combinations (OC) may decrease contraceptive effectiveness[392]. The mechanism of interaction is thought that tetracyclines may alter intestinal flora which, in turn, may alter the enterohepatic circulation of combination contraceptives [204]. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracycline, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202]. In a large retrospective chart review, there was no significant difference in OC failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
3) Severity: major
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tigecycline and oral combination contraceptives (OC) may result in decreased contraceptive efficacy. Although there was no increased risk of OC failure in a study of women with acne (n=34) who used OC concomitantly with antibiotics, including tetracyclines, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives[202]. Evidence from a large retrospective chart review showed there was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3%. If at any time, a 1% to 3% contraceptive failure rate is unacceptable to the patient, an additional form of contraception should be recommended [183].
7) Probable Mechanism: alteration in gut flora, leading to decreased estrogen

reabsorption
8) Literature Reports

a) There was no significant difference in oral contraceptive (OC) failure rates among women who received OC with or without concomitant antibiotics, including tetracyclines; and the OC failure rate in both groups did not exceed a typical contraceptive failure rate of 1% to 3% in a retrospective chart review and follow-up survey. Of 356 women who received antibiotics and OC concurrently over 311.2 woman-years, 5 pregnancies occurred yielding a rate of 1.6 pregnancies per 100 woman-years or a 1.6%/year failure rate. Of 425 control patients who received OC without antibiotics for 1244.9 woman-years, 12 pregnancies occurred yielding a rate of 0.96 pregnancies per 100 woman-years or 0.96%/year failure rate. The difference in failure rate between these groups was not significant (95% CI on the difference, -0.81 to 2.1; p=0.4) and ruled out a substantial difference (greater than 2.1% per year). The women in the control group consisted of 263 women who received OC but did not concomitantly use OC with antibiotics and 162 OC users who never concomitantly used antibiotics. Among women who never concomitantly used antibiotics (n=162) over 551.2 woman-years, 7 pregnancies occurred, yielding a rate of 1.3 pregnancies per 100 woman-years or 1.3%/year failure rate [183].

b) There was no increased risk of contraceptive failure with concomitant antibiotic use in a study of 34 patients with acne who used oral antibiotics, including tetracycline (n=17) and erythromycin (n=20), concomitantly with low estrogen oral contraceptives for a total period of 71 women-years.. The calculated contraceptive failure rate was 1.4 per 100 women-years for the study, which was not significantly different than an accepted and documented contraceptive failure rate of 0.27 per 100 women-years (p=0.17). Of the 34 patients, one became pregnant while using the norethindrone, ethinyl estradiol, and mestranol combination concomitantly with oral tetracycline (12 months duration of use); the patient stated that she did not miss any doses of the contraceptive combination or had any changes in her menstrual cycle. Two other patients reported menstrual irregularities; one reported spotting while using the ethinyl estradiol and ethynodiol diacetate combination concomitantly with terfenadine and minocycline treatment, and another reported heavy cramping while using the norethindrone acetate and ethinyl estradiol combination concomitantly with tetracycline. Although this study determined that there was no increased risk of contraceptive failure with concomitant antibiotic use, the data suggests that tetracycline and its derivatives may interact with low-dose estrogen contraceptives [202].

c) Tigecycline is a glycylcycline antibiotic structurally similar to tetracycline antibiotics and may have similar adverse effects [392]. The interaction between oral contraceptives and tetracycline-type antibiotics has been suggested to be due to an alteration of the gut flora. The normal gut flora is thought to be responsible for the hydrolysis of the glucuronide moiety (estrogen metabolite found in the bile) to free drug. When the gut flora is altered, enterohepatic recirculation is reduced and the metabolite is simply excreted. This causes a decrease in body levels of the estrogen and reduced effectiveness [204].

d) A study which documented 163 cases of oral contraceptive failure in reliable pill takers found that 23% (37 cases) of these failures were associated with antibiotic use. Of these 163 cases, 6 were attributed to the use of tetracyclines, including doxycycline, minocycline, and lymecycline. The authors recommended a 7-day abstinence period or a barrier method of contraceptive following a course of antibiotics [270].

Tipranavir

1) Interaction Effect: decreased estrogen concentration and increased risk of developing a non-serious rash
2) Summary: In pharmacokinetic studies, a single dose of 0.035 milligrams (mg) of ethinyl estradiol coadministered with tipranavir, in combination with ritonavir, dosed as tipranavir/ritonavir 500/100 mg (n=21), 750/200 mg (n=13) twice daily resulted in decreased ethinyl estradiol maximum serum concentrations (Cmax) and area under the concentration-time curve (AUC) by approximately 50%. Alternative methods of nonhormonal contraception should be considered when estrogen-based oral contraceptives are administered concurrently with tipranavir and 200 milligrams of ritonavir. Patients using estrogens as hormone replacement therapy should be monitored for signs of estrogen deficiency. Additionally, there may be an increased risk of developing a non-serious rash when tipranavir is coadministered with estrogens[397].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: established
6) Clinical Management: Concurrent administration of ethinyl estradiol with tipranavir and ritonavir results in decreased concentrations of ethinyl estradiol. Consider using alternative methods of nonhormonal contraception when estrogen-based oral contraceptives are administered concurrently with tipranavir and 200 milligrams of ritonavir. Additionally, monitor patients using estrogens as hormone replacement therapy for signs of estrogen deficiency. There may be an increased risk of developing a non-serious rash when tipranavir is coadministered with estrogens[397].
7) Probable Mechanism: unknown

Tirzepatide

1) Interaction Effect: decreased absorption of oral contraceptives
2) Summary: Administration of a combined oral contraceptive (0.35 mg ethinyl estradiol and 0.25 mg norgestimate) and a single dose of tirzepatide 5 mg, reduced mean Cmax and AUC of ethinyl estradiol, norgestimate, and norelgestromin and delayed Tmax. Advise patients to switch to a non-oral contraceptive method, or add a barrier method of contraception for at least 4 weeks after initiation of tirzepatide and for 4 weeks after each tirzepatide dose escalation. Non-oral hormonal contraceptives are not likely to be affected by tirzepatide[423].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of tirzepatide with oral contraceptives may decrease absorption of the oral contraceptive. Advise patients to switch to a non-oral contraceptive method, or add a barrier method of contraception for at least 4 weeks after initiation of tirzepatide and for 4 weeks after each tirzepatide dose escalation. Non-oral hormonal contraceptives are not likely to be affected by tirzepatide[423].
7) Probable Mechanism: delayed gastric emptying
8) Literature Reports

a) Following the administration of a combined oral contraceptive (0.35 mg ethinyl estradiol and 0.25 mg norgestimate) and a single dose of tirzepatide 5 mg, mean Cmax of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in Tmax of 2.5 to 4.5 hours also was observed [423].

Tizanidine

1) Interaction Effect: increased tizanidine plasma concentrations resulting in increased hypotensive and sedative effects
2) Summary: The concomitant use of tizanidine and oral contraceptives is not recommended. In a retrospective analysis of population pharmacokinetic data, 50% lower clearance of tizanidine was reported in women taking oral contraceptives than in women not on oral contraceptives following single and multiple 4-mg doses of tizanidine. If coadministration is clinically necessary, initiate tizanidine at a dose of 2 mg and increase daily by 2 to 4 mg based on therapeutic response. Reduce the dose or discontinue tizanidine therapy if hypotension, bradycardia, or excessive drowsiness occurs[475][476].
3) Severity: major
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Concomitant use of tizanidine and oral contraceptives is not recommended. If coadministration is required, initiate tizanidine at a dose of 2 mg and increase daily by 2 to 4 mg based on response to therapy. Reduce the dose or discontinue tizanidine therapy if hypotension, bradycardia, or excessive drowsiness occurs[475][476].
7) Probable Mechanism: inhibition of CYP1A2-mediated tizanidine metabolism by the contraceptive
8) Literature Reports

a) One study reported higher serum levels of tizanidine in women taking oral contraceptives than in men [477]. In a retrospective analysis of population pharmacokinetic data, 50% lower clearance of tizanidine was reported in women taking oral contraceptives than in women not on oral contraceptives. Patients were given single and multiple 4-mg doses of tizanidine [475][476].

Topiramate

1) Interaction Effect: decreased plasma levels of hormonal contraceptive
2) Summary: Topiramate is a mild inducer of CYP3A4[284]. Coadministration of CYP3A4 inducers, such as topiramate, with drugs that are metabolized by CYP3A4, including contraceptive hormones, may result in decreased hormone plasma concentrations and subsequently decreased contraceptive effectiveness. Reduced contraceptive effectiveness could result in unintended pregnancy or breakthrough bleeding. Patients should use additional contraception or an alternate nonhormonal contraceptive method [285][286][287] during coadministration and for at least 28 days after discontinuation of topiramate [176].
3) Severity: major
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concomitant use of topiramate and combination oral contraceptives may result in decreased contraceptive efficacy. Advise patients to report any changes in their bleeding patterns if topiramate is used concomitantly with estrogen-containing contraceptives[284]. In women who are taking topiramate concomitantly with hormonal contraceptives, including combination and progestin-only contraceptives, recommend the patient use additional contraception or alternate contraceptive method [285][286][287] during coadministration and for at least 28 days after discontinuation of topiramate [176]. An expert Working Group that was convened by the WHO in 2008 to revise the third edition of the Medical Eligibility Criteria for Contraceptive Use recommended patients avoid the concomitant use of topiramate with combined oral contraceptives, the transdermal patch, the vaginal ring, or progestin-only pills due to the risk of decreased contraceptive efficacy [288].

7) Probable Mechanism: increased metabolism of hormonal contraceptive
8) Literature Reports

a) A randomized, open-label, 5-group study in healthy volunteers concluded that topiramate doses less than or equal to 200 mg/day do not interact with oral contraceptives containing ethinyl estradiol and norethindrone. In two 28-day cycles, 5 groups of female subjects received oral doses of ethinyl estradiol/norethindrone (Ortho-Novum(R) 1/35) alone in the first cycle and then in combination with topiramate or carbamazepine during the second cycle. Coadministration of daily topiramate in nonobese (50 mg, n=11; 100 mg, n=10; 200 mg, n=12) and obese (BMI 30 to 35; n=12; topiramate 200 mg) women resulted in nonsignificant changes in the AUC of ethinyl estradiol and nonsignificant changes in the AUC and plasma concentrations of norethindrone compared with the contraceptive alone. When carbamazepine 600 mg/day was coadministered with ethinyl estradiol/norethindrone (n=10), significant decrease in AUC of each drug was observed; 42% and 58%, respectively. Carbamazepine increased oral clearance in both contraceptives by 127% and 69%, respectively [179].

b) In a study of 12 women with epilepsy who were receiving stable valproic acid monotherapy and oral contraception with ethinyl estradiol 35 mcg/norethindrone 1 mg (21 days on/7 days off), the coadministration of topiramate (200 to 800 mg/day) for four 28-day cycles significantly decreased systemic exposure to ethinyl estradiol. Starting on the first 3 days of cycle 2 through cycle 4, topiramate 100 mg, 200 mg, and 400 mg were given twice daily, respectively. Although, the addition of topiramate did not change the norethindrone pharmacokinetic parameters, the mean AUC of ethinyl estradiol was decreased by 18%, 21%, and 30% with daily topiramate doses of 200 mg, 400 mg, and 800 mg, respectively, in cycles 2 through 4 compared with cycle 1 (control cycle) and mean serum clearance (CL/F) of ethinyl estradiol was 14.7% to 33% higher. It is suggested that the modest effect of topiramate on ethinyl estradiol pharmacokinetics may be due to topiramate being a weak inducer of cytochrome P450 [289].

Tranexamic Acid

1) Interaction Effect: an increased risk of thrombotic events
2) Summary: Concomitant use of hormonal contraceptives and tranexamic acid is contraindicated due to further increased risk of thrombotic events, especially in women who are obese, or smoke cigarettes, and more so, in smokers over the age of 35 years[199]. Concomitant use of tranexamic acid and all hormonal contraceptives should be avoided, and an effective alternative nonhormonal contraceptive method should be used [200]. Venous and arterial thrombotic events have been reported during postmarketing surveillance of women concomitantly treated with combined hormonal contraceptives and tranexamic acid [199].
3) Severity: contraindicated
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: Due to further increased risk of thrombotic events, especially in women who are obese, or smoke cigarettes, and more so, in smokers over the age of 35 years, coadministration of combination hormonal contraceptives and tranexamic acid is contraindicated[199]. Concomitant use of tranexamic acid and all hormonal contraceptives should be avoided, and an effective alternative nonhormonal contraceptive method should be used [200].
7) Probable Mechanism: unknown

Triazolam

1) Interaction Effect: triazolam toxicity (excessive sedation, confusion)
2) Summary: Combination contraceptives may inhibit the oxidative metabolism of triazolam causing an increase in serum levels of the benzodiazepine[373].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Monitor patients receiving concurrent combination contraceptives and triazolam therapy for an increased response to the benzodiazepine. Reductions in the triazolam dose may be needed.
7) Probable Mechanism: decreased hepatic metabolism of triazolam
8) Literature Reports

a) Low-dose oral contraceptives were shown to cause a 32% decrease in clearance and 44% increase in the AUC of triazolam. The increase in systemic availability of triazolam is similar to that observed after cimetidine or isoniazid, drugs known to inhibit oxidative drug metabolism. Reports of the effect of oral contraceptives on the elimination of oxidized drugs have demonstrated that oral contraceptives impair oxidative metabolism in the liver. This effect was believed to be mediated by the estrogen component of oral contraceptives [372].

Trimipramine

1) Interaction Effect: possible attenuation of antidepressant effectiveness; tricyclic toxicity (drowsiness, hypotension, akathisia)
2) Summary: In isolated cases, the pharmacologic effects of tricyclic antidepressants may be increased or decreased by estrogens[322], with paradoxical loss of antidepressant effect yet tricyclic toxicity being manifested simultaneously [323]. The effects of the interaction appear to be estrogen dose-related [324] and may be of clinical

importance primarily in patients previously stabilized on tricyclic therapy who are being started on estrogen therapy [325].
3) Severity: minor
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: If signs or symptoms of altered tricyclic response are noted, dose adjustment downward of either the estrogen or tricyclic component may be successful in restoring effectiveness or resolving toxicity. However, drug withdrawal may be required.
7) Probable Mechanism: possible inhibition of hepatic metabolism of the tricyclic antidepressant
8) Literature Reports

a) Some studies evaluated the qualitative effects of concomitant administration of estrogen and TCAs. In one trial, 30 depressed female prisoners were randomly assigned to four treatment groups. Ten patients received placebo, 10 received imipramine (150 mg daily) and placebo, five patients received imipramine (150 mg daily) and ethinyl estradiol (50 mcg daily), while five patients received imipramine (150 mg daily) and ethinyl estradiol (25 mcg daily). The 10 patients that received placebo did not improve over the six weeks of the study. The 10 patients taking estrogen and imipramine demonstrated a significantly greater improvement in symptoms than did the 10 patients taking imipramine alone. However, after two weeks, the five patients that received imipramine and high-dose estrogen had not improved as much as the patients receiving imipramine and low-dose estrogen. The only side-effect reported was drowsiness, which only affected the patients taking imipramine. Following the discontinuation of ethinyl estradiol, a time period of two weeks was required for the high-dose estrogen group to do as well as the low-dose group. This effect was attributed to the presence of residual estrogen in the high-dose group. In another group, five women received imipramine 150 mg and ethinyl estradiol 50 mrg daily did not improve as much as 10 patients receiving only imipramine. Also, the patients on the combination had severe side-effects including lethargy, coarse tremor and systolic hypotension [313].

b) A 32-year-old female taking conjugated estrogens 2.5 mg and imipramine 100 mg developed lethargy, tremors, and signs of depersonalization. After two years of therapy, the patient increased her estrogen dose to 5 mg and then 7.5 mg daily. The patient became nauseated, had constant headaches, and low normal blood pressure. All lab work was normal. Upon discontinuing the estrogen, the side effects abated. Some investigators have proposed that the side effects resulted from enhanced TCA effects secondary to estrogen inhibition of hepatic microsomal enzymes [314][315].

c) In a study women received clomipramine and oral contraceptives or clomipramine alone. At the beginning of the study there were 30 women taking the combination, but 12 subsequently dropped out. The 18 patients on the combination were matched with 18 patients taking clomipramine alone. No significant difference was noted in the patients' responses to clomipramine. It was proposed that there was no significant difference in side-effects between the groups; however, the groups were matched after patients had dropped out of the study. Had the patients been matched prior to the study, different conclusions may have been drawn [316].

d) The effects of oral contraceptives on clomipramine was studied in 42 women between the ages of 18 and 40. Twenty-three women took clomipramine 25 mg at bedtime while 19 took clomipramine 25 mg at bedtime with oral contraceptives. Over the four-week study, three control patients (two due to side-effects) and five in the experimental group (two due to side-effects) dropped out. Venous blood samples were drawn at weekly intervals for measurement of serum clomipramine concentrations. No difference in serum concentrations was noted between the groups. However, this result may be partially due to the low dose of clomipramine given [317].

e) The onset of akathisia was reported in 3 patients receiving conjugated estrogens and tricyclic antidepressants concurrently. A 24-year-old patient receiving clomipramine 120 mg daily for anorexia nervosa and conjugated estrogens 1.25 mg daily for amenorrhea developed restless legs and a constant desire to move continuously. Estrogen was discontinued and benztropine 2 mg was administered, resulting in marked reduction and resolution within 48 hours. Akathisia and disorientation developed in a 55-year-old patient on conjugated estrogen 1.25 mg daily who was prescribed amitriptyline 50 mg daily for depression. Within hours of amitriptyline, the patient was confused, restless, and possessed an inner desire to move continuously. Symptoms disappeared after discontinuing amitriptyline. A third case of akathisia was reported in a 35-year-old patient who received conjugated estrogen 1.25 mg daily and amitriptyline 50 mg daily. Akathisia developed within a few hours after taking the first dose of amitriptyline and resolved within 48 hours following discontinuation of the antidepressant [318].

f) The absolute bioavailability of imipramine increased in women who received low-dose oral contraceptives (50 mcg or less of ethinyl estradiol) from 27% to 44% (p less than 0.05) as evident by an increase in the area under the plasma concentration time curve [319].

g) Estrogens may inhibit the oxidation of TCAs by affecting hepatic microsomal enzymes [320]. Many TCAs are metabolized via oxidation and conjugation pathways. Inhibition of the oxidation of TCAs could result in accumulation and toxicity due to decreased

clearance. Estrogens are suspected of possessing other effects on the central nervous system resulting in an antidepressant effect [321].

Troleandomycin

1) Interaction Effect: altered contraceptive effectiveness and risk of hepatotoxicity
2) Summary: Troleandomycin combined with oral contraceptives has been associated with liver dysfunction[462][463][464][465]; erythromycin may have less propensity for such [466]. Theoretically, macrolide antibiotics may alter intestinal flora and affect enterohepatic circulation of estrogens/progestins; however, contraceptive efficacy was maintained during roxithromycin treatment [467].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Monitor for symptoms of hepatotoxicity or use a less hepatotoxic antibiotic. Advise patients to use a barrier method of birth control in addition to the combination contraceptive.
7) Probable Mechanism: inhibition of combination contraceptive metabolism
8) Literature Reports

a) Concomitant troleandomycin and oral contraceptive therapy may be associated with an increased risk for hepatotoxicity. Twenty-four cases of jaundice have been reported in women taking both troleandomycin and an oral contraceptive. The women had previously taken oral contraceptives for several months to years without evidence of hepatotoxicity. In general, 2 to 15 days after starting troleandomycin 1 to 3 grams daily, intense pruritus developed and was followed by jaundice 2 to 5 days later. Serum bilirubin, alkaline phosphatase, and serum alanine aminotransferase were typically elevated. Eight patients had evidence of cholestasis. After drug therapy was discontinued, jaundice and pruritus gradually disappeared, but persisted more than 1 month in 20 patients and more than 2 months in 6 patients. Twenty patients later resumed taking oral contraceptives without recurrence of the jaundice [459].

b) Twelve patients receiving oral contraceptives developed intrahepatic cholestasis 2 to 20 days after beginning troleandomycin therapy [460]. Three cases of jaundice were reported in women on oral contraceptives and troleandomycin [461].

Ulipristal

1) Interaction Effect: reduced efficacy of ulipristal or progestin-based hormonal contraceptives
2) Summary: Progestin-containing contraceptives may reduce the effectiveness of ulipristal in delaying ovulation. Conversely, ulipristal may reduce hormonal contraceptive effects. Combined oral contraceptive use within 1 day of ulipristal administration did not affect ovulation rates; however, use within 2 days impaired the ability of ulipristal to delay ovulation. Progestin-only contraceptive use within 1 day of ulipristal administration increased the ovulation rate within 6 days of ulipristal administration. Additionally, progestin-only contraceptive use within 2 days of ulipristal administration was associated with a reduction in the ability of the progestin to inhibit cervical mucus permeability. Start hormonal contraception no sooner than 5 days after ulipristal use. A reliable barrier method should also be used until the patient's next menstrual period. Follow instructions on the initiation or resumption of specific hormonal contraceptives after ulipristal intake[433].
3) Severity: major
4) Onset: rapid
5) Substantiation: established
6) Clinical Management: Progestin-containing contraceptives may reduce the effectiveness of ulipristal in delaying ovulation. Conversely, ulipristal may reduce hormonal contraceptive effects. Start hormonal contraception no sooner than 5 days after ulipristal use. A reliable barrier method should also be used until the patient's next menstrual period. Follow instructions on the initiation or resumption of specific hormonal contraceptives after ulipristal intake[433].
7) Probable Mechanism: competition for progesterone receptor binding
8) Literature Reports

a) In clinical trials, ovulation rates were similar among women who started ethinyl estradiol 30 mcg/levonorgestrel 150 mcg (COC) within 1 day of ulipristal use during the follicular phase of the menstrual cycle vs women using placebo plus COC. Ovulation occurred in 33.3% of subjects who received ulipristal plus COC vs 32.4% of subjects who received placebo plus COC [434].

b) When a combined oral contraceptive containing ethinyl estradiol 30 mcg/levonorgestrel 150 mcg was started 2 days after ulipristal intake, the ability of ulipristal to delay ovulation, as assessed by transvaginal ultrasound, was reduced; follicular rupture occurred in 27% of subjects in less than 5 days, compared to 3% of subjects after ulipristal alone [433].

c) The effects on ovarian activity of delaying versus immediately resuming combination oral contraceptives (COCs) after ulipristal intake were investigated in women who had been using contraceptives containing ethinyl estradiol 30 mcg/levonorgestrel 150 mcg once daily for 21 days followed by 7 days of placebo pills for at least one cycle (N=49). All subjects missed 3 consecutive pills (Days 5 to 7) during the first week of pills in the subsequent cycle and took ulipristal on the following day (Day 8). These subjects were

randomized to resume their COCs either on the same day as ulipristal intake vs 5 days later. No ovulations with potential risk of pregnancy occurred in either group in the 5 days following ulipristal. However, in the group that waited 5 days to resume taking COCs, 17.4% of women did ovulate later in the cycle (Days 18 to 26) whereas no ovulations occurred in the group that resumed COC intake on the same day as ulipristal [433].

d) Compared with women who used ulipristal alone, more women in the follicular phase of their menstrual cycle ovulated within 6 days of ulipristal use when they started desogestrel 75 mcg within a day of ulipristal intake. Conversely, ulipristal was associated with a reduction in the ability of desogestrel to inhibit cervical mucus permeability; thickening of cervical mucus was slowed by 3 to 4 days among patients who used ulipristal 2 days before desogestrel initiation compared with those who used desogestrel alone [434].

Valproic Acid

1) Interaction Effect: decreased valproate exposure and increased risk of seizures
2) Summary: Concomitant use of valproate, valproic acid, or divalproex sodium and an estrogen-containing hormonal contraceptive may increase the clearance of valproate, which may result in decreased exposure. This may cause an increase in seizure frequency. Monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products[436].
3) Severity: major
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Concomitant use of valproate, valproic acid, or divalproex sodium and an estrogen-containing hormonal contraceptive may increase the clearance of valproate, which may result in decreased exposure. This may cause an increase in seizure frequency. Monitor serum valproate concentrations and clinical response when adding or discontinuing estrogen containing products[436].
7) Probable Mechanism: increased valproate clearance

Voriconazole

1) Interaction Effect: increased levels of voriconazole and of ethinyl estradiol and norethindrone
2) Summary: Coadministration of voriconazole with an oral combination contraceptive containing ethinyl estradiol and norethindrone has resulted in increased plasma concentrations of voriconazole, ethinyl estradiol, and norethindrone. When these agents are coadministered, monitor patients for adverse events related to voriconazole (peripheral edema, visual disturbance) and ethinyl estradiol/norethindrone (abnormal menstruation, breast tenderness, edema)[208][209].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: established
6) Clinical Management: Use caution when prescribing voriconazole to patients who are using oral contraceptives, as concomitant use may cause elevated plasma concentrations of voriconazole, ethinyl estradiol, and norethindrone. Monitor patients for increased adverse effects related to voriconazole (peripheral edema, visual disturbance) and ethinyl estradiol/norethindrone (abnormal menstruation, breast tenderness, edema)[208].
7) Probable Mechanism: altered CYP450-mediated metabolism of voriconazole, ethinyl estradiol, and norethindrone
8) Literature Reports

a) Concomitant administration of voriconazole and an oral contraceptive in 16 healthy women resulted in increased systemic exposure to all analytes relative to monotherapy, according to an open-label, fixed-sequence, three-period study. In period 1, women (mean age, 25.9 years; range, 19 to 36 years) received voriconazole 400 mg every 12 hours on day 1 and 200 mg every 12 hours on days 2 through 4. During period 2, women were given an oral contraceptive containing ethinyl estradiol 0.035 mg/norethindrone 1 mg every 24 hours on days 12 through 32. In period 3, subjects received combination voriconazole 400 mg every 12 hours on day 57, 200 mg every 12 hours on days 58 through 60, and an oral contraceptive every 24 hours on days 40 through 60. With concurrent administration, there were mean increases in voriconazole AUC and Cmax of 46% (90% confidence interval (CI), 32% to 61%) and 14% (90% CI, 3% to 27%), respectively, compared with monotherapy. Ethinyl estradiol AUC and Cmax increased 61% (90% CI, 50% to 72%) and 36% (90% CI, 28% to 45%), respectively. Norethindrone AUC and Cmax increased 53% (90% CI, 44% to 64%) and 15% (90% CI, 3% to 28%), respectively. Regardless of causality, the most commonly-reported adverse events during combination therapy were headache, abnormal vision, dizziness, nausea, and chromatopsia [208].

Warfarin

1) Interaction Effect: decreased or increased anticoagulant effectiveness
2) Summary: Concomitant use of a combination contraceptive and warfarin may result in enhanced or reduced anticoagulant efficacy of warfarin[243][245][242]. One study of 12 patients demonstrated an enhanced response to anticoagulant therapy when given concurrently with oral contraceptive [242]. In one case report, warfarin dose adjustments were required with the concomitant use of 3 different hormonal contraceptives within a 1-year period [243]. In another case report, emergency contraception with progestogen

only in a patient receiving warfarin resulted in an enhanced anticoagulant effect evident by an INR of 8.1 [245]. Although the mechanism of this interaction has not been determined, ethinyl estradiol inhibition of CYP1A2- and CYP2C19-mediated warfarin metabolism is the postulated primary mechanism [243]. Therefore, prothrombin time and INR should be closely monitored when hormonal contraceptive and anticoagulants are coadministered.
3) Severity: moderate
4) Onset: delayed
5) Substantiation: probable
6) Clinical Management: Concurrent use of warfarin and a combination oral contraceptive has the potential for decreased or increased anticoagulant efficacy. If these drugs are used together, consider closely monitor prothrombin time or INR.
7) Probable Mechanism: unknown
8) Literature Reports

a) Oral contraceptives potentiated anticoagulant efficacy, as measured by prothrombin time ratio, in 12 women (mean age, 34.5 yr) when treated concomitantly with a combination contraceptive (11, oral; 1, parenteral depot) and an anticoagulant (nicoumalone) compared with an anticoagulant alone. Anticoagulation was being used for Bjork-Shiley valvular prosthesis (n=9) and embolic mitral valve disease (n=3). Patients were followed for a total of 374 patient-months of which 230 months and 144 months were concomitant use with a mean anticoagulant dose of 2.05 mg (phase A) and anticoagulant alone at a mean dose of 2.53 mg (phase B), respectively. Although the anticoagulant dose requirement was lower during phase A (p less than 0.01), prothrombin time ratio was higher at 1.67 during phase A compared with 1.5 during phase B (p less than 0.01). It is postulated that the estrogens in the oral contraceptives may inhibit hepatic cell microsome enzymes. This may enhance the anticoagulant effect due to slowed breakdown of the anticoagulant [242].

b) Warfarin dose requirements were altered when 3 different hormonal contraceptives were used by a 33-year-old woman initially maintained on warfarin 38.5 mg/wk (historical max dose, 42 mg/wk) for long-term anticoagulation after aortic valve replacement. Monophasic ethinyl estradiol 0.02 mg/norethindrone 1 mg/day was also being given. Because of increased thrombosis risk, her oral contraceptive was replaced with an etonogestrel subdermal implant which required a 55.8% warfarin dose increase (60 mg/wk) to obtain goal INR (range, 2.5 to 3.5). After 10 months, the implant was removed due to increased menstrual bleeding. Nine days later, her INR increased to 6.5. During the next 48 days, no systemic contraceptives were used and her warfarin dose was titrated to 55.5 mg/wk. Oral norethindrone 0.35 mg/day was initiated and the warfarin dose stabilized at 53.5 mg/wk; however, norethindrone was discontinued 39 days later. Subsequently, no further warfarin dose adjustments were needed and the patient decided to avoid hormonal contraception. Ethinyl estradiol inhibition of CYP1A2- and CYP2C19-mediated warfarin metabolism is the postulated primary mechanism of this drug interaction which is considered probable based on the Horn Interaction Probability Scale [243].

c) A case report describes an enhanced anticoagulant effect of warfarin after giving a 35-year-old woman levonorgestrel for emergency contraception. The patient had familial type I (quantitative) antithrombin deficiency and a history of deep venous thrombosis and pulmonary thromboembolism. She had been stable on warfarin 7 mg per day with an INR) of 2.1. Three days after receiving emergency contraception, her INR was reported to be 8.1. Warfarin treatment was discontinued for two days and the patient's INR dropped to 2.5. No hemorrhagic complications occurred [244].

Zolmitriptan

1) Interaction Effect: an increased risk of zolmitriptan adverse effects
2) Summary: In a retrospective analysis of pharmacokinetic data, the mean plasma concentrations of zolmitriptan were higher in females taking oral contraceptives compared with those not taking oral contraceptives. Specifically, the Cmax and AUC of zolmitriptan were 30% and 50% higher, respectively, and the time to maximum concentration (Tmax) was prolonged by one-half hour. The effect that zolmitriptan may have on the pharmacokinetics of oral contraceptives has not been evaluated[428].
3) Severity: moderate
4) Onset: delayed
5) Substantiation: theoretical
6) Clinical Management: When zolmitriptan is administered concurrently to a patient on combination contraceptive therapy, monitor the patient for an increased incidence of zolmitriptan adverse effects, including paresthesias, nausea, dizziness, and chest tightness.
7) Probable Mechanism: inhibition of zolmitriptan metabolism

Drug-Food Combinations

Caffeine

1) Interaction Effect: enhanced CNS stimulation
2) Summary: Concomitant use of combination contraceptives and caffeine ingestion increases the half-life of caffeine by 45% to 90% and decreases the clearance of caffeine by 40% to 65%. The mechanism is thought to involve inhibition by combination

contraceptives of caffeine metabolism[480][481][482]. In some patients, caffeine ingestion may need to be reduced due to excessive CNS stimulation.
3) Severity: moderate
4) Onset: rapid
5) Substantiation: probable
6) Clinical Management: Advise patients that consumption of beverages or medications containing caffeine may result in increased CNS stimulation and possible insomnia. Advise patients to decrease caffeine intake while taking combination contraceptives.
7) Probable Mechanism: inhibition of caffeine metabolism by combination contraceptives
8) Literature Reports

a) Caffeine was administered orally to 13 healthy males, 9 healthy females taking no oral contraceptive steroids, and 9 healthy females taking oral contraceptives for more than 6 months. All subjects abstained from drugs, alcohol, and tobacco smoking during the study. In addition, they refrained from drinking caffeine-containing beverages for at least 2 days prior to the study. After an overnight fast, the subjects received 250 mg of caffeine. The half-life of caffeine was significantly prolonged in the oral contraceptive user as compared with the male and female controls (10.7 hours vs 6.2 hours). Total plasma clearance was significantly less in women taking oral contraceptives. Plasma protein binding and volume of distribution of caffeine were similar in both groups of females. Similar pharmacokinetic parameters were observed for men and women not taking oral contraceptives, except for the volume of distribution which was smaller in men [478].

b) The effects of low-dose estrogen (50 mcg or less) oral contraceptives on the pharmacokinetics of caffeine have been studied. Eighteen non-smoking women participated in the study. Nine of these subjects were taking a low-dose oral contraceptive. All patients abstained from drinking caffeine-containing food and beverages for 48 hours prior to the study. After an overnight fast, each subject received 162 mg caffeine base orally [479]. This study demonstrated a prolonged elimination half-life and decreased clearance of caffeine as well as a significant delay in time to peak caffeine concentration in patients taking low-dose estrogen oral contraceptives.

Drug-Lab Modifications

Metyrapone test

1) Interaction Effect: reduced responses to the metyrapone test
2) Summary: Estradiol therapy may resulted in a reduced response to the metyrapone test[483]. Use caution when interpreting results of this test in patients receiving estradiol.
3) Severity: minor
4) Onset: unspecified
5) Substantiation: theoretical
6) Clinical Management: Use caution when interpreting results of the metyrapone test in patients receiving estradiol as a reduced response may occur[483].
7) Probable Mechanism: an unknown mechanism

IV Compatibility (single)

No results available

Pregnancy & Lactation

A) Teratogenicity/Effects in Pregnancy

1) Micromedex Pregnancy Rating: Contraindicated

a) Avoid use of this drug during pregnancy and prescribe an alternative. Evidence has demonstrated fetal abnormalities or risks when used during pregnancy. Advise women of childbearing potential of fetal risk.

See Drug Consult reference: PREGNANCY RISK CATEGORIES

2) Crosses Placenta: Unknown

3) Clinical Management

a) Estradiol is contraindicated during pregnancy [484][485][62].

4) Literature Reports

a) Estradiol is contraindicated during pregnancy. However, inadvertent use of estrogens and progestins as an oral contraceptive during early pregnancy appears to cause little or no increased risk of birth defects (including cardiac anomalies and limb reduction effects) [5][484][19][485][62].

b) Estradiol gel is not indicated for use in pregnant women. Although there are no data regarding the use of estradiol gel during pregnancy, epidemiologic studies and meta-analyses regarding the exposure of combined hormonal contraceptives, containing estrogen and progestins, before conception and during early pregnancy have not reported an increased risk of genital or nongenital

birth defects, including cardiac anomalies and limb-reduction effects. Animal studies have not been conducted with the use of estradiol gel to determine embryo/fetal toxicity [33].

c) The Collaborative Perinatal Project monitored 614 mother-child pairs who had been exposed to estrogens during the first trimester. Forty-eight of these pairs had exposure to estradiol. Although an increase in the expected frequency of congenital anomalies (cardiovascular, eye, ear, Downs syndrome) was observed for estrogens as a group, no such increase was seen with estradiol [486]. A retrospective analysis found a higher number of infants with congenital heart defects were exposed to oral contraceptives when compared with a control group of healthy children. Two out of 18 infants with heart defects were exposed to hormones in utero [487].

d) A retrospective cohort study examined more than 2000 infants exposed to female sex hormones between 1954 and 1963. Compared with a control group, the total number of malformations and malformations of the genitals in male infants were higher among exposed children than unexposed [488]. It is important to note that modern contraceptives contain lower doses of hormones than those used at the time these infants were exposed.

e) A genetically male infant was born with full female genitalia as well as camptomelic syndrome. The mother took oral contraceptives (norethindrone 0.5 to 1 mg plus ethinyl estradiol 0.035 mg) 18 months prior to conception and 6 months into pregnancy. The infant died at 3.5 months of age due to multiple malformations [489].

f) A review and meta-analysis of prospective studies to date of the association between oral contraceptive use during or just prior to pregnancy and the frequency of congenital malformations in offspring was reported. No significant elevations in relative risk were found for all malformations taken together, or for heart defects or limb reduction defects, which were both evaluated separately [490].

g) A case involving neonatal choreoathetosis and maternal use of oral contraceptives throughout pregnancy (0 to 30 weeks gestation) was reported. Diagnosis was made at 10 days of age when the infant was examined for difficulty with feeding secondary to pronounced grimacing and tongue-thrusting. The choreoathetosis resolved without treatment or complications one week later. Other studies have found that injection of 17-beta-estradiol into rats will cause an increase in the number of striatal dopamine receptors and excess dopamine activity is a basis for the development of choreic movements [491].

h) There is no firm evidence linking oral contraceptives with any fetal anomalies except masculinization of the female external genitalia. Exposure after 8 weeks of gestation would presumably be required for this effect to occur [492].

i) Oral contraceptive use immediately prior to or during pregnancy appears to present a risk not exceeding 5% with regard to the incidence of visible malformations. Data on the contraceptive usage of 3,002 mothers of children with malformations was prospectively collected. Compared to matched control mothers, the types of malformations seen were similar among contraceptive users and nonusers. A risk ratio of 0.95 was reported for the oral contraceptive users, which actually represents a slightly smaller risk of malformation in infants [493].

B) Breastfeeding

1) World Health Organization Rating: Avoid breastfeeding if possible. May inhibit lactation.

2) Micromedex Lactation Rating: Infant risk cannot be ruled out.

a) Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.

3) Clinical Management

a) Estradiol is not indicated for use in women of reproductive potential and should not be used during lactation; however, exercise caution in the event that estradiol is administered to a lactating woman [5][484].

b) Progestin-only oral contraceptives are preferred in breastfeeding and may be started 2 weeks postpartum. Alternatively, depot medroxyprogesterone acetate or hormonal implants can be started after 6 weeks postpartum. Combined estrogen-progestin contraceptives may be started at 6 weeks postpartum; however, the newborn's feedings should be carefully monitored as use of combined oral contraceptives is associated with a reduced quality and quantity of breast milk [499].

4) Literature Reports

a) Estradiol is not indicated for use in women of reproductive potential and should not be used during lactation. Estrogens are excreted into breast milk in small quantities [5][484][495] and have not been associated with adverse effects in the nursing infant. In the past, estrogens were used to suppress postpartum lactation [496][495].

b) Estrogen use in the nursing mother may be associated with decreased milk production and quality of the breast milk [33][5][484], including decreased composition of nitrogen and protein content of the milk [497]. The reduction in milk production may occur at any time during breastfeeding, but is less likely to occur once breastfeeding is well established [33].

c) Transdermal estradiol, administered to nursing women, did not affect estradiol or estrone concentrations in the nursing infant, nor did it affect infant growth, according to a clinical trial involving 19 mothers with post-partum depression, who were randomized to receive either transdermal estradiol, at doses ranging from 50 to 200 mcg/day, sertraline, or placebo [498].

5) Drug Levels in Breastmilk

a) Parent Drug

1) Milk to Maternal Plasma Ratio

a) 0.07 to 0.3 [508]

2) Peak Concentration in Infant

a) Use of estradiol transdermal patches (up to 200 mcg/day) in breastfeeding mothers with postpartum depression produced no significant differences in infant estradiol levels when compared with the use of placebo or sertraline (N=19 mother-infant pairs) [498].

b) Active Metabolites

1) Estrone

a) Peak Concentration in Infant

1) Use of estradiol transdermal patches (up to 200 mcg/day) in breastfeeding mothers with postpartum depression produced no significant differences in infant estrone levels compared with the use of placebo or sertraline (N=19 mother-infant pairs) [498].

Monitoring

A) Estradiol

1) Therapeutic

a) Laboratory Parameters

1) Advanced Androgen-Dependent Carcinoma of the Prostate

a) The effectiveness of estrogen therapy can be assessed by phosphatase determinations and by symptomatic improvement of the patient [7].

2) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Most estrogen administration and dosages should be guided by individual patient clinical response rather than by hormone levels [19][7][11][12], however, laboratory parameters, such as estradiol and follicle stimulating hormone, may be useful in some cases [8].

3) Prevention of Postmenopausal Osteoporosis

a) Periodic measurements of bone mineral density and biochemical markers should be assessed [8].

b) Physical Findings

1) Advanced Androgen-Dependent Carcinoma of the Prostate

a) The effectiveness of estrogen therapy can be assessed by phosphatase determinations and by symptomatic improvement of the patient [7].

2) Breast Cancer

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [7].

3) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Most estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [19][7][11][12]; however, laboratory parameters, such as estradiol and follicle stimulating hormone, may be useful in some cases [8].

4) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels [19][7][13][38][35][8][11][12]. Periodically re-evaluate postmenopausal women to determine if treatment is still necessary [69].

5) Postmenopausal Vulvar and Vaginal Atrophy

a) Estrogen administration and dosage should be guided by individual patient clinical response [5] rather than by hormone levels [19][7][13][8][11][12][14][15].

2) Toxic

a) Laboratory Parameters

1) Monitor serum calcium in patients with pre-existing severe hypocalcemia or in patients with breast cancer and bone metastases [5][7][13][38][35][8][11][12][14][15][94].

2) Monitor plasma triglycerides in patients with pre-existing hypertriglyceridemia [5][7][13][38][35][8][11][12][14][15][94].

3) Monitor thyroid function in patients with pre-existing hypothyroidism in order to maintain free thyroid hormone levels in an appropriate range [5][7][13][38][35][8][19][11][12][69][14][15][94].

b) Physical Findings

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

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TAB 175-26 (continued)

1) Perform yearly breast examinations and patients should perform self-examinations of the breasts every month. Mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results [5][19][7][13][38][35][8][11][12][69][14][15][94].

2) Monitor blood pressure at regular intervals during estrogen use [5][7][13][38][35][8][11][12][14][15][94].

3) Observe carefully for exacerbation of conditions in patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction [5][19][7][13][38][35][8][11][12][69][14][15][94].

4) Periodic monitoring of bone maturation and effects on epiphyseal centers is recommended when estrogen is administered to patients whose bone growth is not complete [10][7][8][11][12][14][94].

5) Directed or random endometrial sampling, when indicated, should be performed to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding [5].

B) Estradiol Acetate

1) Therapeutic

a) Laboratory Parameters

1) Measurement of serum FSH and estradiol levels have not been shown to be useful [59].

b) Physical Findings

1) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating postmenopausal vasomotor symptoms [61]

b) Periodically reevaluate the need for continued treatment [59].

2) Postmenopausal Vulvar and Vaginal Atrophy

a) Improvement in vulvar or vaginal atrophy is indicative of efficacy.

b) Periodically reevaluate the need for continued treatment [59].

2) Toxic

a) Laboratory Parameters

1) Monitor thyroid function in women dependent on thyroid hormone replacement therapy [59].

2) Perform adequate diagnostic measures, including endometrial sampling, as clinically indicated in women with undiagnosed persistent or recurring abnormal vaginal bleeding [59].

b) Physical Findings

1) Carefully evaluate patients for ulceration or erosion of the vaginal or bladder wall [59].

2) Perform yearly breast examinations in all patients and schedule mammography examinations based on patient age, risk factors, and prior mammogram results [59].

3) Carefully observe patients for fluid retention in women who may be affected (eg, cardiac or renal impairment) [59].

C) Estradiol Cypionate

1) Therapeutic

a) Physical Findings

1) Female Hypogonadism

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating female hypogonadism [55].

2) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by individual patient clinical response rather than by hormone levels when treating postmenopausal vasomotor symptoms [55].

2) Toxic

a) Laboratory Parameters

1) Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding [55].

2) Serum calcium should be monitored in patients with preexisting severe hypocalcemia or in patients with breast cancer and bone metastases [55].

3) Plasma triglycerides should monitored in patients with preexisting hypertriglyceridemia [55].

4) Thyroid function should be monitored in patients with preexisting hypothyroidism in order to maintain free thyroid hormone levels in an appropriate range [55].

b) Physical Findings

1) All women should receive yearly breast examinations by a healthcare provider and should perform self-examinations of the breasts every month. Mammography examinations should be

scheduled based on patient age, risk factors, and prior mammogram results [55].

2) An eye examination should be scheduled if there is a sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. Estrogens should be discontinued pending examination and discontinued permanently if examination reveals papilledema or retinal vascular lesions [55].

3) Blood pressure should be monitored at regular intervals during estrogen use [55].

4) Patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction should be carefully observed for exacerbation of their condition [55].

D) Estradiol Valerate

1) Therapeutic

a) Laboratory Parameters

1) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

2) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

3) Postmenopausal Vulvar and Vaginal Atrophy

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

b) Physical Findings

1) Hypoestrogenism due to Hypogonadism, Castration or Primary Ovarian Failure

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

2) Postmenopausal Vasomotor Symptoms

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

3) Postmenopausal Vulvar and Vaginal Atrophy

a) Estrogen administration and dosage should be guided by clinical response rather than by serum hormone levels (estradiol, follicle stimulating hormone) [57].

2) Toxic

a) Laboratory Parameters

1) Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding [57].

2) Serum calcium should be monitored in patients with pre-existing severe hypocalcemia or in patients with breast cancer and bone metastases [57].

3) Plasma triglycerides should be monitored in patients with pre-existing hypertriglyceridemia [57].

4) Thyroid function should be monitored in patients with pre-existing hypothyroidism in order to maintain free thyroid hormone levels in an appropriate range [57].

b) Physical Findings

1) All women should receive yearly breast examinations by a healthcare provider and should perform self-examinations of the breasts every month. Mammography examinations should be scheduled based on patient age, risk factors, and prior mammogram results [57].

2) An eye examination should be scheduled if there is a sudden partial or complete loss of vision or a sudden onset of proptosis, diplopia, or migraine. Estrogens should be discontinued pending examination and discontinued permanently if examination reveals papilledema or retinal vascular lesions [57].

3) Blood pressure should be monitored at regular intervals during estrogen use [57].

4) Patients with conditions that may be influenced by fluid retention such as cardiac or renal dysfunction should be carefully observed for exacerbation of their condition [57].

5) Periodic monitoring of bone maturation and effects on epiphyseal centers is recommended when estrogen is administered to patients whose bone growth is not complete [57].

Do Not Confuse

No results available

MECHANISM OF ACTION

Mechanism of Action

A) Estradiol

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

5) All estrogens act similarly and there is no evidence that there are biological differences among various estrogen preparations, other than their ability to bind to receptors once inside target cells. There is no evidence that one estrogen is more carcinogenic than another or that one preparation is safer than another. Differences among various estrogens primarily arise from the dose administered and relative potency (Schiff and Ryan, 1980). All estrogens exert their primary effects on the interphase DNA-protein complex (chromatin) by binding to a receptor usually located in the cytoplasm of a target cell and initiation of translocation of the hormone-receptor complex to the nucleus [513]. The specificity of estrogen action depends upon the presence and concentration of "estrogen targets", which are defined as tissues containing a high concentration of estrogen receptors. These include the endometrium, myometrium, oviduct, vagina, fallopian tube, cervix, brain, liver, placenta, ovarian cells and Leydig's cell. Other tissues reportedly containing estrogen receptors include kidney, prostate, pancreas, heart and skin [513].

6) In breast tissue, estrogens stimulate the growth and differentiation of the ductal epithelium, induce mitotic activity of ductal cylindric cells, and stimulate the growth of connective tissue. In addition, estrogens exert histamine-like effects on the microcirculation of the breast and stimulate the growth of breast cancer cells [514].

7) The mechanism by which estrogens prevent postmenopausal bone loss is not clear. Estrogens cause a clear decrease in calcium excretion and result in a calcium balance indistinguishable from normal premenopausal women [515][516][97]. Though the precise mechanism remains unknown, changes in vitamin D metabolism (increased 1-hydroxylation of 25-OH-D) as well as increased levels of serum calcitonin have been implicated [517][518]; (Taggart et al, 1982). One study has also shown that estrogen therapy reduces the sensitivity of postmenopausal osteoporotic bone to the resorptive effects of parathyroid hormone [519]. Further study is needed.

B) Estradiol Acetate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [170][60].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and

gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

5) All estrogens act similarly and there is no evidence that there are biological differences among various estrogen preparations, other than their ability to bind to receptors once inside target cells. There is no evidence that one estrogen is more carcinogenic than another or that one preparation is safer than another. Differences among various estrogens primarily arise from the dose administered and relative potency (Schiff and Ryan, 1980). All estrogens exert their primary effects on the interphase DNA-protein complex (chromatin) by binding to a receptor usually located in the cytoplasm of a target cell and initiation of translocation of the hormone-receptor complex to the nucleus [513]. The specificity of estrogen action depends upon the presence and concentration of "estrogen targets", which are defined as tissues containing a high concentration of estrogen receptors. These include the endometrium, myometrium, oviduct, vagina, fallopian tube, cervix, brain, liver, placenta, ovarian cells and Leydig's cell. Other tissues reportedly containing estrogen receptors include kidney, prostate, pancreas, heart and skin [513].

6) In breast tissue, estrogens stimulate the growth and differentiation of the ductal epithelium, induce mitotic activity of ductal cylindric cells, and stimulate the growth of connective tissue. In addition, estrogens exert histamine-like effects on the microcirculation of the breast and stimulate the growth of breast cancer cells [514].

7) The mechanism by which estrogens prevent postmenopausal bone loss is not clear. Estrogens cause a clear decrease in calcium excretion and result in a calcium balance indistinguishable from normal premenopausal women [515][516][97]. Though the precise mechanism remains unknown, changes in vitamin D metabolism (increased 1-hydroxylation of 25-OH-D) as well as increased levels of serum calcitonin have been implicated [517][518]; (Taggart et al, 1982). One study has also shown that estrogen therapy reduces the sensitivity of postmenopausal osteoporotic bone to the resorptive effects of parathyroid hormone [519]. Further study is needed.

C) Estradiol Cypionate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [55].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

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D) Estradiol Valerate

1) Estrogens bind to nuclear receptors in estrogen-responsive tissues. Estrogens modulate the pituitary secretion of the gonadotropins, luteinizing hormone and follicle stimulating hormone through a negative feedback mechanism. Estrogens reduce the elevated levels of these hormones in postmenopausal women [57].

2) Estrogens are important for developing and maintaining the female reproductive system and secondary sex characteristics. Estrogens promote growth and development of the vagina, uterus, and fallopian tubes, and enlargement of the breasts. Indirectly, they stimulate and limit linear skeletal growth. Estrogens have wide-spread effects on metabolism such as transporting of proteins and electrolyte balance [114][509].

3) Estrogens are necessary for maintaining the normal menstrual cycle. During the follicular phase of the menstrual cycle, when estrogen levels are high, there is a proliferation of the vaginal and uterine mucosa and increased cervical secretions. As estrogen levels decline at the end of the cycle, menstruation begins [505][510]; (Naftolin & Tolis, 1978).

4) In non-pregnant women, estrogens (and progesterone) support the physiologic processes resulting in ovulation and preparation of the uterine endometrium to support conception. At the time of menopause, ovarian follicles are incapable of responding to gonadotropin stimulation with progressive maturation. The ovaries cease to produce estrogens and progesterone, and gonadotropin levels rise dramatically as androgen and estrogen levels decrease. Menopause is clinically defined as a duration of amenorrhea of 6 to 12 months in a woman over 45 years of age [511]. In the premenopausal period, estradiol secretion from the ovaries is the major source of estrogen production. Extraglandular production of estrone occurs from androstenedione, derived from both the adrenals and ovaries. In the menopause, ovarian estradiol production diminishes and a peripheral conversion of adrenal androstenedione to estrone becomes the principle source of estrogen [512].

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PHARMACOKINETICS

Pharmacokinetics

Onset and Duration

A) Onset

1) Estradiol

a) Initial Response

1) Oral

a) Estrogen replacement: 3 days [9].

1) On the third consecutive day of dosing, the mean serum concentration of estradiol and estrone increased to 59 and 302 picograms/milliliter (pg/mL) above baseline, respectively,

after oral estradiol 2 milligrams daily were administered to postmenopausal women [9].

b) Menopausal symptoms: 2 to 4 weeks [500][501]

1) Time to significant improvement of menopausal symptoms relative to baseline was 2 to 4 weeks [500][501].

2) Transdermal

a) Estrogen replacement: 4 hours [9][11][12]

1) After a single application of estradiol transdermal patches that provided 0.05 and 0.1 milligrams of estradiol per day, blood levels of estradiol were increased within 4 hours after administration [9].

2) Following application to the abdomen of estradiol transdermal patches that provided 0.0375 and 0.1 milligrams (mg) of estradiol per day and application to the buttocks of estradiol transdermal patches that provided 0.1 mg of estradiol per day, estradiol levels were increased above baseline within 4 hours after administration [11][12].

2) Estradiol Cypionate

a) Initial Response

1) Menopausal vasomotor symptoms, intramuscular: 1 to 5 days [55].

a) Comparative clinical trials have demonstrated that relief of vasomotor symptoms in menopausal women occurs approximately within 1 to 5 days after a single intramuscular injection of estradiol cypionate 5 milligrams [55].

B) Duration

1) Estradiol

a) Single Dose

1) Transdermal

a) Estrogen replacement: within 24 hours [9]

1) After a single application of estradiol transdermal patches that provided 0.05 and 0.1 milligrams of estradiol per day, mean serum estradiol concentrations of 32 and 67 picograms/milliliter (pg/mL), respectively, were maintained above baseline over the application period. Serum concentration levels of estrone averaged 9 and 27 pg/mL above baseline, respectively. Serum concentrations of estradiol and estrone returned to preapplication levels within 24 hours after removal of the patch [9].

b) Multiple Dose

1) Transdermal

a) Estrogen replacement: 12 to 24 hours [11][12]

1) In a multiple-dose study involving 17 healthy postmenopausal women, estradiol transdermal systems were applied to the abdomen at a dose of 0.05 and 0.1 milligrams (mg)/day) or to the buttocks at a dose of 0.1 mg/day. Plasma concentrations of estradiol and estrone remained slightly above baseline at 12 hours after removal of the transdermal systems. In another study, the levels return to baseline values with 24 hours after the patch removal [11][12].

2) Estradiol Cypionate

a) Single Dose

1) Menopausal vasomotor symptoms, intramuscular: average of 5 weeks [55].

a) Comparative clinical trials have demonstrated that relief of vasomotor symptoms in menopausal women was maintained for 1 to 8 weeks (average 5 weeks) after a single intramuscular injection of estradiol cypionate 5 milligrams [55].

2) Vaginal estrogenic effect, intramuscular: 3 to 4 weeks [55]

a) Comparative clinical trials have demonstrated that after a single intramuscular injection of estradiol cypionate 5 milligrams, the average duration of estrogenic effect, as measured by vaginal smear, was approximately 3 to 4 weeks [55].

Drug Concentration Levels

A) Estradiol

1) Therapeutic Drug Concentration

a) Transdermal Gel

1) Estrogel(R): 28.3 picograms/mL [13]

a) By day 14, the time-averaged serum estradiol and estrone concentrations over the 24-hour dose interval after administration of 1.25 grams estradiol topical gel to one arm were 28.3 and 48.6 picograms/milliliter, respectively. The serum concentrations of estradiol reached steady state after the third daily application of 2.5 grams topical estradiol gel (1.25 grams applied to each arm) [13].

2) Divigel(R): 9.8, 21, 30.5 picograms/mL (0.25, 0.5, and 1 mg daily dose, respectively) [38]

a) The steady state serum concentration of estradiol is achieved by day 12 following daily application of estradiol topical gel 0.1% to the skin of the upper thigh. The mean serum estradiol levels on day 14 after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 9.8 picograms/milliliter (pg/mL). The mean steady state serum concentration of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 21 pg/mL. The mean steady state serum concentration of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 30.5 pg/mL[38].

b) Transdermal Patch

1) Alora(R)

a) The average base-line adjusted steady state concentrations of estradiol during a 2 year, randomized, double-blind, controlled trial involving 355 hysterectomized women were 18.6, 35.9, and 50.1 picograms/milliliter for the 0.025, 0.05, and 0.075 milligrams/day dose, respectively [8].

The mean steady state serum concentrations of estradiol after administration of Alora(R) patches are presented below. Studies 1 and 2 were of 3 months duration and Study 3 was of 2 years duration [8]:

Dose (milligrams/day)	Study 1 (pg/mL)	Study 2 (pg/mL)	Study 3 (pg/mL)
0.025	--	--	24.5
0.05	46.9	38.8	42.6
0.075	--	--	56.7
0.1	99.2	97.0	--
pg/mL: picogram/milliliter			

2) Estraderm(R)

a) Steady state serum estradiol levels of 30 picograms/mL and estrone levels of 12 picograms/mL were reported in a 3-week multiple-application study (n=14) receiving Estraderm(R) 0.05 twice a week [9].

3) Vivelle(R) and Vivelle-Dot(R)

a) The mean steady state plasma concentrations of estradiol after administration of Vivelle(R) are summarized below [11][12]:

Dose (milligrams/day)	Application Site	Cavg (picograms/milliliter)
0.0375	Abdomen	34
0.05	Abdomen	57
0.075	Abdomen	72
0.1	Abdomen	89
0.1	Buttock	104
Cavg: average plasma concentration		

4) Transdermal Spray

a) Evamist(TM): 19.6, 30.7, and 30.9 picograms/mL (1, 2, or 3 sprays daily, respectively) [36]

1) By day 14, the mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 19.6 picograms/milliliter (pg/mL). The mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 30.7 pg/mL. The mean steady state concentration of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 30.9 pg/mL [36].

5) Vaginal Insert

a) Vaginal, insert (estradiol): 3.6 to 4.6 picograms/mL (pg/mL; Day 14) [5]

1) Following 14 days of once-daily administration in postmenopausal women (n=54), average 24-hour concentration of estradiol was 3.6 +/- 1.8 pg/mL with the 4-mcg insert and 4.6 +/- 2.3 pg/mL with the 10-mcg insert, compared with a placebo level of 4.3 +/- 2.8 mcg/mL [5].

b) Vaginal, insert (estrone): 13.6 to 19.3 picograms/mL (pg/mL; Day 14) [5]

1) Following 14 days of once-daily administration in postmenopausal women (n=54), average 24-hour concentration of estrone was 13.6 +/- 4.8 pg/mL with the 4-mcg insert and 19.3 +/- 10.2 pg/mL with the 10-mcg insert, compared with a placebo level of 17.8 +/- 7.5 mcg/mL [5].

6) Vaginal Ring

a) The steady state concentration values at 48 hours, 4 weeks, and 12 weeks for estradiol and estrone, as well as baseline-adjusted estradiol and estrone following a single estradiol vaginal ring application in 14 healthy postmenopausal women are summarized below [15]:

	Css-48 hr (picograms/milliliter)	Css-4w (picograms/milliliter)	Css-12w (picograms/milliliter
Estradiol	11.2	9.5	8.0
Baseline-adjusted Estradiol	3.6	2	0.4
Estrone	52.5	43.8	47.0
Baseline-adjusted Estrone	6.2	-2.4	0.8
Css: Steady state serum concentration; hr: hours; w: week			

b) The mean steady state serum estradiol concentrations after 1 to 4 estradiol vaginal rings (delivering 2 milligrams estradiol per ring) were inserted at three month intervals during a phase II study involving 222 postmenopausal women were 7.8, 7.0, 7.0, and 8.1 picograms/milliliter at 12, 24, 36, and 48 weeks, respectively. Similar results were seen in estrone concentrations [15].

2) Peak Concentration

a) Transdermal Gel

1) Estrogel(R): 46.4 picograms/mL (1.25 g daily) [13]

a) The mean Cmax of estradiol on day 14 was 46.4 picograms/milliliter after estradiol topical gel 1.25 grams was administered to 24 postmenopausal women once daily on the posterior surface of the arm from wrist to shoulder for 14 days. The mean Cmax of estrone was 64.2 picograms/milliliter [13].

2) Divigel(R): 14.7, 28.4, and 51.5 picograms/mL (0.25, 0.5, and 1.0 mg daily) [38]

a) In postmenopausal women, the mean Cmax of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 14.7 picograms/milliliter (pg/mL). The mean Cmax of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 28.4 pg/mL. The mean Cmax of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 51.5 pg/mL[38].

b) Transdermal Patch

1) Alora(R): 92 to 144 picograms/mL [8]

The mean Cmax of Alora(R) over an 84-hour dosing interval is presented below (* denotes Cmax for hip was statistically different from Cmax for abdomen) [8]:

Dose (milligrams/day)	Application Site	N	Dosing	Cmax (picograms/milliliter)
0.05	Abdomen	20	Multiple	92
0.075	Abdomen	20	Multiple	120
0.1	Abdomen	42	Multiple	144
0.05	Abdomen	31	Single	53
0.05	Buttock	31	Single	67
0.05	Hip*	31	Single	69
Cmax: Peak serum concentrations				

2) Climara(R): 32 to 174 picograms/mL [92]

a) The average Cmax of estradiol during a 3-week multiple application study in which 24 postmenopausal women wore the 25 square centimeter (cm(2)) Climara(R) system was 100 picograms/milliliter (pg/mL). Serum estrone Cmax level was 60 pg/mL [92].

b) In a single dose study in which 38 postmenopausal women wore a 25 square centimeter (cm(2)) Climara(R) system for one week either on the abdomen or buttocks, the serum Cmax for estradiol was 25% higher with the buttock application than with the abdomen application [92].

A summary of calculated Cmax values for estradiol during evaluation of Climara(R) is outlined in the following table [92]:

Delivery Rate (milligrams/day)	Surface Area (square centimeters)	Application Site	N	Dosing	Cmax (picograms/milliliter)
0.025	6.5	Abdomen	24	Single	32
0.05	12.5	Abdomen	102	Single	71
0.1	25	Abdomen	139	Single	147
0.1	25	Buttock	38	Single	174

3) Vivelle(R), Vivelle-Dot(R): 46 to 145 picograms/mL [11][12]

The mean plasma Cmax values of estradiol after administration of Vivelle(R) at steady state are summarized below [11][12]:

Dose (milligrams/day)	Application Site	Cmax (picograms/milliliter)
0.0375	Abdomen	46
0.05	Abdomen	83
0.075	Abdomen	99
0.1	Abdomen	133
0.1	Buttock	145
Cmax: Peak plasma concentration		

c) Transdermal Spray

1) Evamist(TM): 36.4, 57.4, and 54.1 picograms/mL (1, 2, or 3 sprays daily, respectively) [36]

a) By day 14, the mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 36.4 picograms/milliliter (pg/mL). The mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 57.4 pg/mL. The mean Cmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 54.1 pg/mL [36].

d) Vaginal Ring

1) The Cmax values for estradiol and estrone, as well as baseline-adjusted estradiol and estrone following a single estradiol vaginal ring application in 14 healthy postmenopausal women are summarized below:

	Cmax in picograms/milliliter
Estradiol	63.2
Baseline-adjusted Estradiol	55.6
Estrone	66.3
Baseline-adjusted Estrone	20
Cmax: Peak serum levels	

The initial estradiol Cmax after application of a second ring in the same women resulted in an approximate 38% lower Cmax, thought to be due to reduced systemic absorption via the treated vaginal epithelium [15].

e) Vaginal Insert

1) Vaginal, insert (estradiol): 4.8 to 7.3 picograms/mL (pg/mL; Day 14); 4.3 to 4.8 pg/mL (Day 84) [5]

a) Following 14 days of once-daily administration in postmenopausal women (n=54), mean Cmax of estradiol was 4.8 +/- 2.3 pg/mL with the 4-mcg insert and 7.3 +/- 2.4 pg/mL with the 10-mcg insert, compared with a placebo level of 5.5 +/- 3.4 mcg/mL. After Day 14, women received 1 insert twice weekly. At Day 84, estradiol concentrations compared to baseline concentrations were: 4.3 vs 3.9 pg/mL for 4 mcg; 4.8 vs 5 pg/mL for 10 mcg; and 4.4 vs 4.5 pg/mL for placebo [5].

2) Vaginal, insert (estrone): 16 to 23.9 picograms/mL (pg/mL; Day 14) [5]

a) Following 14 days of once-daily administration in postmenopausal women (n=54), mean Cmax of estrone was16 +/- 5.5 pg/mL with the 4-mcg insert and 23.9 +/- 13.4 pg/mL with the 10-mcg insert, compared with a placebo level of 22.8 +/- 10.9 mcg/mL [5].

f) Vaginal Tablets

1) Vaginal, tablets (estradiol): 47 to 51 picograms/mL [94]

a) During a double-blind, randomized trial, the mean Cmax of estradiol at day 1, 14, and 84 was 51, 47, and 49 picograms/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

2) Vaginal, tablets (estrone): 35 to 39 picograms/mL [94]

a) During a double-blind, randomized trial, the mean Cmax of estrone at day 1, 14, and 84 was 35, 39, and 35 picograms/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

3) Time to Peak Concentration

a) Transdermal Gel

1) Divigel(R): 16, 10, and 8 hr (0.25, 0.5, and 1 mg daily dose, respectively) [38]

a) In postmenopausal women, the median Tmax of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 16 hours. The median Tmax of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 10 hours. The median Tmax of estradiol after multiple daily doses of estradiol topical gel 1 milligram was 8 hours [38].

b) Transdermal Spray

1) Evamist(TM): 20, 18, and 20 hr (1, 2, or 3 sprays daily, respectively) [36]

a) By day 14, the median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 20 hours (hr). The median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 18 hr. The median Tmax of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 20 hr [36].

c) Vaginal Ring

1) Estring(R): 0.5 to 1 hour [15]

a) The time to attain peak serum estradiol levels after insertion of estradiol vaginal ring during a phase 1 study involving 14 postmenopausal women was 0.5 to 1 hour [15].

4) Area Under the Curve

a) Transdermal

1) Divigel(R): 236, 504, and 732 picograms x hr/mL (0.25, 0.5, and 1.0 mg daily dose, respectively) [38]

a) In postmenopausal women, the mean AUC of estradiol after multiple daily doses of estradiol topical gel delivering 0.25 milligram was 236 picograms x hour/milliliter (pg x hr/mL), respectively. The mean AUC of estradiol after multiple daily doses of estradiol topical gel 0.5 milligram was 504 pg x hr/mL. The mean AUC of estradiol after multiple daily doses of estradiol topical gel 1.0 milligram was 732 pg x hr/mL[38].

2) Evamist(TM): 471, 736, and 742 pg x hr/mL (1, 2, or 3 sprays daily dose, respectively) [36]

a) By day 14, the mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of one 90 microliter (mcL) spray delivering 1.53 milligrams (mg) estradiol was 471 picograms x hour/milliliter (pg x hr/mL). The mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of two 90 mcL sprays delivering a total of 3.06 mg estradiol was 736 pg x hr/mL. The mean AUC of estradiol after multiple daily doses of estradiol transdermal spray was administered at a dose of three 90 mcL sprays delivering a total of 4.59 mg estradiol was 742 pg x hr/mL [36].

b) Vaginal

1) Vaginal, tablets (estradiol): 538 to 567 picograms x hr/mL [94]

a) During a double-blind, randomized trial, the mean AUC of estradiol at day 1, 14, and 84 was 538, 567, and 563 picograms x hour/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

2) Vaginal, tablets (estrone): 649 to 744 picograms x hr/mL [94]

a) During a double-blind, randomized trial, the mean AUC of estrone at day 1, 14, and 84 was 649, 744, and 681 picograms x hour/milliliter, respectively, during administration of estradiol 25 mcg vaginal tablets over a 12-week period [94].

B) Estradiol Acetate

1) Peak Concentration

a) Oral: estradiol, 56.7, 90.1, and 177.3 pg/mL (0.45, 0.9, and 1.8 mg daily) [170]

b) Oral: baseline adjusted estrone, 155.0, 313.9, and 680.6 pg/mL (0.45, 0.9, and 1.8 mg daily) [170]

1) In 18 healthy postmenopausal women, the mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 56.7 and 155.0 picograms/milliliter (pg/mL), respectively. The mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 90.1 and 313.9 pg/mL, respectively. The mean Cmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 177.3 and 680.6 pg/mL, respectively [170].

c) Vaginal, ring: estradiol, 1129 to 1665 pg/mL (0.05 mg/day) [60]

d) Vaginal, ring: estrone, 141 pg/mL (0.05 mg/day) [60]

e) Vaginal, ring: estrone sulfate, 2365 pg/mL (0.05 mg/day) [60]

1) The mean Cmax of estradiol, estrone, and estrone sulfate after administration of estradiol acetate vaginal ring which delivered 0.05 milligram/day (mg/day) of estradiol was 1129 to 1665, 141, and 2365 picograms/milliliter (pg/mL) [60].

2) Time to Peak Concentration

a) Oral: estradiol, 0.43 to 0.75 hr [170]

b) Oral: baseline adjusted estrone, 5.0 to 6.0 hr [170]

1) In 18 healthy postmenopausal women, the median Tmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 0.50 and 6.0 hours, respectively. The median Tmax of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 0.43 and 5.0 hours, respectively. The median Tmax of estradiol and baseline-adjusted estrone

after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 0.75 and 6.0 hours, respectively [170].

c) Vaginal, ring: estradiol, 0.7 to 0.9 hr [60]

d) Vaginal, ring: estrone, 6.2 hr [60]

e) Vaginal, ring: estrone sulfate, 9.3 hr [60]

1) The mean Tmax of estradiol, estrone, and estrone sulfate after administration of estradiol acetate vaginal ring which delivered 0.05 milligram/day (mg/day) of estradiol was 0.7 to 0.9, 6.2, and 9.3 hours [60].

3) Area Under the Curve

a) Oral: estradiol, 565.0, 1066.5, and 2211.3 pg x hr/mL (0.45, 0.9, and 1.8 mg daily) [170]

b) Oral: baseline adjusted estrone, 2363.8, 4980.9, and 11510.8 pg x hr/mL (0.45, 0.9, and 1.8 mg daily) [170]

1) In 18 healthy postmenopausal women, the mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 565.0 and 2363.8 picograms x hour/milliliter (pg x hr/mL), respectively. The mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 1066.5 and 4980.9 pg x hr/mL, respectively. The mean AUC of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 2211.3 and 11510.8 pg x hr/mL, respectively [170].

ADME

Absorption

A) Estradiol

1) Bioavailability

a) Transdermal

1) Transdermal, patch: 20 times higher than oral [92][9]

a) The systemic availability of estradiol after transdermal administration is approximately 20 times greater than that after oral administration due to the lack of first pass metabolism during transdermal administration [92][9].

b) Vaginal

1) Vaginal ring: approximately 8% [15]

a) Approximately 8% (95% confidence interval: 2.8 - 12.8%) of the daily amount release locally from Estring(R) was absorbed systemically unchanged in postmenopausal women [15].

2) Transdermal

a) Emulsion: exposure increased by sunscreen use [35]

1) The exposure to estradiol is increased by approximately 35% when sunscreen is applied 10 and 25 minutes prior to application of estradiol emulsion, and by 15% when sunscreen is applied 25 minutes after the application of the estradiol emulsion [35].

b) Gel: passive diffusion [13][38]

1) Estradiol gel is absorbed via a passive diffusion process with the rate of diffusion across the stratum corneum being the rate-limiting factor [13][38].

c) Patch: passive diffusion [8]

1) Estradiol, when administered as a transdermal patch, is absorbed via a passive diffusion process with the rate of diffusion across the stratum corneum being the rate-limiting factor [8].

2) The average daily absorbed dose of estradiol after transdermal estradiol systems (Alora(R)) were worn over a continuous four day interval during 251 separate occasions (n=123) was 0.003 milligrams per square centimeter (cm(2)) active surface area. The nominal mean in vivo daily delivery rates of estradiol from the 9, 18, 27, and 36 cm(2) systems were 0.027, 0.054, 0.081, and 0.11 milligrams/day, respectively [8].

3) Vaginal

a) Ring: rapid for first hour; declines to constant rate for the remaining 3 months [15].

1) Absorption from estradiol occurs rapidly for the first hour but then declines to a steady rate for the remainder of the 3-month dosing interval. Estradiol is rapidly absorbed through the vaginal mucosa [60][15].

B) Estradiol Acetate

1) Bioavailability

a) Oral, rapidly absorbed [170].

1) Estradiol was rapidly absorbed following administration of oral estradiol acetate [170].

b) Vaginal, rapid for first hour; declines to constant rate for the remaining 3 months [60].

1) Absorption from estradiol acetate occurs rapidly for the first hour but then declines to a steady rate for the remainder of the 3-month dosing interval. Estradiol acetate and estradiol are both rapidly absorbed through the vaginal mucosa [60].

2) Effects of Food

a) Oral, no effect on systemic availability [170]

1) Compared to the fasted state, the Cmax of estradiol following administration of 1.8 milligrams oral estradiol acetate was decreased by 36% when given with food. However, the AUC was comparable between the fed and fasted states [170].

C) Estradiol Cypionate

1) Bioavailability

a) Intramuscular, absorbed over several weeks [55].

1) When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of estradiol cypionate as an oily preparation is slowed. A single intramuscular injection is absorbed over several weeks [55].

D) Estradiol Valerate

1) Bioavailability

a) Intramuscular, absorbed over several weeks [57].

1) When conjugated with aryl and alkyl groups for parenteral administration, the rate of absorption of estradiol cypionate as an oily preparation is slowed. A single intramuscular injection is absorbed over several weeks [57].

Distribution

A) Distribution Sites

1) Estradiol

a) Protein Binding

1) Estrogens circulate in the blood bound primarily bound to sex hormone binding globulin (SHBG) and to albumin [7][13][38][35][8][92][11][12][36][14][15][94].

2) Estradiol Acetate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily bound to sex hormone binding globulin (SHBG) and to albumin [170][60].

3) Estradiol Cypionate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily to sex hormone binding globulin (SHBG) and to albumin [55].

4) Estradiol Valerate

a) Protein Binding

1) Estrogens circulate in the blood bound primarily to sex hormone binding globulin (SHBG) and to albumin [57].

B) Distribution Kinetics

1) Estradiol

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [7][13][38][35][8][92][11][12][36][14][15][94].

2) Estradiol Acetate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [170][60].

3) Estradiol Cypionate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex hormone target organs [55].

4) Estradiol Valerate

a) Volume of Distribution

1) The distribution of exogenous and endogenous estrogens is similar. Estrogens are widely distributed in the body and are found in higher concentrations in the sex

hormone target organs [57].

Metabolism

A) Metabolism Sites and Kinetics

1) Estradiol

a) Liver, primary [7][13][38][35][8][92][9][11][12][36][14][15][94]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Orally administered estradiol is rapidly metabolized in the liver to estrone and its conjugates which contributes to higher circulating levels of estrone than estradiol [8][9][11][12].

3) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [7][13][38][35][8][92][9][11][12][36][14][15].

4) Estradiol from the transdermal gel preparations does not undergo first pass metabolism and provides estradiol/estrone ratios at steady state in the range of 0.42 to 0.65 [13][38].

5) Vaginal delivery of estradiol does not undergo first pass metabolism [15][94].

b) Skin, small extent [8][9][11][12]

1) Transdermal estradiol is metabolized by the skin to a small extent. Transdermal administration produces therapeutic plasma levels of estradiol with lower levels of estrone and estrone conjugates. Therefore, smaller total doses are required for transdermal administration of estradiol compared with oral administration of estradiol [8][9][11][12].

2) Estradiol Acetate

a) Liver, primary [170][60]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [170][60].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [170][60].

3) Estradiol Cypionate

a) Liver, primary [55]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol acetate is hydrolyzed to estradiol. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [55].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [55].

4) Estradiol Valerate

a) Liver, primary [57]

1) Exogenous estrogens, like endogenous estrogens, are transformed in the liver. Estradiol is converted reversibly to estrone and both can be converted to estriol, the major urinary metabolite. Additionally, estrogens undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut which is followed by reabsorption. A significant proportion of the circulating estrogens in postmenopausal women exists as sulfate conjugates, especially estrone sulfate [57].

2) In vitro and in vivo studies indicate that estrogens are partially metabolized by cytochrome P450 3A4 [57].

B) Metabolites

1) Estradiol

a) Estradiol, active [7][13][38][35][8][92][9][11][12][36][14][15][94]

1) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [7][13][38][35][8][92][9][36][14][15][94].

b) Estrone, active [7][13][38][35][8][92][9][36][14][15][94]

c) Estriol, active[7][13][38][35][8][92][9][36][14][15][94]

2) Estradiol Acetate

a) Estradiol, active [170][60]

1) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [170][60].

b) Estrone, active [170][60]

c) Estriol, active[170][60]

3) Estradiol Cypionate

a) Estrone, active [55]

b) Estriol, active[55]

c) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [55].

4) Estradiol Valerate

a) Estrone, active [57]

b) Estriol, active[57]

c) Estradiol is the principal intracellular human estrogen and is substantially more potent at the receptor site than its metabolites, estrone and estriol [57].

Excretion

A) Kidney

1) Estradiol

a) Renal Clearance (rate)

1) Transdermal

a) Transdermal, patch (Alora(R)): 53 to 69 L/hr [8]

The mean clearance of Alora(R) over an 84-hour dosing interval is presented below [8]:

Dose (milligrams/day)	Application Site	N	Dosing	Clearance (liters/hour)
0.05	Abdomen	20	Multiple	54
0.075	Abdomen	20	Multiple	53
0.1	Abdomen	42	Multiple	61
0.05	Abdomen	31	Single	69
0.05	Buttock	31	Single	66
0.05	Hip*	31	Single	62

b) Renal Excretion (%)

1) 5% to 8% unchanged [15]

a) At 4 and 12 weeks after application of estradiol vaginal ring, the mean percent dose that was excreted in the urine as estradiol was 5% and 8%, respectively [15].

2) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [7][13][38][35][8][92][9][11][12][36][14][15][94].

2) Estradiol Acetate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [170][60].

3) Estradiol Cypionate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [55].

4) Estradiol Valerate

a) Renal Excretion (%)

1) Estradiol, estrone, and estriol, as well as their glucuronide and sulfate conjugates, are excreted in urine [57].

B) Bile

1) Estradiol

a) Estrogens undergo biliary secretion of conjugates into the intestine [7][13][38][35][8][92][9][11][12][36][14][15][94][502][503][504][505][114][506][507].

2) Estradiol Acetate

a) Estrogens undergo biliary secretion of conjugates into the intestine [170][60][502][503][504][505][114][506][507].

3) Estradiol Cypionate

a) Estrogens undergo biliary secretion of conjugates into the intestine, hydrolyzed and reabsorbed [55][502][503][504][505][114][506][507].

4) Estradiol Valerate

a) Estrogens undergo biliary secretion of conjugates into the intestine, hydrolyzed and reabsorbed [57][502][503][504][505][114][506][507].

Elimination Half-life

A) Parent Compound

1) Transdermal Gel

a) Estrogel(R): 36 hours [13][38]

1) The apparent terminal half-life for estradiol was 36 hours following administration of 1.25 g of Estrogel(R) and 36 hours [13].

b) Divigel(R): 10 hours [38]

1) The apparent terminal half-life of Divigel(R) was about 10 hours [38].

2) Transdermal Patch

a) Alora(R): 1.75 hours [8]

1) The apparent mean serum half-life of estradiol when administered as the Alora(R) transdermal patch was 1.75 +/- 2.87 hours [8].

b) Vivelle(R): 4.4 hours [11]

c) Vivelle-Dot(R): 5.9 to 7.7 hours [12]

B) Metabolites

1) Estradiol Acetate

a) Oral: estradiol, 21.4 hr to 25.9 hr [170]

b) Oral: baseline adjusted estrone, 15.9 hr to 17.6 hr [170]

1) In 18 healthy postmenopausal women, the mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.45 milligrams was 25.9 and 15.9 hours, respectively. The mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 0.9 milligrams was 22.2 and 16.1 hours, respectively. The mean half-life of estradiol and baseline-adjusted estrone after multiple-dose administration of oral estradiol acetate 1.8 milligrams was 21.4 and 17.6 hours, respectively [170].

Extracorporeal Elimination

A) Hemodialysis

1) Dialyzable: Total serum estradiol concentrations are higher in postmenopausal women with end stage renal disease (ESRD) receiving maintenance hemodialysis at baseline and following oral doses of estradiol. Therefore, the traditional transdermal doses used in patients with normal renal function may be excessive for patients with ESRD who are receiving hemodialysis[92]

PATIENT EDUCATION

Medication Counseling

No results available

Patient Handouts

A) Estradiol (Absorbed through the skin)
Estradiol

Treats hot flashes and other symptoms of menopause or low estrogen.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to estradiol, or if you have liver disease, breast cancer, or certain other types of cancer. Do not use it if you have a

history of blood clotting problems, or if you had a heart attack or stroke. Do not use this medicine if you may be pregnant, or if you have unusual vaginal bleeding that has not been checked by your doctor.

How to Use This Medicine:

Liquid Mixture, Gel/Jelly, Spray

Take your medicine as directed. Your dose may need to be changed several times to find what works best for you. This medicine is usually applied once a day, at the same time each day.
Use this medicine only on your skin. Rinse it off right away if it gets on a cut or scrape. Do not get the medicine in your eyes, nose, or mouth.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Wash your hands with soap and water before and after you use this medicine.
To use the emulsion:

Apply the emulsion to your legs. The usual daily dose is 2 foil pouches, 1 for each leg.
Cut or tear open the first pouch at the notches near the top. Squeeze out all of the medicine from the pouch onto the top of your left thigh. Rub the medicine thoroughly into your thigh and calf, for about 3 minutes. Repeat these steps to apply the medicine in the second pouch to the right thigh and calf.
Allow the medicine to dry completely before you get dressed. Wait at least 25 minutes before you put on sunscreen.

To use the gel:

Gel pump: You get the correct dose of estradiol each time you press the pump. You may need to prime the pump by pumping 3 times (EstroGel®) or 10 times (Elestrin™) the first time you use it. Follow the patient instructions for the container you use. After you prime the pump, do not press the pump more than 1 time each time you use it.
Apply the gel to clean, dry, and unbroken skin. Spread the gel as thinly as possible over the entire area on the inside and outside of 1 arm from your wrist to your shoulder. Do not apply the medicine directly to your breasts or in or around your vagina.
Do not allow others to come in contact with the area of skin where you applied the gel for at least 1 hour after you use the medicine. Do not allow others to apply the gel for you. Allow the medicine to dry for at least 5 minutes before you get dressed.
Apply sunscreen at least 25 minutes after using Elestrin™ gel. Avoid applying sunscreen on the same application site for 7 days or more.
Gel packet: Cut or tear the Divigel® packet. Squeeze the packet contents onto your upper thigh. Gently spread the gel over your upper thigh, covering a space about the size of 2 palm prints. You do not need to massage or rub in the gel. Allow the gel to dry completely before you put on clothes. Alternate between your right and left upper thigh each day.
Do not allow others to come in contact with the area of skin where you applied the gel for at least 1 to 2 hours after you use the medicine. Do not allow others to apply the gel for you.

To use the spray:

The spray form comes in an applicator that delivers the same amount of estradiol with each spray. You need to prime the pump of a new spray applicator before you use it. Hold the spray upright and pump it 3 times. You only need to prime the pump the first time you use a new spray applicator.
Apply the medicine to clean, dry, and unbroken skin on the inside of your forearm between the elbow and the wrist. Do not apply the medicine directly to your breasts or in or around the vagina.
Allow the medicine to dry for at least 2 minutes before you get dressed. Wait at least 1 hour before you wash your skin.
If your doctor tells you to increase your dose, move the applicator to an area of the skin next to your previous application site before you apply the next dose. Do this for each spray.
Do not rub Evamist® spray into your skin.
Always place the protective cover back on the applicator.
Do not use the applicator for more than 56 sprays.
Apply sunscreen at least 1 hour before you apply Evamist®.

The estradiol gel and spray are flammable. Do not use these medicines near an open flame or while smoking.
Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some foods and medicines can affect how estradiol works. Tell your doctor if you are using St John's wort, carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, thyroid medicine, or a blood thinner (such as warfarin).
Do not put cosmetics or skin care products on the treated skin.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor. This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, edema (body swelling), endometriosis, epilepsy, migraine headaches, porphyria, lupus, thyroid problems, heart disease, high blood pressure, high cholesterol or triglycerides, inherited angioedema, or a history of cancer. Tell your doctor if you had liver problems caused by pregnancy or estrogen.
This medicine may cause the following problems:

Higher risk of heart attack, stroke, or blood clots
Higher risk of endometrial cancer, breast cancer, or uterine cancer
Gallbladder disease
Higher risk of dementia

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results. You may need to stop using this medicine before you have surgery or if you need to stay in bed for a long time.
Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments. You should have regular exams and mammograms as directed by your doctor.
Keep all medicine out of the reach of children. Never share your medicine with anyone.
Do not allow children or pets to touch the skin where you applied the medicine. If this happens, wash the child or pet's skin with soap and water.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Breast lumps
Chest pain, trouble breathing, or coughing up blood
Loss of vision, double vision, or other vision changes
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Sudden and severe stomach pain, with or without nausea, vomiting, fever, and lightheadedness
Swelling in your hands, ankles, or feet
Unusual vaginal bleeding or heavy bleeding

If you notice these less serious side effects, talk with your doctor:

Changes in weight or hair growth
Headache
Nausea, vomiting, or stomach cramps
Runny or stuffy nose, sore throat, or fever
Skin redness or itching where the medicine is applied
Swollen or tender breasts

If you notice other side effects that you think are caused by this medicine, tell your doctor.
B) Estradiol (By injection)
Estradiol

Treats hot flashes and other symptoms of menopause. Also treats prostate cancer in men, and treats lack of estrogen caused by a disorder of the ovaries in women.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to hormone medicines. Do not use this medicine if you are pregnant, or if you have abnormal vaginal bleeding that has not been checked by a doctor. You should not use this medicine if you have a history of cancer of the breast, ovary, or uterus. Do not use if you have liver disease or a history of heart attack, stroke, or blood clots.

How to Use This Medicine:
Injectable

Your doctor will prescribe your exact dose and tell you how often it should be given. This medicine is given as a shot into one of your muscles. You may receive this medicine once a week, once every 2 weeks, or once every 4 weeks.
If you have not had your uterus removed (hysterectomy), you may need to use another hormone medicine together with estradiol. Carefully follow your doctor's instructions about all medicines you are using.
A nurse or other health provider will give you this medicine.
You may be taught how to give your medicine at home. Make sure you understand all instructions before giving yourself an injection. Do not use more medicine or use it more often than your doctor tells you to.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Use a new needle and syringe each time you inject your medicine.

If a Dose is Missed:

Call your doctor or pharmacist for instructions.

How to Store and Dispose of This Medicine:

If you store this medicine at home, keep it at room temperature, away from heat and direct light. Do not allow the medicine to get cold.
Throw away used needles in a hard, closed container that the needles cannot poke through. Keep this container away from children and pets.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any leftover medicine, containers, and other supplies. Throw away old medicine after the expiration date has passed.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Warnings While Using This Medicine:

It is unlikely that you will become pregnant while you are going through menopause. But, you should know that using this medicine while you are pregnant could harm your unborn baby. If you think you have become pregnant while using the medicine, tell your doctor right away. If you have recently had an infant, tell your doctor if you are breast feeding.
Make sure your doctor knows if you have asthma, epilepsy, migraine headaches, heart disease, or kidney disease. Also tell your doctor if you have endometriosis, gallbladder disease, liver disease, lupus, porphyria, or an underactive thyroid.
This medicine should not be used to treat or prevent heart disease or stroke. In fact, hormone therapy can increase your risk of certain heart or blood vessel problems. Tell your doctor if you have a history of heart attack, stroke, high blood pressure, congestive heart failure, blood clots, or circulation problems.
Your risk of heart disease or stroke from this medicine is higher if you smoke. Your risk is also increased if you have diabetes or high cholesterol, or if you are overweight. Talk with your doctor about ways to stop smoking. If you have diabetes, keep it under control. Ask your doctor about diet and exercise to control your weight and blood cholesterol level.
This medicine may also increase your risk of other medical problems, including certain types of cancer. Talk with your doctor about how these risks might affect you.
Tell any doctor or dentist who treats you that you are using this medicine. You may need to stop using this medicine several days before you have surgery or medical tests. This medicine may also affect the results of certain medical tests.

Possible Side Effects While Using This Medicine:

Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Blistering, peeling, red skin rash.
Breast changes or lumps.
Chest pain, or coughing up blood.
Dark-colored urine or pale stools, yellowing of your skin or the whites of your eyes.
Nausea, vomiting, loss of appetite, pain in your upper stomach.
Numbness or weakness in your arm or leg, or on one side of your body.
Pain in your lower leg (calf).
Shortness of breath, cold sweat, and bluish-colored skin.
Sudden or severe headache, problems with vision, speech, or walking.
Swelling in your hands, ankles, or feet.
Vaginal bleeding or spotting.

If you notice these less serious side effects, talk with your doctor:

Joint pain.
Breast pain or tenderness, discharge from your nipples.
Hair loss, increased hair growth, or skin changes.
Mood changes or depression.
Problems or discomfort when wearing contact lenses.
Vaginal itching or discharge.
Weight gain or loss.

If you notice other side effects that you think are caused by this medicine, tell your doctor.

C) Estradiol (By mouth)

Estradiol

Treats symptoms caused by menopause or removal of the ovaries, and treats prostate or breast cancer. Also prevents osteoporosis.

When This Medicine Should Not Be Used:
You should not use this medicine if you have had an allergic reaction to estrogen medicines, if you are pregnant or breastfeeding, if you have had a blood clot, or if you have vaginal bleeding that has not been checked by a doctor. You should not use this medicine if you have had cancer of the uterus, or in certain cases of breast cancer.

How to Use This Medicine:
Tablet
Your doctor will tell you how much of this medicine to take and how often. Do not take more medicine or take it more often than your doctor tells you to.
You may take your medicine with food or milk to avoid stomach upset.

If a Dose is Missed:
If you miss a dose or forget to take your medicine, take it as soon as you can. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose.
Do not use extra medicine to make up for a missed dose.

How to Store and Dispose of This Medicine:
Store the medicine at room temperature, away from heat, moisture, and direct light.
Ask your pharmacist, doctor, or health caregiver about the best way to dispose of any outdated medicine or medicine no longer needed.
Keep all medicine out of the reach of children and never share your medicine with anyone.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.
Make sure your doctor knows if you are also using a blood thinner (Coumadin®).

Warnings While Using This Medicine:
Although it is unlikely that a postmenopausal woman might become pregnant, you should know that using this medicine while you are pregnant could harm the unborn baby. If you think you have become pregnant while using the medicine, tell your doctor right away.
Make sure your doctor knows if you have gallbladder disease, diabetes, heart disease, high blood pressure, high levels of calcium in your blood (hypercalcemia), liver disease, asthma, epilepsy, migraine headaches, kidney disease, high cholesterol, or blood clots.
Taking large doses of estrogens over a long period of time may increase your risk of some kinds of cancer. If you have questions about this risk, talk with your doctor.
Your doctor will need to check your progress at regular visits while you are using this medicine (usually every 6 to 12 months). Be sure to keep all appointments.
Make sure any doctor or dentist who treats you knows that you are using this medicine. This medicine may affect the results of certain medical tests.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:
Blistering, peeling, red skin rash
Lumps in breast (women and men)
Numbness or weakness in your arm or leg, pain in your chest or leg (calf)
Severe headache or vomiting, dizziness, slurred speech
Shortness of breath, coughing up blood
Swelling in your hands, ankles, or feet
Vaginal bleeding of unknown cause

If you notice these less serious side effects, talk with your doctor:
Changes in hair growth
Changes in your vision
Nausea, vomiting, stomach cramps, bloated feeling
Swollen and tender breasts (women and men)
Vaginal itching or discharge

If you notice other side effects that you think are caused by this medicine, tell your doctor.
D) Estradiol (Into the vagina)
Estradiol

Treats hot flashes, painful sexual intercourse, and other symptoms of menopause or low estrogen.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use it if you had an allergic reaction to estradiol, or if

you are pregnant, or have unusual vaginal bleeding that has not been checked by your doctor. Do not use it if you have liver disease, breast or uterine cancer, problems with blood clots, or had a heart attack or stroke.

How to Use This Medicine:

Cream, Insert, Suppository

Your doctor will tell you how much medicine to use. Do not use more than directed.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Vaginal cream:

Measure the cream using the marks on the plastic applicator. Make sure you use the correct mark for your specific dose.

Vaginal ring:

Once the ring is in place, you should not be able to feel it. If you feel uncomfortable, the ring may not be inserted far enough. Gently push the ring farther into your vagina. If you feel pain, talk to your doctor.
The ring may move down accidently. This can happen if you strain to have a bowel movement. Gently push the ring back into place. If the ring comes all the way out, rinse it with warm water and put it back in. Call your doctor if the ring comes out several times.
Remove the ring after 90 days and insert a new one as needed.
Do not flush a used vaginal ring down the toilet. Wrap it with tissue or toilet pair and throw it in the trash.

Vaginal insert:

The insert should be used only in your vagina. Do not swallow the insert.
It is best to use this medicine at the same time each day.
Imvexxy™: Push an insert through the foil of the blister package and hold it with the larger end between your fingers. You may choose to put the insert into your vagina using the lying down or standing up position. Put the insert about 2 inches into your vagina, with the smaller end up, using your finger.
Vagifem®: Do not take the insert out of the applicator. If the insert comes out of the applicator when you open it, carefully put it back in. If the insert falls out of the applicator when you try to insert it, throw it away and use a new applicator and insert.

Store the unopened packages of this medicine at room temperature, away from heat, moisture, and direct light.

Drugs and Foods to Avoid:

Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some medicines can affect how estradiol works. Tell your doctor if you are using carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, St John's wort, or thyroid medicines.
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.
Ask your doctor before you use other products or medicines in your vagina. You may need to remove the ring first.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor. This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, edema, endometriosis, epilepsy, migraine headaches, porphyria, lupus, thyroid problems, heart disease, high blood pressure, high cholesterol, hereditary angioedema, bone problems, or a history of cancer. Tell your doctor if you had liver problems caused by pregnancy or estrogen. Tell your doctor if you have any problems with your vagina or in your pelvic area, including prolapse. Tell your doctor if you are having a surgery that requires inactivity for a long time.
This medicine may cause the following problems:

Increased risk of heart attack, stroke, or blood clots
Increased risk of endometrial, breast, ovarian, or uterine cancer
Possible risk of dementia (especially in women 65 years of age or older)
Gallbladder disease
Eye or vision problems
High blood pressure
High cholesterol or fats in the blood

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.
Your doctor will check your progress and the effects of this medicine at regular visits. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Breast lumps or tenderness
Chest pain that may spread, coughing up blood, trouble breathing
Fever, diarrhea, muscle pain, dizziness, fainting
Numbness or weakness on one side of your body, sudden or severe headache, problems with speech or walking
Redness, pain, burning, or itching in or near your vagina
Sudden and severe stomach pain, nausea, vomiting
Swelling in your hands, ankles, or feet
Unusual vaginal bleeding, spotting, discharge, or itching
Vision changes

If you notice these less serious side effects, talk with your doctor:

If you notice other side effects that you think are caused by this medicine, tell your doctor.

E) Estradiol Patch (Absorbed through the skin)
Estradiol

Treats symptoms of menopause (including hot flashes and vaginal problems) in women with a uterus. Also treats low estrogen levels and prevent osteoporosis after menopause.

When This Medicine Should Not Be Used:
This medicine is not right for everyone. Do not use if you had an allergic reaction to estradiol, or if you have unusual vaginal bleeding that has not been checked by your doctor. Do not use it if you have liver disease, breast cancer, estrogen-dependent tumors, bleeding problems, blood clots, dementia, heart or blood vessel disease, or had a heart attack or stroke.

How to Use This Medicine:
Patch

Your doctor will tell you how many patches to use, where to apply them, and how often to apply them. Do not use more patches or apply them more often than your doctor tells you to.
Read and follow the patient instructions that come with this medicine. Talk to your doctor or pharmacist if you have any questions.
Wash your hands with soap and water before and after applying a patch.
Leave the patch in its sealed wrapper until you are ready to put it on. Tear the wrapper open carefully. NEVER CUT the wrapper or the patch with scissors. Do not use any patch that has been cut by accident.
The patient instructions will show the body areas where you can wear the patch. When putting on each new patch, choose a different place within these areas. Do not put the new patch on the same place you wore the last one. Be sure to remove the old patch before applying a new one.
Place the patch on a clean, dry area of your lower stomach or upper buttock area, where there is no oil, lotion, or powder. Do not apply the patch on or near your breasts, over cut or broken skin, or in a spot where it might rub off (including the waistline).
Press the patch firmly in place with your hand for about 10 seconds.
Change your patch on the same days of each week, to help you remember.
If you have any adhesive left on your skin after you remove the patch, allow it to dry for 15 minutes. Then gently rub the sticky area with oil or lotion to remove the adhesive.
You may take a bath, shower, or swim while wearing a patch.
Fold the used patch in half with the sticky side together. Place it in a sturdy childproof container and throw away, out of the reach of children and pets. Do not flush the patch down the toilet.
Missed dose: If you forget to wear or change a patch, put one on as soon as you can. If it is almost time to put on your next patch, wait until then to apply a new patch and skip the one you missed. Do not apply extra patches to make up for a missed dose.
If a patch falls off, just put it back on a different area. If the patch does not stick completely, put on a new patch, but continue to follow your original schedule for changing to a new one.
Store the patches at room temperature in a closed container, away from heat, moisture, and direct light. Do not open the pouch until you are ready to use the patch.

Drugs and Foods to Avoid:
Ask your doctor or pharmacist before using any other medicine, including over-the-counter medicines, vitamins, and herbal products.

Some foods and medicines can affect how estradiol works. Tell your doctor if you are using carbamazepine, clarithromycin, erythromycin, itraconazole, ketoconazole, phenobarbital, rifampin, ritonavir, St John's wort, thyroid medicine, or a blood thinner (including warfarin).
Do not eat grapefruit or drink grapefruit juice while you are using this medicine.

Warnings While Using This Medicine:

Pregnancy after menopause is not likely, but if you think you could be pregnant, tell your doctor.
This medicine could harm an unborn baby.
Tell your doctor if you are breastfeeding, or if you have kidney disease, asthma, diabetes, endometriosis, seizures, migraine headaches, porphyria, lupus, thyroid problems, hereditary angioedema, edema (swelling), high blood pressure, high cholesterol or triglycerides, obesity, or a history of cancer. Tell your doctor if you have had your uterus (womb) removed (hysterectomy) or if you are having surgery that will require inactivity for a long time.
This medicine may cause the following problems:

Increased risk of heart attack, stroke, or blood clots
Increased risk of endometrial cancer, breast cancer, or uterine cancer
Possible risk of dementia, especially in women 65 years of age and older
Gallbladder disease
Eye or vision problems
High blood pressure
High cholesterol or fats in the blood
Thyroid problems

Tell any doctor or dentist who treats you that you are using this medicine. This medicine may affect certain medical test results.
Your doctor will do lab tests at regular visits to check on the effects of this medicine. Keep all appointments.
Keep all medicine out of the reach of children. Never share your medicine with anyone.

Possible Side Effects While Using This Medicine:
Call your doctor right away if you notice any of these side effects:

Allergic reaction: Itching or hives, swelling in your face or hands, swelling or tingling in your mouth or throat, chest tightness, trouble breathing
Blurred or other changes in vision
Breast lumps or tenderness
Chest pain that may spread,, trouble breathing, or coughing up blood
Dark urine or pale stools, nausea, vomiting, loss of appetite, stomach pain, yellow skin or eyes
Fever, diarrhea, muscle pain, dizziness, fainting
Numbness or weakness on one side of your body, sudden or severe headache, problems with vision, speech, or walking
Rapid weight gain, swelling in your hands, ankles, or feet
Redness, pain, burning, or itching in or near your vagina
Unusual vaginal bleeding or heavy bleeding

If you notice these less serious side effects, talk with your doctor:

Headache
Runny or stuffy nose
Skin redness or itching where the patch is placed

If you notice other side effects that you think are caused by this medicine, tell your doctor.

TOXICOLOGY

Clinical Effects

No results available

Range of Toxicity

No results available

Treatment

No results available

ABOUT

How Supplied

No results available

Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms

Estradiol
Estradiol, Micronized
Estradiol Acetate
Estradiol Benzoate
Estradiol Cyp
Estradiol Cypionate
Estradiol Enanthate
Estradiolum
Estradiol Valerate

C) Orphan Drug Status

1) This drug has one or more orphan drug designations, which may include approval or withdrawal of status: Access citation for FDA Orphan Drug Information [54].

D) Physicochemical Properties

1) Estradiol

a) Molecular Weight

1) 272.39 [757]

b) Solubility

1) Soluble in dioxane; slightly soluble in chloroform and ether; sparingly soluble in alcohol and acetone; and practically insoluble in water [758]

2) Estradiol Acetate

a) Molecular Weight

1) 314.42 [759]

3) Estradiol Valerate

a) Molecular Weight

1) 356.50 [57]

Storage & Stability

A) Estradiol

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

4) NIOSH: In the compounding and administration of a hazardous topical drug, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator, and use eye/face and respiratory protection if not prepared in a control device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection, and if there is inhalation potential use respiratory protection [52].

b) Transdermal route

1) Emulsion

a) Apply and rub emulsion into thighs and calves for 3 minutes on each side until thoroughly absorbed. Rub excess on both hands and buttocks and allow to dry completely before covering with clothing. Wash hands after application [35].

2) Gel

a) Divigel(R)

1) Apply entire contents of the single-dose packet to clean, dry skin of left or right upper thigh. The gel should not be applied to face, breasts, in or around vagina, or to irritated skin. Avoid contact with eyes. Allow to dry before dressing and do not wash application site within 1 hour after application. Wash hands with soap and water after application [38].

b) Estrogel(R)

1) Prime the metered dose pump by fully depressing the spout 2 times for the 93 g pump or 3 times for the 50 and 25 g pumps prior to the first use. Collect gel into palm of hand and apply directly onto dry, clean, unbroken skin of the upper arm and shoulder area. The gel should not be applied directly to breast. Apply gel gently from wrist to shoulder and allow to dry for up to 5 minutes before dressing. It is not necessary to massage or rub in the ge. Wash hands with soap and water after application [13].

c) Elestrin(R)

1) To prime the pump, push the head down slowly and allow it to spring back automatically; repeat until gel comes out. Throw away the first amount of gel (not a full dose) into the trash. Once the pump head has come all the way back up, the pump is ready to use [34].

2) If taking a bath or shower or using a sauna, apply dose afterwards. Dry skin completely before application. Apply dose at the same time each day [34].

3) Hold the pump with the tip facing clean, dry, unbroken skin of the application area of the arm, and press the pump firmly and fully for each pump needed. Gently spread the gel over the entire area of the upper arm and shoulder using 2 fingers. Do not apply to the breast or in or around the vagina. Wash hands after application [34].

4) Allow the gel to dry for at least 5 minutes before dressing, and keep the area dry for as long as possible. Avoid fire, flame, or smoking until the gel has dried. Do not allow others to come in contact with the application area for at least 2 hours. If swimming, wait at least 2 hours before going into the water. Do not apply sunscreen to the area where the gel was applied for at least 25 minutes, and do not apply for 7 or more consecutive days [34].

5) If a dose is missed, do not double the dose. If the next dose is less than 12 hours away, wait and apply the dose the next day. If it is more than 12 hours until the next dose, apply the missed dose and resume normal dosing the next day [34].

3) Transdermal System

a) Place system on clean, dry skin, preferably on the lower abdomen, upper quadrant of the buttock, or outer aspect of the hip. Do not apply to the breasts or waistline. Rotate sites of application with 1 week allowed between applications to a particular site [29][19][8][12].

b) Press Climara (R) system firmly in place for at least 10 seconds, making sure there is good contact, especially around the edges [10]

c) If Climara(R) or Minivelle(R) system falls off reapply to different site; if reapplication not possible, apply new patch to another location for remainder of dosing interval [29][19]

d) Swimming, bathing, or using a sauna may decrease the adhesion of the Climara (R) system and the delivery of estradiol [10]

e) Remove Climara(R) system carefully and slowly, fold it in half, and throw it away. If any adhesive remains on the skin, allow the area to dry for 15 minutes, then gently rub with an oil-based cream or lotion to remove residue [10].

4) Spray

a) Prior to initial application, prime pump by spraying 3 sprays with the cover on. With container being held vertically upright, apply to adjacent, nonoverlapping areas on the inner surface of the forearm, starting near the elbow. Allow to dry for 2 minutes before covering with clothing, and do not wash the site for 1 hour after application. Women should cover the application site with clothing if another person may come into contact with that area of the skin after the spray dries [53].

c) Vaginal route

1) Cream

a) The prescribed dose should be measured using the supplied applicator. Gently insert applicator with measured dose deeply into vagina and press plunger downward to original position. Clean the applicator with mild soap and warm water after use [14].

2) Ring

a) The vaginal ring should be inserted as deeply as possible into the upper one-third of the vaginal vault; the exact position is not critical. To remove the ring, hook a finger through the ring and pull. If the ring is removed or falls out any time during the 90-day treatment period, rinse the ring in lukewarm water and reinsert [15].

3) Insert

a) Using the supplied applicator for Vagifem(R), gently insert into the vagina as far as it can comfortably go without force, or until half of the applicator is inside the vagina, whichever is less [16].

b) Insert Imvexxy(TM) intravaginally with the smaller end up for a depth of about 2 inches into the vaginal canal [5].

B) Estradiol Acetate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: Use of single gloves by anyone handling intact tablets or capsules or administering from a unit-dose package is recommended [52].

3) NIOSH: In the preparation of tablets or capsules, including cutting, crushing, or manipulating, or the handling of uncoated tablets, use double gloves and a protective gown. Prepare in a ventilated control device, if possible. Use respiratory protection if not prepared in a control device. During administration, wear single gloves, and wear eye/face protection if the formulation is hard to swallow or if the patient may resist, vomit, or spit up [52].

b) Vaginal route

1) Administration

a) Wash hands thoroughly before and after inserting vaginal ring [59]

b) Press the opposite sides of the vaginal ring and insert into the vagina [59]

c) The patient may reposition estradiol acetate vaginal ring with finger if needed. If the ring is totally expelled from the vagina, it should be rinsed with lukewarm water and reinserted [59].

d) To remove, wash hands and hook finger through ring and gently pull downward [59].

C) Estradiol Cypionate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Preparation

a) If crystals form because estradiol cypionate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming and shaking the vial [55].

D) Estradiol Valerate

1) Preparation

a) General Information

1) NIOSH Group 2 Non-antineoplastics [52]

2) NIOSH: In the preparation and administration of injections, use double gloves and a protective gown. Prepare in a biological safety cabinet or a compounding aseptic containment isolator; eye/face and respiratory protection may be needed. Prepare compounds in a closed system drug transfer device. During administration, if there is a potential that the substance could splash or if the patient may resist, use eye/face protection. Administer certain dosage forms via a closed system drug transfer device [52].

b) Intramuscular route

1) Administration

a) Estradiol valerate injection may be administered with a small gauge needle due to its low viscosity. A dry needle and syringe should be used since use of a wet needle or syringe may cause the solution to become cloudy [57].

b) Inject deep into the upper, outer quadrant of the gluteal muscle [57]

c) If crystals form because estradiol valerate vials had been stored at lower temperatures than what is recommended, they may be redissolved by warming [57].

d) Since the 40-milligram vial provides a high concentration in a low volume, particular care should be taken to administer the full prescribed dose [57].

E) Estradiol

1) Oral route

a) Tablet

1) Store at a controlled room temperature, 20 to 25 degrees C (68 to 77 degrees F); protect from light and close lid tightly [62].

2) Topical application route, Transdermal route

a) Gel/Jelly

1) Store at a controlled room temperature, between 20 and 25 degrees C (68 and 77 degrees F); excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [74][520][65].

3) Transdermal route

a) Patch, Extended Release

1) Store between 20 and 25 degrees C (66 and 77 degrees F). Store in the protective pouch and apply immediately after removal [29][67][66][521][19]. Excursions permitted between 15 and 30

degrees C (59 and 86 degrees F) [29][521][19].

b) Spray

1) Store at room temperature, between 20 and 25 degrees C (68 and 77 degrees F); do not freeze. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [69].

4) Vaginal route

a) Cream

1) Store at room temperature; protect from temperatures above 40 degrees C (104 degrees F) [73].

b) Insert, Extended Release

1) Store at a controlled room temperature between 15 and 25 degrees C (59 and 77 degrees F) [5][142], with excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [5].

c) Insert, Extended Release

1) Store at a controlled room temperature, 25 degrees C (77 degrees F); do not refrigerate. Excursions permitted between 15 and 30 degrees C (59 and 86 degrees F) [16].

F) Estradiol Acetate

1) Oral route

a) Tablet

1) Store estradiol acetate tablets at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [170].

2) Vaginal route

a) Insert, Extended Release

1) Store estradiol acetate vaginal ring at 25 degrees Celsius (77 degrees Fahrenheit); excursions permitted to 15 to 30 degrees Celsius (59 to 86 degrees Fahrenheit) [60].

G) Estradiol Cypionate

1) Intramuscular route

a) Oil

1) Store estradiol cypionate injection at controlled room temperature (20 to 25 degrees Celsius or 68 to 77 degrees Fahrenheit) [55].

H) Estradiol Valerate

1) Intramuscular route

a) Oil

1) Store estradiol valerate injection at room temperature [57].

Trade Names

No results available

Regulatory Status

No results available

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670. Product Information: DAKLINZA(TM) oral tablets, daclatasvir oral tablets. Bristol-Myers Squibb (per manufacturer), Princeton, NJ, 2015.

671. Product Information: DEXAMETHASONE Intensol(TM) oral concentrate solution, dexamethasone oral concentrate solution. Roxane Laboratories, Inc. (per manufacturer), Columbus, OH, 2007.

672. Product Information: VALIUM(R) oral tablets, diazepam oral tablets. Genentech USA, Inc. (per FDA), South San Francisco, CA, 2013.

673. Product Information: CARDIZEM(R) oral tablets, diltiazem HCl oral tablets. Valeant Pharmaceuticals North America LLC (per FDA), Bridgewater, NJ, 2014.

674. Product Information: DOCEFREZ intravenous injection, docetaxel intravenous injection. Caraco Pharmaceutical Laboratories, Ltd. (per FDA), Detroit, MI, 2014.

675. Product Information: domperidone oral suspension, domperidone oral suspension. Zentiva (per EMC), Guildford, Surrey, United Kingdom, 2014.

676. Product Information: COPIKTRA(TM) oral capsules, duvelisib oral capsules. Verastem Inc (per FDA), Needham, MA, 2018.

677. Product Information: SUSTIVA(R) oral capsules, oral tablets, efavirenz oral capsules, oral tablets. Bristol-Myers Squibb Company (per FDA), Princeton, NJ, 2017.

678. Product Information: ORILISSA(TM) oral tablets, elagolix oral tablets. AbbVie Inc (per FDA), North Chicago, IL, 2018.

679. Product Information: ZEPATIER(TM) oral tablets, elbasvir, grazoprevir oral tablets. Merck Sharp & Dohme Corp. (per manufacturer), Whitehouse Station, NJ, 2016.

680. Product Information: TRIKAFTA(TM) oral tablets, elexacaftor, tezacaftor, ivacaftor oral tablets; ivacaftor oral tablets. Vertex Pharmaceuticals Incorporated (per manufacturer), Boston, MA, 2019.

681. Product Information: E.E.S.(R) oral suspension, oral film-coated tablets, erythromycin ethylsuccinate oral suspension, oral film-coated tablets. Arbor Pharmaceuticals, Inc. (per FDA), Atlanta, GA, 2012.

682. Product Information: LUNESTA(R) oral tablets, eszopiclone oral tablets. Sunovion Pharmaceuticals Inc. (per FDA), Marlborough, MA, 2014.

683. Product Information: Tavalisse(TM) oral tablets, fostamatinib disodium hexahydrate oral tablets. Rigel Pharmaceuticals Inc (per FDA), South San Francisco, CA, 2018.

684. Product Information: DAURISMO(TM) oral tablets, glasdegib oral tablets. Pfizer Labs (per FDA), New York, NY, 2018.

685. Product Information: INTUNIV(R) oral extended-release tablets, guanfacine oral extended-release tablets. Shire US Inc (per FDA), Lexington, MA, 2016.

686. Product Information: HALDOL(R) Decanoate 100 intramuscular injection, haloperidol decanoate intramuscular injection. Janssen Pharmaceuticals, Inc. (per DailyMed), Titusville, NJ, 2013.

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689. Product Information: Locoid(R) topical cream, hydrocortisone butyrate 0.1% topical cream. Valeant Pharmaceuticals North America LLC (per FDA), Bridgewater, NJ, 2014.

690. Product Information: LOCOID LIPOCREAM(R) topical cream, hydrocortisone butyrate 0.1% topical cream. Valeant Pharmaceuticals North America LLC (per DailyMed), Bridgewater, NJ, 2014.

691. Product Information: ZYDELIG(R) oral tablets, idelalisib oral tablets. Gilead Sciences Inc (per FDA), Foster City, CA, 2018.

692. Product Information: ifosfamide intravenous injection, ifosfamide intravenous injection. Teva Pharmaceuticals USA, Inc. (per DailyMed), North Wales, PA, 2015.

693. Product Information: GLEEVEC(R) oral tablets, imatinib mesylate oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2015.

694. Product Information: CAMPTOSAR(R) intravenous injection, irinotecan intravenous injection. Pharmacia & Upjohn Co (per Manufacturer), New York, NY, 2014.

695. Product Information: ONIVYDE(TM) intravenous injection solution, irinotecan liposome intravenous injection solution. Merrimack Pharmaceuticals, Inc.(per manufacturer), Cambridge, MA, 2015.

696. Product Information: NOURIANZ(TM) oral tablets, istradefylline oral tablets. Kyowa Kirin Inc (per FDA), Bedminster, NJ, 2019.

697. Product Information: SPORANOX(R) oral capsules, itraconazole oral capsules. Janssen Pharmaceuticals, Inc. (per FDA), Titusville, NJ, 2015.

698. Product Information: TYKERB(R) oral tablets, lapatinib oral tablets. GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2015.

699. Product Information: VITRAKVI(R) oral capsules, oral solution, larotrectinib oral capsules, oral solution. Loxo Oncology Inc (per FDA), Stamford, CT, 2018.

700. Product Information: DAYVIGO(TM) oral tablets, lemborexant oral tablets. Eisai Inc (per FDA), Woodcliff Lake, NJ, 2019.

701. Product Information: lercanidipine HCl oral film-coated tablets, lercanidipine HCl oral film-coated tablets. Actavis UK Ltd (per EMC), Devon, United Kingdom, 2014.

702. Product Information: CONJUPRI(R) oral tablets, levamlodipine oral tablets. CSPC Ouyi Pharmaceutical Co., Ltd (per FDA), Princeton, NJ, 2019.

703. Product Information: KALETRA(R) oral capsules, lopinavir ritonavir oral capsules. AbbVie Inc. (per FDA), North Chicago, IL, 2015.

704. Product Information: CAPLYTA(R) oral capsules, lumateperone oral capsules. Intra-Cellular Therapies Inc (per FDA), New York, NY, 2019.

705. Product Information: ZEPZELCA(TM) intravenous injection, lurbinectedin intravenous injection. Jazz Pharmaceuticals Inc (per FDA), Palo Alto, CA, 2020.

706. Product Information: SYMPROIC(R) oral tablets, naldemedine oral tablets. Purdue Pharma L.P. (per FDA), Stamford, CT, 2018.

707. Product Information: Starlix(R) oral tablets, nateglinide oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2011.

708. Product Information: VIRACEPT(R) oral tablets, oral powder for solution, nelfinavir mesylate oral tablets, oral powder for solution. ViiV Healthcare Company (per FDA), Research Triangle Park, NC, 2015.

709. Product Information: NERLYNX(TM) oral tablets, neratinib oral tablets. Puma Biotechnology, Inc (per FDA), Los Angeles, CA, 2017.

710. Product Information: PROCARDIA XL(R) oral extended release tablets, nifedipine oral extended release tablets. Pfizer Labs (per FDA), New York, NY, 2015.

711. Product Information: SULAR(R) oral film coated extended release tablets, nisoldipine oral film coated extended release tablets. Shionogi Inc. (per DailyMed), Florham Park, NJ, 2013.

712. Product Information: ZOFRAN(R) intravenous injection, ondansetron HCl intravenous injection. GlaxoSmithKline (per FDA), Research Triangle Park, NC, 2013.

713. Product Information: ISTURISA(R) oral tablets, osilodrostat oral tablets. Recordati Rare Disease Inc (per FDA), Lebanon, NJ, 2020.

714. Product Information: paclitaxel intravenous injection, paclitaxel intravenous injection. WG Critical Care, LLC (per FDA), Paramus, NJ, 2015.

715. Product Information: IBRANCE(R) oral capsules, palbociclib oral capsules. Pfizer Labs (per manufacturer), New York, NY, 2017.

716. Product Information: TECHNIVIE(TM) oral tablets, ombitasvir paritaprevir ritonavir oral tablets. AbbVie Inc. (per Manufacturer), North Chicago, IL, 2015.

717. Product Information: PEMAZYRE(TM) oral tablets, pemigatinib oral tablets. Incyte Corporation (per FDA), Wilmington, DE, 2020.

718. Product Information: TURALIO(TM) oral capsules, pexidartinib oral capsules. Daiichi Sankyo Inc (per FDA), Basking Ridge, NJ, 2019.

719. Product Information: progesterone intramuscular injection, progesterone intramuscular injection. Watson Pharma, Inc. (per DailyMed), Parsippany, NJ, 2013.

720. Product Information: quinidine gluconate oral extended-release tablets, quinidine gluconate oral extended-release tablets. Richmond Pharmaceuticals, Inc. (per DailyMed), Richmond, VA, 2011.

721. Product Information: RANEXA(R) oral extended-release tablets, ranolazine oral extended-release tablets. Gilead Sciences, Inc. (per FDA), Foster City, CA, 2016.

722. Product Information: PRANDIN(R) oral tablets, repaglinide oral tablets. Novo Nordisk Inc. (per FDA), Plainsboro, NJ, 2017.

723. Product Information: KISQALI(R) oral tablets, ribociclib oral tablets. Novartis Pharmaceuticals Corporation (per FDA), East Hanover, NJ, 2017.

724. Product Information: NURTEC(TM) orally disintegrating tablets, rimegepant orally disintegrating tablets. Biohaven Pharmaceuticals Inc (per FDA), New Haven, CT, 2020.

725. Product Information: QINLOCK(TM) oral tablets, ripretinib oral tablets. Deciphera Pharmaceuticals LLC (per FDA), Waltham, MA, 2020.

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729. Product Information: ONGLYZA(R) oral tablets, saxagliptin oral tablets. AstraZeneca Pharmaceuticals LP (per FDA), Wilmington, DE, 2017.

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732. Product Information: KOSELUGO(TM) oral capsules, selumetinib oral capsules. AstraZeneca Pharmaceuticals LP (per FDA), Wilmington, DE, 2020.

733. Product Information: OLYSIO(R) oral capsules, simeprevir oral capsules. Janssen Therapeutics (per FDA), Titusville, NJ, 2015.

734. Product Information: ODOMZO(R) oral capsules, sonidegib oral capsules. Novartis Pharmaceuticals (per FDA), East Hanover, NJ, 2015.

735. Product Information: SUTENT(R) oral capsules, sunitinib malate oral capsules. Pfizer Labs (per FDA), New York, NY, 2015.

736. Product Information: tamoxifen citrate oral tablets, tamoxifen citrate oral tablets. Watson Laboratories (per manufacturer), Corona, CA, 2011.

737. Product Information: TEPADINA(R) intravenous, intracavitary, intravesical injection, thiotepa intravenous, intracavitary, intravesical injection . ADIENNE SA (per FDA), Cedar Park, TX, 2017.

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739. Product Information: Yondelis intravenous infusion powder concentrate for solution, trabectedin intravenous infusion powder concentrate for solution. Pharma Mar, S.A (per EMA), Madrid, Spain, 2015.

740. Product Information: trazodone HCl oral tablets, trazodone HCl oral tablets. Sun Pharmaceutical Industries , Inc. (per DailyMed), Cranbury, NJ, 2014.

741. Product Information: TUKYSA(TM) oral tablets, tucatinib oral tablets. Seattle Genetics Inc (per FDA), Bothell, WA, 2020.

742. Product Information: Verelan(R) sustained-release oral capsules, verapamil HCl sustained-release oral capsules. Kremers Urban Pharmaceutical Inc. (per FDA), Princeton, NJ, 2014.

743. Product Information: vinblastine sulfate intravenous injection, vinblastine sulfate intravenous injection. Bedford Laboratories (per manufacturer), Bedford, OH, 2012.

744. Product Information: Vincasar PFS(R) intravenous injection solution, vincristine sulfate intravenous injection solution. Teva Pharmaceuticals USA, Inc. (per DailyMed), North Wales, PA, 2014.

745. Product Information: MARQIBO(R) intravenous injection, vincristine sulfate liposome intravenous injection. Acrotech Biopharma LLC (per FDA), East Windsor, NJ, 2020.

746. Product Information: vinorelbine intravenous injection solution, vinorelbine intravenous injection solution. Hospira Inc (per DailyMed), Lake Forest, IL, 2016.

747. Product Information: ZONTIVITY(R) oral tablets, vorapaxar oral tablets. Merck Sharp & Dohme Corp. (per FDA), Whitehouse Station, NJ, 2015.

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749. Product Information: VOSEVI(TM) oral tablets, sofosbuvir velpatasvir voxilaprevir oral tablets. Gilead Sciences Inc (per manufacturer), Foster City, CA, 2017.

750. Product Information: Sonata(R) oral capsules, zaleplon oral capsules. King Pharmaceuticals, Inc. (per FDA), Bristol, TN, 2013.

751. Product Information: GEODON(R) intramuscular injection, ziprasidone mesylate intramuscular injection. Roerig (per FDA), New York, NY, 2014.

752. Product Information: AMBIEN(R) oral tablets, zolpidem tartrate oral tablets. sanofi-aventis U.S. LLC (per FDA), Bridgewater, NJ, 2014.

753. US Pharmacopeial Convention: Hazardous Drugs - Handling in Healthcare Settings. In: 2017 USP Compounding Compendium, US Pharmacopeial Convention, Rockville, MD, 2016.

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758. Reynolds JEF (Ed): Martindale: The Extra Pharmacopeia (CD-ROM Version), Micromedex, Inc, Englewood, CO, 1988.

759. Product Information: Femring(R) vaginal ring, estradiol acetate vaginal ring. Warner Chilcott (US), LLC, Rockaway, NJ, 2010.

760. Institute for Safe Medication Practices: ISMP's list of confused drug names. Institute for Safe Medication Practices. Huntingdon Valley, PA. 2005. Available from URL: http://ismp.org/Tools/confuseddrugnames.pdf.

Last Modified: November 21, 2022

TAB 175-28

Agency Responses to Plaintiffs' Questions: March 1, 2023

Plaintiffs' Question: *Please provide a complete list of the diagnostic codes (ICD-10 codes) programmed in FMMIS for the following drugs (listed by generic name): estradiol (all formulations and combinations listed in the PDL); testosterone (all formulations listed in the PDL); testosterone cypionate (all formulations listed in the PDL); testosterone enanthate (all formulations listed in the PDL); triptorelin pamoate (both the kit and the vial); leuprolide acetate (all formulations listed in the PDL); Metformin HCL (all formulations listed in the PDL).*

Agency Response: The diagnosis codes for drugs subject to an automatic prior authorization or bypass are located at https://ahca.myflorida.com/medicaid/Prescribed_Drug/drug_criteria_pdf/Automated_PA.pdf. This list includes those established for triptorelin pamoate and leuprolide acetate. For prescription drugs that are not on that list and do not require a prior authorization, the Agency does not verify the diagnosis code prior to paying the claim.

Plaintiffs' Question: *Please answer whether the prescribed drug criteria listed at https://ahca.myflorida.com/6edicaid/prescribed_drug/drug_criteria.shtml is an exhaustive list of the criteria relied upon by AHCA in reviewing whether a prescribed drug is medically necessary. If the above is not an exhaustive list, please provide documents indicating all other criteria on which AHCA relies in determining whether a prescribed drug is medically necessary for a particular patient, either during the prior authorization process, or after a claim has been paid (as described by Mr. Brackett).*

Agency Response: Yes, this is an exhaustive list.

Plaintiffs' Question: *Please answer whether Florida's Medicaid managed care plans are required to cover all drugs included in the PDL and, if so, whether the plans must follow the prior authorization requirements as indicated in the PDL.*

Agency Response: Yes, health plans participating in the Statewide Medicaid Managed Care program must cover all drugs on the Preferred Drug List and cannot be more restrictive when covering drugs that have a specific criteria.

Plaintiffs' Question: *Please identify the person who made edits to the GAPMS report on cross-sex hormone therapy dated May 20, 2022 as well as all individuals who accessed the document.*

Agency Response: The Agency identified the employee as Shantrice Greene, who worked as a senior pharmacist. She is no longer with the Agency.

Plaintiffs' Question: *Please provide the number of individuals who received Medicaid coverage for puberty suppression medications to treat gender dysphoria from January 1, 2015 to August 21, 2022.*

Agency Response: Please refer to the data file that was completed on March 1, 2023.

Plaintiffs' Question: *Please provide the number of grievances and the number of appeals filed with Florida Medicaid managed care plans regarding services excluded pursuant to Fla. Admin. Code R. 59G-1.050(7).*

Agency Response: The Agency found one complaint regarding the coverage of services under the challenged exclusion.

Plaintiffs' Question: *Please state whether, and if so, how many, Medicaid fair hearings have resulted in a reversal of a decision to deny coverage for any of the services listed at 59G-1.050(7), prior to the effective date of the Challenged Exclusion.*

Agency Response: The Agency identified zero fair hearings that were prior to the challenged exclusion.

Plaintiffs' Question: *Please provide the number of Medicaid fair hearings regarding a request for coverage of services listed at 59G-1.050(7) since August 21, 2022 including information about the adverse action being appealed and the final outcome.*

Agency Response: The Agency identified zero fair hearings that occurred after the implementation of the challenged exclusion.

Plaintiffs' Question: *Please identify the Florida Department of Health employee(s) who provided the name "Michelle Cretella" or the name of any other consultant who AHCA relied upon or consulted with in the drafting of the 2022 GAPMS Memo.*

Agency Response: All communication that occurred between the Agency and the Department of Health occurred through verbal conversations. Agency staff that participated in these discussions do not recall the specific Department of Health employee who provided the name.

Plaintiffs' Question: *Please identify all individuals who AHCA considered but decided not to use for assistance with drafting the June 2022 GAPMS report on treatment for gender dysphoria.*

Agency Response: Agency staff engaged in verbal communications with individuals that were referred by Dr. Michelle Cretella and do not recall the names of those individuals that were consulted.

Plaintiffs' Question: *Regarding the emails between AHCA and Magellan dated April 20, 2022 to June 3, 2022 (Def_000145166 to Def 000145169), please answer the following:*

- **Question:** *What does CCM mean?*
- **Agency Response:** Change Control Memo
- **Question:** *What does "gender code = B (Both)" mean?*
- **Agency Response:** That a covered outpatient prescription drug can be prescribed to both males and females.
- **Question:** *What is the "internal Gender Dysphoria criteria?"*
- **Agency Response:** The criteria provided to Magellan to utilize when reviewing prior authorization requests for GnRH antagonists.
- **Question:** *What is meaning of the following paragraph: "This internal document serves for GnRHanalog use to delay puberty in adolescents with Gender Dysphoria, but it does not speak to the use of hormone therapy (i.e.anastrozole, etc.).This document was provided by the Agency due to a fair hearing request received for Lupron for a recipient with this diagnosis. All requests*

required vetting by AHCA before a final determination is made, and MMA will continue to do so as instructed."

- **Agency Response:** This paragraph specifically references the internal prior authorization review criteria for GnRH antagonists and requires Magellan only to review requests for that one drug category and not any that involve hormones such as testosterone or estrogen.

TAB 175-36

AACAP Statement Responding to Efforts to ban Evidence-Based Care for Transgender and Gender Diverse Youth

November 8, 2019

Variations in gender expression represent normal and expectable dimensions of human development. They are not considered to be pathological. Health promotion for all youth encourages open exploration of all identity issues, including sexual orientation, gender identity, and/or gender expression according to recognized practice guidelines (1, 2). Research consistently demonstrates that gender diverse youth who are supported to live and/or explore the gender role that is consistent with their gender identity have better mental health outcomes than those who are not (3, 4, 5).

State-based legislation regarding the treatment of transgender youth that directly oppose the evidence-based care recognized by professional societies across multiple disciplines is a serious concern. Many reputable professional organizations, including the American Psychological Association, the American Psychiatric Association, the American Academy of Pediatrics, and the Endocrine Society, which represent tens of thousands of professionals across the United States, recognize natural variations in gender identity and expression and have published clinical guidance that promotes nondiscriminatory, supportive interventions for gender diverse youth based on the current evidence base. These interventions may include, and are not limited to, social gender transition, hormone blocking agents, hormone treatment, and affirmative psychotherapeutic modalities.

The American Academy of Child and Adolescent Psychiatry (AACAP) supports the use of current evidence-based clinical care with minors. AACAP strongly opposes any efforts – legal, legislative, and otherwise – to block access to these recognized interventions. Blocking access to timely care has been shown to increase youths' risk for suicidal ideation and other negative mental health outcomes. Consistent with AACAP's policy against conversion therapy (2), AACAP recommends that youth and their families formulate an individualized treatment plan with their clinician that addresses the youth's unique mental health needs under the premise that all gender identities and expressions are not inherently pathological.

1. Adelson, S. L., & the American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). (2012). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender non-conformity, and gender discordance in children and adolescents. Journal of the American Academy of Child & Adolescent Psychiatry, 51, 957– 974. http://dx.doi.org/10.1016/j.jaac.2012.07.004.
2. American Academy of Child and Adolescent Psychiatry (AACAP) Sexual Orientation and Gender Identity Issues Committee. (2018). Conversion Therapy Policy Statement. Retrieved from: https://www.aacap.org/AACAP/Policy_Statements/2018/Conversion_Therapy.aspx.
3. Olson KR, Durwood L, DeMeules M, McLaughlin KA. (2016). Mental health of transgender children who are supported in their identities. Pediatrics, 137(3).

4. Ryan C, Russell ST, Huebner D, Diaz R, Sanchez J. (2010) Family acceptance in adolescence and the health of LGBT young adults. J Child Adolesc Psychiatr Nurs., 23(4):205–213.
5. Substance Abuse and Mental Health Services Administration, A Practitioner's Resource Guide: Helping Families to Support Their LGBT Children. (2014). HHS Publication No. PEP14-LGBTKIDS. Rockville, MD: Substance Abuse and Mental Health Services Administration. Retrieved from: https://store.samhsa.gov/system/files/pep14-lgbtkids.pdf.

TAB 175-37

All Policies

Pl. Trial Ex. 037

Care for the Transgender and Gender Nonbinary Patient

The American Academy of Family Physicians (AAFP) recognizes that diversity in gender identity and expression is a normal part of the human existence and does not represent pathology. The AAFP supports access to gender-affirming care for gender-diverse patients, including children and adolescents. Gender-affirming health care is part of comprehensive primary care for many gender-diverse patients, and may include supportive behavioral health care, gender-affirming hormones, puberty blockade, medical procedures, and surgical interventions.

Family physicians are uniquely suited to provide gender-affirming care because of their whole-person focus, ability to create care plans that meet the needs of diverse individuals, and longitudinal relationship with the patient across the entire lifespan. Family physicians who do not provide this care should take steps to ensure that patients requiring gender-affirming services are appropriately referred.

Transgender and gender nonbinary people often face social and economic marginalization, and experience a variety of barriers to healthcare, including overt discrimination, inadequate health insurance coverage, legislative interference in the physician-patient relationship, and poor physicia knowledge of appropriate treatment. The AAFP supports gender-affirming care as an evidence-informed intervention that can promote health equity for gender-diverse individuals, although wide sociopolitical efforts are necessary to further mitigate these barriers and advance equity. The AAF asserts the full spectrum of gender-affirming care should be legal and should remain a treatment decision between a physician and their patient.

The AAFP supports education on gender diversity and gender-affirming care at all levels of medical education, including medical school, residency and continuing professional development. (October 2020 BOD) (July 2022 BOD)

TAB 175-38

Pl. Trial Ex. 038

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents

Jason Rafferty, MD, MPH, EdM, FAAP, COMMITTEE ON PSYCHOSOCIAL ASPECTS OF CHILD AND FAMILY HEALTH, COMMITTEE ON ADOLESCENCE, SECTION ON LESBIAN, GAY, BISEXUAL, AND TRANSGENDER HEALTH AND WELLNESS

abstract

FREE

As a traditionally underserved population that faces numerous health disparities, youth who identify as transgender and gender diverse (TGD) and their families are increasingly presenting to pediatric providers for education, care, and referrals. The need for more formal training, standardized treatment, and research on safety and medical outcomes often leaves providers feeling ill equipped to support and care for patients that identify as TGD and families. In this policy statement, we review relevant concepts and challenges and provide suggestions for pediatric providers that are focused on promoting the health and positive development of youth that identify as TGD while eliminating discrimination and stigma.

INTRODUCTION

In its dedication to the health of all children, the American Academy of Pediatrics (AAP) strives to improve health care access and eliminate disparities for children and teenagers who identify as lesbian, gay, bisexual, transgender, or questioning (LGBTQ) of their sexual or gender identity.[1,2] Despite some advances in public awareness and legal protections, youth who identify as LGBTQ continue to face disparities that stem from multiple sources, including inequitable laws and policies, societal discrimination, and a lack of access to quality health care, including mental health care. Such challenges are often more intense for youth who do not conform to social expectations and norms regarding gender. Pediatric providers are increasingly encountering such youth and their families, who seek medical advice and interventions, yet they may lack the formal training to care for youth that identify as transgender and gender diverse (TGD) and their families.[3]

This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population, providing brief, relevant background on the basis of current available research

Department of Pediatrics, Hasbro Children's Hospital, Providence, Rhode Island; Thundermist Health Centers, Providence, Rhode Island; and Department of Child Psychiatry, Emma Pendleton Bradley Hospital, East Providence, Rhode Island

Dr Rafferty conceptualized the statement, drafted the initial manuscript, reviewed and revised the manuscript, approved the final manuscript as submitted, and agrees to be accountable for all aspects of the work.

Policy statements from the American Academy of Pediatrics benefit from expertise and resources of liaisons and internal (AAP) and external reviewers. However, policy statements from the American Academy of Pediatrics may not reflect the views of the liaisons or the organizations or government agencies that they represent.

The guidance in this statement does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

All policy statements from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

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TABLE 1 Relevant Terms and Definitions Related to Gender Care

Term	Definition
Sex	An assignment that is made at birth, usually male or female, typically on the basis of external genital anatomy but sometimes on the basis of internal gonads, chromosomes, or hormone levels
Gender identity	A person's deep internal sense of being female, male, a combination of both, somewhere in between, or neither, resulting from a multifaceted interaction of biological traits, environmental factors, self-understanding, and cultural expectations
Gender expression	The external way a person expresses their gender, such as with clothing, hair, mannerisms, activities, or social roles
Gender perception	The way others interpret a person's gender expression
Gender diverse	A term that is used to describe people with gender behaviors, appearances, or identities that are incongruent with those culturally assigned to their birth sex; gender-diverse individuals may refer to themselves with many different terms, such as transgender, nonbinary, genderqueer,[7] gender fluid, gender creative, gender independent, or noncisgender. "Gender diverse" is used to acknowledge and include the vast diversity of gender identities that exists. It replaces the former term, "gender nonconforming," which has a negative and exclusionary connotation.
Transgender	A subset of gender-diverse youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time; the term "transgender" also encompasses many other labels individuals may use to refer to themselves.
Cisgender	A term that is used to describe a person who identifies and expresses a gender that is consistent with the culturally defined norms of the sex they were assigned at birth
Agender	A term that is used to describe a person who does not identify as having a particular gender
Affirmed gender	When a person's true gender identity, or concern about their gender identity, is communicated to and validated from others as authentic
MTF; affirmed female; trans female	Terms that are used to describe individuals who were assigned male sex at birth but who have a gender identity and/or expression that is asserted to be more feminine
FTM; affirmed male; trans male	Terms that are used to describe individuals who were assigned female sex at birth but who have a gender identity and/or expression that is asserted to be more masculine
Gender dysphoria	A clinical symptom that is characterized by a sense of alienation to some or all of the physical characteristics or social roles of one's assigned gender; also, gender dysphoria is the psychiatric diagnosis in the *DSM-5*, which has focus on the distress that stems from the incongruence between one's expressed or experienced (affirmed) gender and the gender assigned at birth.
Gender identity disorder	A psychiatric diagnosis defined previously in the *DSM-IV* (changed to "gender dysphoria" in the *DSM-5*); the primary criteria include a strong, persistent cross-sex identification and significant distress and social impairment. This diagnosis is no longer appropriate for use and may lead to stigma, but the term may be found in older research.
Sexual orientation	A person's sexual identity in relation to the gender(s) to which they are attracted; sexual orientation and gender identity develop separately.

This list is not intended to be all inclusive. The pronouns "they" and "their" are used intentionally to be inclusive rather than the binary pronouns "he" and "she" and "his" and "her." Adapted from Bonifacio HJ, Rosenthal SM. Gender variance and dysphoria in children and adolescents. *Pediatr Clin North Am*. 2015;62(4):1001–1016. Adapted from Vance SR Jr, Ehrensaft D, Rosenthal SM. Psychological and medical care of gender nonconforming youth. *Pediatrics*. 2014;134(6):1184–1192. DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; FTM, female to male; MTF, male to female.

and expert opinion from clinical and research leaders, which will serve as the basis for recommendations. It is not a comprehensive review of clinical approaches and nuances to pediatric care for children and youth that identify as TGD. Professional understanding of youth that identify as TGD is a rapidly evolving clinical field in which research on appropriate clinical management is limited by insufficient funding.[3,4]

DEFINITIONS

To clarify recommendations and discussions in this policy statement, some definitions are provided. However, brief descriptions of human behavior or identities may not capture nuance in this evolving field. "Sex," or "natal gender," is a label, generally "male" or "female," that is typically assigned at birth on the basis of genetic and anatomic characteristics, such as genital anatomy, chromosomes, and sex hormone levels. Meanwhile, "gender identity" is one's internal sense of who one is, which results from a multifaceted interaction of biological traits, developmental influences, and environmental conditions. It may be male, female, somewhere in between, a combination of both, or neither (ie, not conforming to a binary conceptualization of gender). Self-recognition of gender identity develops over time, much the same way as a child's physical body does. For some people, gender identity can be fluid, shifting in different contexts. "Gender expression" refers to the wide array of ways people display their gender through clothing, hair styles, mannerisms, or social roles. Exploring different ways of expressing gender is common for children and may challenge social expectations. The way others interpret this expression is referred to as "gender perception" (Table 1).[5,6]

These labels may or may not be congruent. The term "cisgender" is used if someone identifies and expresses a gender that is consistent with the culturally defined norms of the sex that was assigned at birth. "Gender diverse" is an umbrella term to describe an ever-evolving array of labels that people may apply when their gender identity, expression, or even perception does not conform

to the norms and stereotypes others expect of their assigned sex. "Transgender" is usually reserved for a subset of such youth whose gender identity does not match their assigned sex and generally remains persistent, consistent, and insistent over time. These terms are not diagnoses; rather, they are personal and often dynamic ways of describing one's own gender experience.

Gender identity is not synonymous with "sexual orientation," which refers to a person's identity in relation to the gender(s) to which they are sexually and romantically attracted. Gender identity and sexual orientation are distinct but interrelated constructs.[8] Therefore, being transgender does not imply a sexual orientation, and people who identify as transgender still identify as straight, gay, bisexual, etc, on the basis of their attractions. (For more information, *The Gender Book*, found at www.thegenderbook.com, is a resource with illustrations that are used to highlight these core terms and concepts.)

EPIDEMIOLOGY

In population-based surveys, questions related to gender identity are rarely asked, which makes it difficult to assess the size and characteristics of the population that is TGD. In the 2014 Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, only 19 states elected to include optional questions on gender identity. Extrapolation from these data suggests that the US prevalence of adults who identify as transgender or "gender nonconforming" is 0.6% (1.4 million), ranging from 0.3% in North Dakota to 0.8% in Hawaii.[9] On the basis of these data, it has been estimated that 0.7% of youth ages 13 to 17 years (~150 000) identify as transgender.[10] This number is much higher than previous estimates, which were extrapolated from individual states or specialty clinics, and is likely an underestimate given the stigma regarding those who openly identify as transgender and the difficulty in defining "transgender" in a way that is inclusive of all gender-diverse identities.[11]

There have been no large-scale prevalence studies among children and adolescents, and there is no evidence that adult statistics reflect young children or adolescents. In the 2014 Behavioral Risk Factor Surveillance System, those 18 to 24 years of age were more likely than older age groups to identify as transgender (0.7%).[9] Children report being aware of gender incongruence at young ages. Children who later identify as TGD report first having recognized their gender as "different" at an average age of 8.5 years; however, they did not disclose such feelings until an average of 10 years later.[12]

MENTAL HEALTH IMPLICATIONS

Adolescents and adults who identify as transgender have high rates of depression, anxiety, eating disorders, self-harm, and suicide.[13–20] Evidence suggests that an identity of TGD has an increased prevalence among individuals with autism spectrum disorder, but this association is not yet well understood.[21,22] In 1 retrospective cohort study, 56% of youth who identified as transgender reported previous suicidal ideation, and 31% reported a previous suicide attempt, compared with 20% and 11% among matched youth who identified as cisgender, respectively.[13] Some youth who identify as TGD also experience gender dysphoria, which is a specific diagnosis given to those who experience impairment in peer and/or family relationships, school performance, or other aspects of their life as a consequence of the incongruence between their assigned sex and their gender identity.[23]

There is no evidence that risk for mental illness is inherently attributable to one's identity of TGD. Rather, it is believed to be multifactorial, stemming from an internal conflict between one's appearance and identity, limited availability of mental health services, low access to health care providers with expertise in caring for youth who identify as TGD, discrimination, stigma, and social rejection.[24] This was affirmed by the American Psychological Association in 2008[25] (with practice guidelines released in 2015[8]) and the American Psychiatric Association, which made the following statement in 2012:

> *Being transgender or gender variant implies no impairment in judgment, stability, reliability, or general social or vocational capabilities; however, these individuals often experience discrimination due to a lack of civil rights protections for their gender identity or expression.... [Such] discrimination and lack of equal civil rights is damaging to the mental health of transgender and gender variant individuals.*[26]

Youth who identify as TGD often confront stigma and discrimination, which contribute to feelings of rejection and isolation that can adversely affect physical and emotional well-being. For example, many youth believe that they must hide their gender identity and expression to avoid bullying, harassment, or victimization. Youth who identify as TGD experience disproportionately high rates of homelessness, physical violence (at home and in the community), substance abuse, and high-risk sexual behaviors.[5,6,12,27–31] Among the 3 million HIV testing events that were reported in 2015, the highest percentages of new infections were among women who identified as transgender[32] and were also at particular risk for not knowing their HIV status.[30]

GENDER-AFFIRMATIVE CARE

In a gender-affirmative care model (GACM), pediatric providers offer developmentally appropriate care that is oriented toward understanding and appreciating the youth's gender experience. A strong, nonjudgmental partnership with youth and their families can facilitate exploration of complicated emotions and gender-diverse expressions while allowing questions and concerns to be raised in a supportive environment.[5] In a GACM, the following messages are conveyed:

- transgender identities and diverse gender expressions do not constitute a mental disorder;
- variations in gender identity and expression are normal aspects of human diversity, and binary definitions of gender do not always reflect emerging gender identities;
- gender identity evolves as an interplay of biology, development, socialization, and culture; and
- if a mental health issue exists, it most often stems from stigma and negative experiences rather than being intrinsic to the child.[27,33]

The GACM is best facilitated through the integration of medical, mental health, and social services, including specific resources and supports for parents and families.[24] Providers work together to destigmatize gender variance, promote the child's self-worth, facilitate access to care, educate families, and advocate for safer community spaces where children are free to develop and explore their gender.[5] A specialized gender-affirmative therapist, when available, may be an asset in helping children and their families build skills for dealing with gender-based stigma, address symptoms of anxiety or depression, and reinforce the child's overall resiliency.[34,35] There is a limited but growing body of evidence that suggests that using an integrated affirmative model results in young people having fewer mental health concerns whether they ultimately identify as transgender.[24,36,37]

In contrast, "conversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. The Substance Abuse and Mental Health Services Administration has concluded that any therapeutic intervention with the goal of changing a youth's gender expression or identity is inappropriate.[33] Reparative approaches have been proven to be not only unsuccessful[38] but also deleterious and are considered outside the mainstream of traditional medical practice.[29,39–42] The AAP described reparative approaches as "unfair and deceptive."[43] At the time of this writing,* conversion therapy was banned by executive regulation in New York and by legislative statutes in 9 other states as well as the District of Columbia.[44]

Pediatric providers have an essential role in assessing gender concerns and providing evidence-based information to assist youth and families in medical decision-making. Not doing so can prolong or exacerbate gender dysphoria and contribute to abuse and stigmatization.[35] If a pediatric provider does not feel prepared to address gender concerns when they occur, then referral to a pediatric or mental health provider with more expertise is appropriate. There is little research on communication and efficacy with transfers in care for youth who identify as TGD, particularly from pediatric to adult providers.

DEVELOPMENTAL CONSIDERATIONS

Acknowledging that the capacity for emerging abstract thinking in childhood is important to conceptualize and reflect on identity, gender-affirmation guidelines are being focused on individually tailored interventions on the basis of the physical and cognitive development of youth who identify as TGD.[45] Accordingly, research substantiates that children who are prepubertal and assert an identity of TGD know their gender as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance.[46] This developmental approach to gender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").[45,47] More robust and current research suggests that, rather than focusing on who a child will become, valuing them for who they are, even at a young age, fosters secure attachment and resilience, not only for the child but also for the whole family.[5,45,48,49]

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@aap.org.

MEDICAL MANAGEMENT

Pediatric primary care providers are in a unique position to routinely inquire about gender development in children and adolescents as part of recommended well-child visits[50] and to be a reliable source of validation, support, and reassurance. They are often the first provider to be aware that a child may not identify as cisgender or that there may be distress related to a gender-diverse identity. The best way to approach gender with patients is to inquire directly and nonjudgmentally about their experience and feelings before applying any labels.[27,51]

Many medical interventions can be offered to youth who identify as TGD and their families. The decision of whether and when to initiate gender-affirmative treatment is personal and involves careful consideration of risks, benefits, and other factors unique to each patient and family. Many protocols suggest that clinical assessment of youth who identify as TGD is ideally conducted on an ongoing basis in the setting of a collaborative, multidisciplinary approach, which, in addition to the patient and family, may include the pediatric provider, a mental health provider (preferably with expertise in caring for youth who identify as TGD), social and legal supports, and a pediatric endocrinologist or adolescent-medicine gender specialist, if available.[6,28] There is no prescribed path, sequence, or end point. Providers can make every effort to be aware of the influence of their own biases. The medical options also vary depending on pubertal and developmental progression.

Clinical Setting

In the past year, 1 in 4 adults who identified as transgender avoided a necessary doctor's visit because of fear of being mistreated.[31] All clinical office staff have a role in affirming a patient's gender identity. Making flyers available or displaying posters related to LGBTQ health issues, including information for children who identify as TGD and families, reveals inclusivity and awareness. Generally, patients who identify as TGD feel most comfortable when they have access to a gender-neutral restroom. Diversity training that encompasses sensitivity when caring for youth who identify as TGD and their families can be helpful in educating clinical and administrative staff. A patient-asserted name and pronouns are used by staff and are ideally reflected in the electronic medical record without creating duplicate charts.[52,53] The US Centers for Medicare and Medicaid Services and the National Coordinator for Health Information Technology require all electronic health record systems certified under the Meaningful Use incentive program to have the capacity to confidentially collect information on gender identity.[54,55] Explaining and maintaining confidentiality procedures promotes openness and trust, particularly with youth who identify as LGBTQ.[1] Maintaining a safe clinical space can provide at least 1 consistent, protective refuge for patients and families, allowing authentic gender expression and exploration that builds resiliency.

Pubertal Suppression

Gonadotrophin-releasing hormones have been used to delay puberty since the 1980s for central precocious puberty.[56] These reversible treatments can also be used in adolescents who experience gender dysphoria to prevent development of secondary sex characteristics and provide time up until 16 years of age for the individual and the family to explore gender identity, access psychosocial supports, develop coping skills, and further define appropriate treatment goals. If pubertal suppression treatment is suspended, then endogenous puberty will resume.[20,57,58]

Often, pubertal suppression creates an opportunity to reduce distress that may occur with the development of secondary sexual characteristics and allow for gender-affirming care, including mental health support for the adolescent and the family. It reduces the need for later surgery because physical changes that are otherwise irreversible (protrusion of the Adam's apple, male pattern baldness, voice change, breast growth, etc) are prevented. The available data reveal that pubertal suppression in children who identify as TGD generally leads to improved psychological functioning in adolescence and young adulthood.[20,57–59]

Pubertal suppression is not without risks. Delaying puberty beyond one's peers can also be stressful and can lead to lower self-esteem and increased risk taking.[60] Some experts believe that genital underdevelopment may limit some potential reconstructive options.[61] Research on long-term risks, particularly in terms of bone metabolism[62] and fertility,[63] is currently limited and provides varied results.[57,64,65] Families often look to pediatric providers for help in considering whether pubertal suppression is indicated in the context of their child's overall well-being as gender diverse.

Gender Affirmation

As youth who identify as TGD reflect on and evaluate their gender identity, various interventions may be considered to better align their gender expression with their underlying identity. This process of reflection, acceptance, and, for some, intervention is known as "gender affirmation." It was formerly referred to as "transitioning," but many view the process as an affirmation and acceptance of who they have always been rather than a transition

TABLE 2 The Process of Gender Affirmation May Include ≥1 of the Following Components

Component	Definition	General Age Range[a]	Reversibility[a]
Social affirmation	Adopting gender-affirming hairstyles, clothing, name, gender pronouns, and restrooms and other facilities	Any	Reversible
Puberty blockers	Gonadotropin-releasing hormone analogues, such as leuprolide and histrelin	During puberty (Tanner stage 2–5)[b]	Reversible[c]
Cross-sex hormone therapy	Testosterone (for those who were assigned female at birth and are masculinizing); estrogen plus androgen inhibitor (for those who were assigned male at birth and are feminizing)	Early adolescence onward	Partially reversible (skin texture, muscle mass, and fat deposition); irreversible once developed (testosterone: Adam's apple protrusion, voice changes, and male pattern baldness; estrogen: breast development); unknown reversibility (effect on fertility)
Gender-affirming surgeries	"Top" surgery (to create a male-typical chest shape or enhance breasts); "bottom" surgery (surgery on genitals or reproductive organs); facial feminization and other procedures	Typically adults (adolescents on case-by-case basis[d])	Not reversible
Legal affirmation	Changing gender and name recorded on birth certificate, school records, and other documents	Any	Reversible

[a] Note that the provided age range and reversibility is based on the little data that are currently available.

[b] There is limited benefit to starting gonadotropin-releasing hormone after Tanner stage 5 for pubertal suppression. However, when cross-sex hormones are initiated with a gradually increasing schedule, the initial levels are often not high enough to suppress endogenous sex hormone secretion. Therefore, gonadotropin-releasing hormone may be continued in accordance with the Endocrine Society Guidelines.[68]

[c] The effect of sustained puberty suppression on fertility is unknown. Pubertal suppression can be, and often is indicated to be, followed by cross-sex hormone treatment. However, when cross-sex hormones are initiated without endogenous hormones, then fertility may be decreased.[68]

[d] Eligibility criteria for gender-affirmative surgical interventions among adolescents are not clearly defined between established protocols and practice. When applicable, eligibility is usually determined on a case-by-case basis with the adolescent and the family along with input from medical, mental health, and surgical providers.[68–71]

from 1 gender identity to another. Accordingly, some people who have gone through the process prefer to call themselves "affirmed females, males, etc" (or just "females, males, etc"), rather than using the prefix "trans-." Gender affirmation is also used to acknowledge that some individuals who identify as TGD may feel affirmed in their gender without pursuing medical or surgical interventions.[7,66]

Supportive involvement of parents and family is associated with better mental and physical health outcomes.[67] Gender affirmation among adolescents with gender dysphoria often reduces the emphasis on gender in their lives, allowing them to attend to other developmental tasks, such as academic success, relationship building, and future-oriented planning.[64] Most protocols for gender-affirming interventions incorporate World Professional Association of Transgender Health[35] and Endocrine Society[68] recommendations and include ≥1 of the following elements (Table 2):

1. Social Affirmation: This is a reversible intervention in which children and adolescents express partially or completely in their asserted gender identity by adapting hairstyle, clothing, pronouns, name, etc. Children who identify as transgender and socially affirm and are supported in their asserted gender show no increase in depression and only minimal (clinically insignificant) increases in anxiety compared with age-matched averages.[48] Social affirmation can be complicated given the wide range of social interactions children have (eg, extended families, peers, school, community, etc). There is little guidance on the best approach (eg, all at once, gradual, creating new social networks, or affirming within existing networks, etc). Pediatric providers can best support families by anticipating and discussing such complexity proactively, either in their own practice or through enlisting a qualified mental health provider.

2. Legal Affirmation: Elements of a social affirmation, such as a name and gender marker, become official on legal documents, such as birth certificates, passports, identification cards, school documents, etc. The processes for making these changes depend on state laws and may require specific documentation from pediatric providers.

3. Medical Affirmation: This is the process of using cross-sex hormones to allow adolescents who have initiated puberty to develop secondary sex characteristics of the opposite biological sex. Some changes are partially reversible if hormones are stopped, but others become

irreversible once they are fully developed (Table 2).

4. Surgical Affirmation: Surgical approaches may be used to feminize or masculinize features, such as hair distribution, chest, or genitalia, and may include removal of internal organs, such as ovaries or the uterus (affecting fertility). These changes are irreversible. Although current protocols typically reserve surgical interventions for adults,[35,68] they are occasionally pursued during adolescence on a case-by-case basis, considering the necessity and benefit to the adolescent's overall health and often including multidisciplinary input from medical, mental health, and surgical providers as well as from the adolescent and family.[69–71]

For some youth who identify as TGD whose natal gender is female, menstruation, breakthrough bleeding, and dysmenorrhea can lead to significant distress before or during gender affirmation. The American College of Obstetrics and Gynecology suggests that, although limited data are available to outline management, menstruation can be managed without exogenous estrogens by using a progesterone-only pill, a medroxyprogesterone acetate shot, or a progesterone-containing intrauterine or implantable device.[72] If estrogen can be tolerated, oral contraceptives that contain both progesterone and estrogen are more effective at suppressing menses.[73] The Endocrine Society guidelines also suggest that gonadotrophin-releasing hormones can be used for menstrual suppression before the anticipated initiation of testosterone or in combination with testosterone for breakthrough bleeding (enables phenotypic masculinization at a lower dose than if testosterone is used alone).[68] Masculinizing hormones in natal female patients may lead to a cessation of menses, but unplanned pregnancies have been reported, which emphasizes the need for ongoing contraceptive counseling with youth who identify as TGD.[72]

HEALTH DISPARITIES

In addition to societal challenges, youth who identify as TGD face several barriers within the health care system, especially regarding access to care. In 2015, a focus group of youth who identified as transgender in Seattle, Washington, revealed 4 problematic areas related to health care:

1. safety issues, including the lack of safe clinical environments and fear of discrimination by providers;
2. poor access to physical health services, including testing for sexually transmitted infections;
3. inadequate resources to address mental health concerns; and
4. lack of continuity with providers.[74]

This study reveals the obstacles many youth who identify as TGD face in accessing essential services, including the limited supply of appropriately trained medical and psychological providers, fertility options, and insurance coverage denials for gender-related treatments.[74]

Insurance denials for services related to the care of patients who identify as TGD are a significant barrier. Although the Office for Civil Rights of the US Department of Health and Human Services explicitly stated in 2012 that the nondiscrimination provision in the Patient Protection and Affordable Care Act includes people who identify as gender diverse,[75,76] insurance claims for gender affirmation, particularly among youth who identify as TGD, are frequently denied.[54,77] In 1 study, it was found that approximately 25% of individuals who identified as transgender were denied insurance coverage because of being transgender.[31] The burden of covering medical expenses that are not covered by insurance can be financially devastating, and even when expenses are covered, families describe high levels of stress in navigating and submitting claims appropriately.[78] In 2012, a large gender center in Boston, Massachusetts, reported that most young patients who identified as transgender and were deemed appropriate candidates for recommended gender care were unable to obtain it because of such denials, which were based on the premise that gender dysphoria was a mental disorder, not a physical one, and that treatment was not medically or surgically necessary.[24] This practice not only contributes to stigma, prolonged gender dysphoria, and poor mental health outcomes,[77] but it may also lead patients to seek nonmedically supervised treatments that are potentially dangerous.[24] Furthermore, insurance denials can reinforce a socioeconomic divide between those who can finance the high costs of uncovered care and those who cannot.[24,77]

The transgender youth group in Seattle likely reflected the larger TGD population when they described how obstacles adversely affect self-esteem and contribute to the perception that they are undervalued by society and the health care system.[74,77] Professional medical associations, including the AAP, are increasingly calling for equity in health care provisions regardless of gender identity or expression.[1,8,23,72] There is a critical need for investments in research on the prevalence, disparities, biological underpinnings, and standards of care relating to gender-diverse populations. Pediatric providers who work with state government and insurance officials can play an essential role in advocating for

stronger nondiscrimination policies and improved coverage.

There is a lack of quality research on the experience of youth of color who identify as transgender. One theory suggests that the intersection of racism, transphobia, and sexism may result in the extreme marginalization that is experienced among many women of color who identify as transgender,[79] including rejection from their family and dropping out of school at younger ages (often in the setting of rigid religious beliefs regarding gender),[80] increased levels of violence and body objectification,[81] 3 times the risk of poverty compared with the general population,[31] and the highest prevalence of HIV compared with other risk groups (estimated as high as 56.3% in 1 meta-analysis).[30] One model suggests that pervasive stigma and oppression can be associated with psychological distress (anxiety, depression, and suicide) and adoption of risk behaviors by such youth to obtain a sense of validation toward their complex identities.[79]

FAMILY ACCEPTANCE

Research increasingly suggests that familial acceptance or rejection ultimately has little influence on the gender identity of youth; however, it may profoundly affect young people's ability to openly discuss or disclose concerns about their identity. Suppressing such concerns can affect mental health.[82] Families often find it hard to understand and accept their child's gender-diverse traits because of personal beliefs, social pressure, and stigma.[49,83] Legitimate fears may exist for their child's welfare, safety, and acceptance that pediatric providers need to appreciate and address. Families can be encouraged to communicate their concerns and questions. Unacknowledged concerns can contribute to shame and hesitation in regard to offering support and understanding,[84] which is essential for the child's self-esteem, social involvement, and overall health as TGD.[48,85–87] Some caution has been expressed that unquestioning acceptance per se may not best serve questioning youth or their families. Instead, psychological evidence suggests that the most benefit comes when family members and youth are supported and encouraged to engage in reflective perspective taking and validate their own and the other's thoughts and feelings despite divergent views.[49,82]

In this regard, suicide attempt rates among 433 adolescents in Ontario who identified as "trans" were 4% among those with strongly supportive parents and as high as 60% among those whose parents were not supportive.[85] Adolescents who identify as transgender and endorse at least 1 supportive person in their life report significantly less distress than those who only experience rejection. In communities with high levels of support, it was found that nonsupportive families tended to increase their support over time, leading to dramatic improvement in mental health outcomes among their children who identified as transgender.[88]

Pediatric providers can create a safe environment for parents and families to better understand and listen to the needs of their children while receiving reassurance and education.[83] It is often appropriate to assist the child in understanding the parents' concerns as well. Despite expectations by some youth with transgender identity for immediate acceptance after "coming out," family members often proceed through a process of becoming more comfortable and understanding of the youth's gender identity, thoughts, and feelings. One model suggests that the process resembles grieving, wherein the family separates from their expectations for their child to embrace a new reality. This process may proceed through stages of shock, denial, anger, feelings of betrayal, fear, self-discovery, and pride.[89] The amount of time spent in any of these stages and the overall pace varies widely. Many family members also struggle as they are pushed to reflect on their own gender experience and assumptions throughout this process. In some situations, youth who identify as TGD may be at risk for internalizing the difficult emotions that family members may be experiencing. In these cases, individual and group therapy for the family members may be helpful.[49,78]

Family dynamics can be complex, involving disagreement among legal guardians or between guardians and their children, which may affect the ability to obtain consent for any medical management or interventions. Even in states where minors may access care without parental consent for mental health services, contraception, and sexually transmitted infections, parental or guardian consent is required for hormonal and surgical care of patients who identify as TGD.[72,90] Some families may take issue with providers who address gender concerns or offer gender-affirming care. In rare cases, a family may deny access to care that raises concerns about the youth's welfare and safety; in those cases, additional legal or ethical support may be useful to consider. In such rare situations, pediatric providers may want to familiarize themselves with relevant local consent laws and maintain their primary responsibility for the welfare of the child.

SAFE SCHOOLS AND COMMUNITIES

Youth who identify as TGD are becoming more visible because gender-diverse expression is increasingly admissible in the media, on social media, and in schools and communities. Regardless of whether a youth with a gender-diverse

identity ultimately identifies as transgender, challenges exist in nearly every social context, from lack of understanding to outright rejection, isolation, discrimination, and victimization. In the US Transgender Survey of nearly 28 000 respondents, it was found that among those who were out as or perceived to be TGD between kindergarten and eighth grade, 54% were verbally harassed, 24% were physically assaulted, and 13% were sexually assaulted; 17% left school because of maltreatment.[31] Education and advocacy from the medical community on the importance of safe schools for youth who identify as TGD can have a significant effect.

At the time of this writing,* only 18 states and the District of Columbia had laws that prohibited discrimination based on gender expression when it comes to employment, housing, public accommodations, and insurance benefits. Over 200 US cities have such legislation. In addition to basic protections, many youth who identify as TGD also have to navigate legal obstacles when it comes to legally changing their name and/or gender marker.[54] In addition to advocating and working with policy makers to promote equal protections for youth who identify as TGD, pediatric providers can play an important role by developing a familiarity with local laws and organizations that provide social work and legal assistance to youth who identify as TGD and their families.

School environments play a significant role in the social and emotional development of children. Every child has a right to feel safe and respected at school, but for youth who identify as TGD, this can be challenging. Nearly every aspect of school life may present safety concerns and require negotiations regarding their gender expression, including name/pronoun use, use of bathrooms and locker rooms, sports teams, dances and activities, overnight activities, and even peer groups. Conflicts in any of these areas can quickly escalate beyond the school's control to larger debates among the community and even on a national stage.

The formerly known Gay, Lesbian, and Straight Education Network (GLSEN), an advocacy organization for youth who identify as LGBTQ, conducts an annual national survey to measure LGBTQ well-being in US schools. In 2015, students who identified as LGBTQ reported high rates of being discouraged from participation in extracurricular activities. One in 5 students who identified as LGBTQ reported being hindered from forming or participating in a club to support lesbian, gay, bisexual, or transgender students (eg, a gay straight alliance, now often referred to as a genders and sexualities alliance) despite such clubs at schools being associated with decreased reports of negative remarks about sexual orientation or gender expression, increased feelings of safety and connectedness at school, and lower levels of victimization. In addition, >20% of students who identified as LGBTQ reported being blocked from writing about LGBTQ issues in school yearbooks or school newspapers or being prevented or discouraged by coaches and school staff from participating in sports because of their sexual orientation or gender expression.[91]

One strategy to prevent conflict is to proactively support policies and protections that promote inclusion and safety of all students. However, such policies are far from consistent across districts. In 2015, GLSEN found that 43% of children who identified as LGBTQ reported feeling unsafe at school because of their gender expression, but only 6% reported that their school had official policies to support youth who identified as TGD, and only 11% reported that their school's antibullying policies had specific protections for gender expression.[91] Consequently, more than half of the students who identified as transgender in the study were prevented from using the bathroom, names, or pronouns that aligned with their asserted gender at school. A lack of explicit policies that protected youth who identified as TGD was associated with increased reported victimization, with more than half of students who identified as LGBTQ reporting verbal harassment because of their gender expression. Educators and school administrators play an essential role in advocating for and enforcing such policies. GLSEN found that when students recognized actions to reduce gender-based harassment, both students who identified as transgender and cisgender reported a greater connection to staff and feelings of safety.[91] In another study, schools were open to education regarding gender diversity and were willing to implement policies when they were supported by external agencies, such as medical professionals.[92]

Academic content plays an important role in building a safe school environment as well. The 2015 GLSEN survey revealed that when positive representations of people who identified as LGBTQ were included in the curriculum, students who identified as LGBTQ reported less hostile school environments, less victimization and greater feelings of safety, fewer school absences because of feeling unsafe, greater feelings of connectedness to their school

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@ aap.org.

community, and an increased interest in high school graduation and postsecondary education.[91] At the time of this writing,* 8 states had laws that explicitly forbade teachers from even discussing LGBTQ issues.[54]

MEDICAL EDUCATION

One of the most important ways to promote high-quality health care for youth who identify as TGD and their families is increasing the knowledge base and clinical experience of pediatric providers in providing culturally competent care to such populations, as recommended by the recently released guidelines by the Association of American Medical Colleges.[93] This begins with the medical school curriculum in areas such as human development, sexual health, endocrinology, pediatrics, and psychiatry. In a 2009–2010 survey of US medical schools, it was found that the median number of hours dedicated to LGBTQ health was 5, with one-third of US medical schools reporting no LGBTQ curriculum during the clinical years.[94]

During residency training, there is potential for gender diversity to be emphasized in core rotations, especially in pediatrics, psychiatry, family medicine, and obstetrics and gynecology. Awareness could be promoted through the inclusion of topics relevant to caring for children who identify as TGD in the list of core competencies published by the American Board of Pediatrics, certifying examinations, and relevant study materials. Continuing education and maintenance of certification activities can include topics relevant to TGD populations as well.

* For more information regarding state-specific laws, please contact the AAP Division of State Government Affairs at stgov@ aap.org.

RECOMMENDATIONS

The AAP works toward all children and adolescents, regardless of gender identity or expression, receiving care to promote optimal physical, mental, and social well-being. Any discrimination based on gender identity or expression, real or perceived, is damaging to the socioemotional health of children, families, and society. In particular, the AAP recommends the following:

1. that youth who identify as TGD have access to comprehensive, gender-affirming, and developmentally appropriate health care that is provided in a safe and inclusive clinical space;
2. that family-based therapy and support be available to recognize and respond to the emotional and mental health needs of parents, caregivers, and siblings of youth who identify as TGD;
3. that electronic health records, billing systems, patient-centered notification systems, and clinical research be designed to respect the asserted gender identity of each patient while maintaining confidentiality and avoiding duplicate charts;
4. that insurance plans offer coverage for health care that is specific to the needs of youth who identify as TGD, including coverage for medical, psychological, and, when indicated, surgical gender-affirming interventions;
5. that provider education, including medical school, residency, and continuing education, integrate core competencies on the emotional and physical health needs and best practices for the care of youth who identify as TGD and their families;
6. that pediatricians have a role in advocating for, educating, and developing liaison relationships with school districts and other community organizations to promote acceptance and inclusion of all children without fear of harassment, exclusion, or bullying because of gender expression;
7. that pediatricians have a role in advocating for policies and laws that protect youth who identify as TGD from discrimination and violence;
8. that the health care workforce protects diversity by offering equal employment opportunities and workplace protections, regardless of gender identity or expression; and
9. that the medical field and federal government prioritize research that is dedicated to improving the quality of evidence-based care for youth who identify as TGD.

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ABBREVIATIONS

AAP: American Academy of Pediatrics
GACM: gender-affirmative care model
GLSEN: Gay, Lesbian, and Straight Education Network
LGBTQ: lesbian, gay, bisexual, transgender, or questioning
TGD: transgender and gender diverse

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ACOG
The American College of Obstetricians and Gynecologists

ACOG COMMITTEE OPINION

Number 823

(Replaces Committee Opinion 512, December 2011, and Committee Opinion 685, January 2017)

Committee on Gynecologic Practice and Committee on Health Care for Underserved Women

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice and Committee on Health Care for Underserved Women in collaboration with committee members Beth Cronin, MD and Colleen K. Stockdale MD, MS.

Health Care for Transgender and Gender Diverse Individuals

ABSTRACT: An estimated 150,000 youth and 1.4 million adults living in the United States identify as transgender. This Committee Opinion offers guidance on providing inclusive and affirming care as well as clinical information on hormone therapy and preventive care; it also cites existing resources for those seeking information on the care of transgender adolescents. The social and economic marginalization of transgender individuals is widespread, which leads to health care inequities and poorer health outcomes for this population. To reduce the inequities experienced by the transgender community, the provision of inclusive health care is essential. Obstetrician–gynecologists should strive to make their offices open to and inclusive for all individuals and should seek out education to address health care disparities, both in their individual practices and in the larger health care system. In order to provide the best care for patients, it is useful to know which health care professionals to include in a referral network for primary care and to have many clinician and surgeon options given the many different therapies available and the different sites at which these therapies are offered. It is important to remember that although hormone therapy is a medically necessary treatment for many transgender individuals with gender dysphoria, not all transgender patients experience gender dysphoria and not everyone desires hormone treatment. Gender-affirming hormone therapy is not effective contraception. Sexually active individuals with retained gonads who do not wish to become pregnant or cause pregnancy in others should be counseled about the possibility of pregnancy if they are having sexual activity that involves sperm and oocytes. Although being knowledgeable about the medications used for gender transition and potential risks and side effects is important, specific certification for prescribing them is not required and should not be a limiting factor in helping patients access care.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists makes the following conclusions and recommendations regarding health care for transgender and gender diverse individuals:

The American College of Obstetricians and Gynecologists opposes discrimination on the basis of gender identity, urges public and private health insurance plans to cover necessary services for individuals with gender dysphoria, and advocates for inclusive, thoughtful, and affirming care for transgender individuals.

- Obstetrician–gynecologists should make their offices inclusive and inviting to all individuals who need obstetric or gynecologic health care. They should take steps to educate themselves and their medical teams about appropriate language and the health care needs of transgender patients.
- Fertility and parenting desires should be discussed early in the process of transition, before the initiation of hormone therapy or gender affirmation surgery.
- Gender-affirming hormone therapy is not effective contraception. Sexually active individuals with retained gonads who do not wish to become pregnant

or cause pregnancy in others should be counseled about the possibility of pregnancy if they are having sexual activity that involves sperm and oocytes.

- The majority of medications used for gender transition are common and can be safely prescribed by a wide variety of health care professionals with appropriate training and education, including, but not limited to, obstetrician–gynecologists, family or internal medicine physicians, endocrinologists, advanced practice clinicians, and psychiatrists.
- Hysterectomy with or without bilateral salpingo-oophorectomy is medically necessary for patients with gender dysphoria who desire this procedure.
- To guide preventive medical care, any anatomical structure present that warrants screening should be screened, regardless of gender identity.

Background

Transgender and *gender diverse* individuals face harassment, discrimination, and rejection within society. Lack of awareness, knowledge, and sensitivity as well as bias from health care professionals leads to inadequate access to, underuse of, and inequities within the health care system for transgender patients. Throughout this document, the term transgender will be used to refer to anyone who identifies as transgender, gender diverse, and *genderqueer*, while acknowledging that there are vast individual differences and variations in preferred terminology. (See Box 1 for related terminology and definitions.) This Committee Opinion provides guidance for obstetrician–gynecologists on both routine screening and transition care. Obstetrician–gynecologists should be aware of the unique needs of transgender individuals and be prepared to assist them with preventive health care, as well as have knowledge of hormone and surgical therapies. The American College of Obstetricians and Gynecologists opposes discrimination on the basis of *gender identity*, urges public and private health insurance plans to cover necessary services for individuals with gender dysphoria and advocates for inclusive, thoughtful, and affirming care for transgender individuals. Although there is some overlap in clinical and psychosocial care for adolescents and adults, there are some issues specific to adolescents. The American College of Obstetricians and Gynecologists supports the provision of appropriate and evidence-based care for transgender and gender diverse adolescents. For guidance on the medical and surgical care of transgender adolescents, see the World Professional Association for Transgender Health (1), the Endocrine Society (2), and the Pediatric Endocrine Society (3).

It is important for obstetrician–gynecologists and other health care professionals to be familiar with appropriate terminology when caring for patients. *Transgender* is a broad term used for people whose gender identity or *gender expression* differs from their assigned *sex* at birth. For the purposes of clarity, *sex* is

Box 1. Terminology and Definitions

Chestfeeding: Some masculine-identified individuals use this term to describe the act of feeding their child from their chest regardless of whether they have had chest surgery.

Cisgender: A term used to describe a person whose gender identity aligns with those typically associated with the sex assigned to them at birth.

Gender Identity: A person's internal sense of self and how they fit into the world, from the perspective of gender.

Gender Dysphoria: Distress that accompanies the incongruence between one's experienced and expressed gender and one's assigned or natal gender.

Gender Expression: The outward manner in which individuals express or display their gender. This may include choices in clothing and hairstyle or speech and mannerisms. Gender identity and gender expression may differ; for example, a woman (transgender or cisgender) may have an androgynous appearance, or a man (transgender or cisgender) may have a feminine form of self-expression.

Transgender: A person whose gender identity differs from the sex that was assigned at birth. May be abbreviated to trans. A transgender man is someone with a male gender identity and a female birth assigned sex; a transgender woman is someone with a female gender identity and a male birth assigned sex. A nontransgender person may be referred to as cisgender (cis means same side in Latin).

Gender Nonconforming: A person whose gender identity differs from that which was assigned at birth, but may be more complex, fluid, multifaceted, or otherwise less clearly defined than a transgender person.

Genderqueer: Blurring the lines around gender identity and sexual orientation. Genderqueer individuals typically embrace a fluidity of gender identity and sometimes sexual orientation.

Nonbinary: Transgender or gender nonconforming person who identifies as neither male nor female.

Sex: Historically has referred to the sex assigned at birth, based on assessment of external genitalia, as well as chromosomes and gonads. In everyday language is often used interchangeably with gender, however there are differences, which become important in the context of transgender people.

Sexual Orientation: Describes sexual attraction only and is not directly related to gender identity. The sexual orientation of transgender people should be defined by the individual. It is often described based on the lived gender; a transgender woman attracted to other women would be a lesbian, and a transgender man attracted to other men would be a gay man.

Gender Fluidity: Having different gender identities at different times

(Continued)

Agender: "Without gender"; individuals identifying as having no gender identity

Gender Expansiveness: Conveys a wider, more flexible range of gender identity or expression than typically associated with the binary gender system

Transmasculine and Transfeminine: Terms to describe gender nonconforming or nonbinary persons, based on the directionality of their gender identity. A transmasculine person has a masculine spectrum gender identity, with the sex of female listed on their original birth certificate. A transfeminine person has a feminine spectrum gender identity, with the sex of male listed on their original birth certificate. In portions of these Guidelines, in the interest of brevity and clarity, transgender men or women are inclusive of gender nonconforming or nonbinary persons on the respective spectra.

They/Them/Their: Neutral pronouns used by some who have a nonbinary or nonconforming gender identity.

Transsexual: A more clinical term which had historically been used to describe those transgender people who sought medical intervention (hormones, surgery) for gender affirmation. This term is less commonly used in present day; however, some individuals and communities maintain a strong and affirmative connection to this term.

Cross Dresser/Drag Queen/Drag King: These terms generally refer to those who may wear the clothing of a gender that differs from the sex which they were assigned at birth for entertainment, self-expression, or sexual pleasure. Some cross dressers and people who dress in drag may exhibit an overlap with components of a transgender identity. The term *transvestite* is no longer used in the English language and is considered pejorative.

Adapted from Human Rights Campaign. Glossary of terms. Available at: http://www.hrc.org/resources/glossary-of-terms. Retrieved June 1, 2020; MacDonald T. Transgender parents and chest/breastfeeding. St. Petersburg, FL: KellyMom; 2018. Available at: https://kellymom.com/bf/got-milk/transgender-parentschestbreastfeeding/. Retrieved June 18, 2020; UCSF Transgender Care. Terminology and definitions. In: Deutsch MB, editor. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. 2nd ed. San Francisco, CA: UCSF Transgender Care; 2016. p. 15-6. Available at: https://transcare.ucsf.edu/guidelines/terminology. Retrieved June 18, 2020; Human Rights Campaign. New Facebook gender options validated by HRC report on gender expansive youth. Washington, DC: HRC; 2014. Available at: https://www.hrc.org/press/newfacebook-gender-options-validated-by-hrc-report-on-gender-expansive-you. Retrieved June 18, 2020; and American Psychiatric Association. What is gender dysphoria? Washington, DC: APA; 2016. Available at: https://www.psychiatry.org/patients-families/gender-dysphoria/what-is-gender-dysphoria. Retrieved May 28, 2020.

defined as the presence of specific anatomy or chromosomes. Gender is a social construct, made up of attitudes, feelings, and behaviors that a culture associates with either males or females; terminology often varies by geographic region, culture, and individual preference (4) (Box 1). *Gender nonconformity* is the extent to which a person's gender identity, role, or expression differs from the cultural norms described for a specific sex (5). *Sexual orientation* refers to sexual attraction only and is separate from gender identity. It is important to differentiate these concepts and terms when caring for patients (Fig. 1).

An estimated 150,000 youth (aged 13–17 years) and 1.4 million adults (aged 18 years and older) living in the United States identify as transgender (6). Analysis of data collected on adults in 19 states by the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System found that 55% of transgender individuals identified as White, 16% identified as African American or Black, 21% identified as Latino or Hispanic, and 8% identified as another race or ethnicity (7). Although more data on the experiences and needs of the transgender community is now available, there are important gaps in the literature and additional research is needed.

The World Professional Association for Transgender Health (an international, multidisciplinary professional society representing the specialties of medicine, psychology, social sciences, and law) released the following statement in 2010: "the expression of gender characteristics, including identities, that are not stereotypically associated with one's assigned sex at birth is a common and culturally diverse human phenomenon [that] should not be judged as inherently pathological or negative" (8). Although a diagnosis of *gender dysphoria* as defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, currently is the only way for many individuals to obtain insurance coverage for necessary services, many experts agree that gender dysphoria is not a psychological condition and does not necessarily belong in the Diagnostic and Statistical Manual of Mental Disorders (Box 2). Gender dysphoria can result in psychologic dysfunction, depression, suicidal ideation, and even death (9). It is important to remember that although some gender nonconforming people will experience gender dysphoria at some point in their lives, not all will; and for many, dysphoria is not persistent if appropriately addressed. The term "gender incongruence" is slated to replace "gender dysphoria" in the International Classification of Diseases, 11th edition.

The social and economic marginalization of transgender individuals is widespread, which leads to health care inequities and poorer health outcomes for this population. The 2015 National Transgender Discrimination Survey, comprised of 27,715 participants from throughout the United States who identified as transgender, trans, genderqueer, nonbinary, and other identities on the transgender identity spectrum, reported that 29% of respondents were currently living in poverty, compared with 14% of the general U.S. population (10). Thirty percent had experienced homelessness during their lifetime and 12% did so during the past year. Notably, homeless transgender individuals may be denied access to shelters or placed in inappropriate housing because of their gender; 26% of homeless

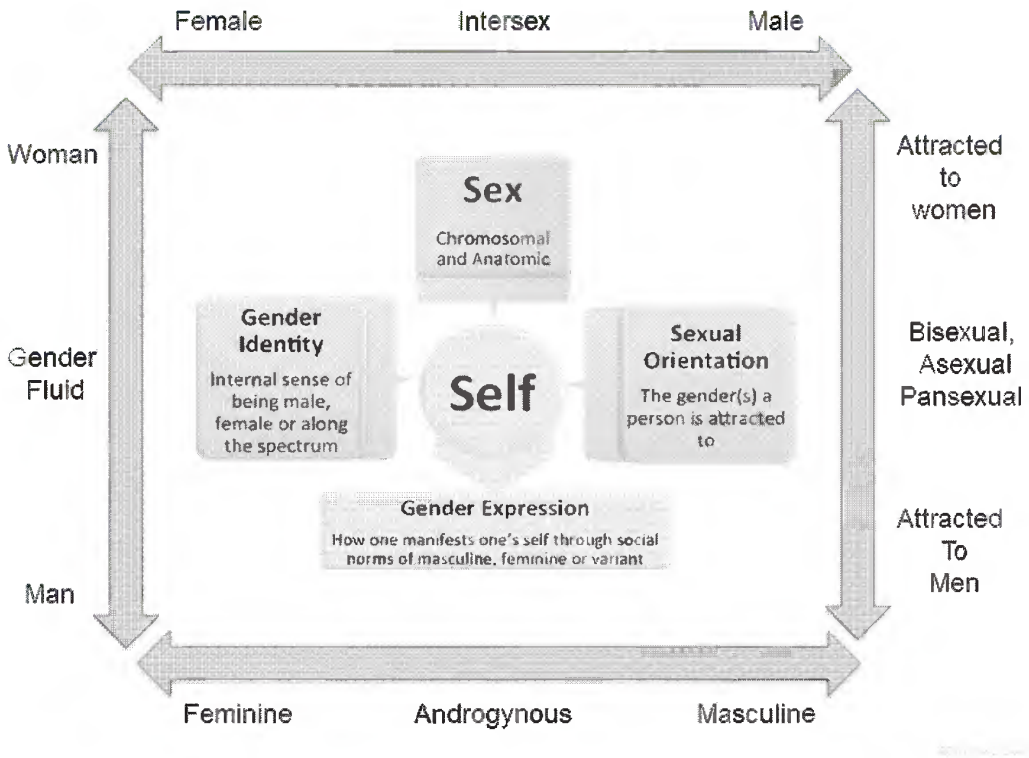

Figure 1. Concepts of Sex and Gender. Reprinted from Concepts of sex and gender. Mayo Clinic. Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved. https://www.mayoclinic.org/healthy-lifestyle/adult-health/in-depth/transgender-facts/art-20266812.

respondents reported avoiding shelters because of fear of being mistreated, and 70% of those using shelters reported some form of mistreatment. Additionally, 20% of respondents reported experience in sex work, drug sales, and other work currently criminalized (10).

To reduce the inequities experienced by the transgender community, the provision of inclusive health care is essential. Obstetrician–gynecologists should strive to make their offices open to and inclusive for all individuals and should seek out education to address health care disparities, both in their individual practices and in the larger health care system.

Barriers to Health Care

Transgender individuals face substantial barriers to accessing health care, including health care professionals' bias and lack of general knowledge about best practices, as well as the failure of many health insurance plans to cover the cost of hormone therapy and supplies, mental health services, or gender affirmation surgery and restrictions on care imposed by prohibitive health care systems. One in four respondents to the Transgender Discrimination Survey had experienced insurance coverage obstacles, such as coverage denials for care related to gender transition or routine care. More than half (55%) had been denied coverage for transition-related surgery, and 25% were denied coverage for hormone therapy (10). These barriers exist despite evidence that such interventions are safe, effective, and medically necessary. The consequences of inadequate care are substantial. Providing accessible, inclusive, gender-affirming care helps to reduce barriers and allow more individuals to obtain the care they need.

Creating a safe and affirming health care environment for all patients, including transgender individuals, is essential. Transgender individuals face discrimination from health care professionals and staff. One-third of respondents reported having at least one negative experience in a health care office related to being transgender, such as being refused care or verbally harassed or having to teach the health care professional about transgender people in order to get appropriate care. In addition, some respondents have experienced physical or sexual abuse in this setting (10). Even higher rates of negative experiences were reported for transgender individuals with disabilities and American Indian, Middle Eastern, and multiracial transgender individuals. For instance, in 2015, 23% of the respondents did not see a doctor when they needed to because of fear of being mistreated as a transgender person

Box 2. The American Psychiatric Association's Diagnostic Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).
3. A strong desire for the primary and/or secondary sex characteristics of the other gender.
4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).
5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Reprinted from American Psychiatric Association (2013). Diagnostic and statistical manual of mental disorders (5th ed.). Washington, DC.

(10). Individuals concerned about the way they may be treated by a health care professional are more likely to obtain hormones from friends or unlicensed sources, putting them at risk of inappropriate dosing and the subsequent sequelae. Accessing care from an obstetrician–gynecologist is specifically challenging because these offices have generally been very gendered, women-specific environments, which can be perceived and experienced as exclusive.

Creating an Inclusive Environment

Presenting to a health care office can be stressful and anxiety provoking for a transgender individual. Obstetrician–gynecologists and office staff can create an inclusive environment for transgender patients that will encourage patients to be forthcoming with their concerns and confident that they will be able to obtain the care that they need.

Steps to create a more inclusive environment include the following:

- Increase health care professional knowledge of and comfort with providing care for transgender and gender nonconforming individuals. This includes avoiding making assumptions about patients' sexual orientation, sexual practices, and surgeries and being cognizant of what questions are appropriate (eg, is the question relevant to the care being provided?).
- Train and empower front desk staff, nursing staff, phone staff, billing staff, and others who interact with patients on appropriate ways to ask about names and pronouns (Box 3).
- Review the office space to ensure that images chosen for signage, educational materials, and artwork represent all individuals who may seek health care services.
- Ask all patients what pronouns they use (Box 3).
- Clearly post a sign with the office's nondiscrimination policy.
- Ensure that at least one restroom is gender neutral and accessible to all patients.
- Use patient forms that include check boxes for all gender and sexual orientation options, include blanks for patients to write in their responses, or both. Both the Institute of Medicine (now the National Academies of Sciences, Engineering, and Medicine [11]) and the Joint Commission (12) recommend collection of sexual orientation and gender identity data. Studies demonstrate that patients want to be asked these questions because they feel it is important for their health care professionals to have this information (13).

Box 3. Pronouns

Obstetrician–gynecologists should ask patients about their name and which pronouns they use. Asking all patients routinely for their gender identity and gender pronouns normalizes the interaction and allows patients to disclose without being targeted; good practice includes reciprocal disclosure (eg, "Hello, I am Dr. X and I use she/her pronouns. Is the name on your chart what you would like me to call you? What pronouns do you use?").

The patient's pronouns should be documented in the patient chart.

Common choices include (note: this is not an exhaustive list):

- She/her/hers
- He/him/his
- They/them/their: Neutral pronouns used by some who have a nonbinary or diverse gender identity.

Other gender-neutral pronouns include zie (ze) or hir.

- Create a system where names used by patients (if other than their legal names), gender markers (eg, on medical charts), and pronouns are used for every patient every time.
- Examine the electronic health record system available in offices and hospitals to determine a universal process to ease the communication process for all staff. The Fenway Institute has an excellent resource to guide this process. (14). The patient's name, if different from the individual's legal name, and pronouns used should be noted in the electronic health record.
- Train employees how to apologize for mistakes if they happen.

Gender Transition

Each individual patient will desire different outcomes. Not all patients will want hormone therapy, and not everyone will desire surgery. Some transmasculine patients may desire only masculinizing chest surgery, and other patients will desire hysterectomy and phalloplasty in addition to chest surgery. Medication and surgery are not required parts of transition and should not be required for legally changing one's name or gender marker on official documents (eg, birth certificate, passport, driver's license). Legal transition will vary depending on state laws. Some patients may request letters of support for changing their name or sex on legal documents, and these should be provided. It is important to remember that although hormone therapy is a medically necessary treatment for many transgender individuals with gender dysphoria, not all transgender patients experience gender dysphoria and not everyone desires hormone treatment.

Historically, a referral letter from a mental health professional was required before initiating a patient's gender-affirming hormone therapy. However, current consensus is that an informed consent process without a separate letter from a mental health care professional is more than adequate for initiating therapy for those patients who wish to medically transition. The majority of medications used for gender transition are common and can be safely prescribed by a wide variety of health care professionals with appropriate training and education, including, but not limited to, obstetrician–gynecologists, family or internal medicine physicians, endocrinologists, advanced practice clinicians, and psychiatrists. Although being knowledgeable about the medications used for gender transition and potential risks and side effects is important, specific certification for prescribing them is not required and should not be a limiting factor in helping patients access care. *Standards of Care (SOC) for the Health of Transsexual, Transgender, and Gender Nonconforming People*, published by the World Professional Association for Transgender Health, is an important resource for health care professionals working with transgender patients (15).

Fertility, Pregnancy, Contraception, and Abortion

Health care professionals' knowledge and awareness about reproductive options need improvement. Pregnancies are possible after transitioning, and perhaps, most important, contraceptive counseling is crucial to prevent undesired pregnancies. Fertility and parenting desires should be discussed early in the process of transition, before the initiation of hormone therapy or gender affirmation surgery. Fertility preservation options for transgender individuals are the same as for those *cisgender* individuals who desire preservation before gonadotoxic cancer therapy or for elective preservation. These options include sperm banking, oocyte preservation, embryo preservation, and in some cases, ovarian or testicular tissue cryopreservation. In addition to the expected pregnancy outcomes with these procedures, patients should be informed of the potential for out-of-pocket costs, which vary by state and insurance coverage.

Transmasculine Individuals

Transmasculine individuals taking testosterone who desire biologically related children may safely achieve pregnancy after the cessation of testosterone. Whether they choose insemination from partner or donor sperm and carry a pregnancy themselves or in vitro fertilization with embryo transfer to a partner or surrogate, transgender masculine individuals have many options for facilitating pregnancy. A 2013 survey of 41 transgender men who experienced pregnancy after transitioning found that two-thirds had used testosterone before pregnancy, with 81% using their own oocytes. Many of the respondents became pregnant within 4 months of stopping testosterone therapy and 32% of these pregnancies were unintended (16). As with cisgender patients, obstetrician–gynecologists should discuss pregnancy intention and prepregnancy health, if appropriate, with transgender patients. The Society of Family Planning provides guidance on contraceptive counseling for transgender and gender diverse people who were assigned female sex at birth (17). Given that contraception can be underutilized in this population because of concerns about adverse effects or access to care, undesired pregnancy is a substantial concern. Abortion access is a critical component to comprehensive reproductive health care for transgender individuals. The 2013 survey also demonstrated that patients experienced low levels of health care professional awareness and knowledge of the needs of transgender individuals (16).

Obstetrician–gynecologists and other health care professionals who care for transmasculine individuals during pregnancy should keep in mind that pregnancy is a gendered experience and pregnancy may trigger feelings of dysphoria or isolation for some patients (18). In addition, some postpartum transgender individuals may not identify as "mothers;" thus, obstetrician–gynecologists and other health care professionals

should be mindful of the language they use. It may be appropriate to use a more neutral term, such as "parent." Some patients may benefit from referral to mental health care professionals with experience in this area. A recent study of patients' experiences recommends providing affirming and inclusive care from prepregnancy through the postpartum period (18). During the postpartum period, patients will need to decide when to restart testosterone. For those making the decision to *chestfeed*, there is little evidence that testosterone passes into breast milk; however, because testosterone may suppress milk production, its use is not recommended until after chestfeeding is complete. Individuals who have had top surgery may still be able to lactate and chestfeed with the help of a support device. Some individuals may have worsening symptoms of dysphoria with lactation, and management of lactation suppression with cabergoline can be discussed with those individuals (19).

Transfeminine Individuals

For those transfeminine individuals preferring to retain their gonads, some may need to use assisted reproductive technologies to achieve pregnancy and others may have return of fertility within months of ceasing hormone therapy. For transfeminine individuals wishing to use their sperm for a pregnancy in a partner or surrogate, some data indicate that long-term estrogen exposure may be associated with testicular damage (20); however, discontinuing hormones for a few months may lead to the return of normal sperm counts. It is best practice to encourage sperm banking before initiation of hormones. Transfeminine individuals who wish to breastfeed may have success with induction of lactation using modifications to the Newman-Goldfarb method (21). A 2018 case report described a transgender woman successfully inducing lactation and continuing breastfeeding at 6 months follow-up (22).

Contraception

Gender-affirming hormone therapy is not effective contraception. Sexually active individuals with retained gonads who do not wish to become pregnant or cause pregnancy in others should be counseled about the possibility of pregnancy if they are having sexual activity that involves sperm and oocytes. Transmasculine individuals should be counseled that lack of menses does not mean they are unable to conceive. All patients should be counseled on barrier use for prevention of sexually transmitted infections. For transmasculine individuals interested in hormonal contraception, testosterone is not a specific contraindication to using any form of contraception. Many transmasculine patients prefer to avoid estrogen-containing methods because they do not want to add estrogen to their system; however, little change is seen in masculinization when these methods are used. Many patients will choose hormonal intrauterine device, contraceptive implant or, depot medroxyprogesterone acetate injection.

Medical Transition

Identifying the patient's goals before initiating masculinizing or feminizing hormone therapy is important. Hormone therapy can be provided in the office, and obstetrician–gynecologists can broaden their skill sets by educating themselves on the provision of transition care. For more details on the provision of hormone therapy for these populations, obstetrician–gynecologists should see resources from the World Professional Association for Transgender Health (8) and the Endocrine Society (20).

Masculinizing Therapy

For many patients, goals of masculinization therapy will include the development of facial hair, deepening of the voice, and increasing body hair and muscle mass. Other effects of masculinizing hormone therapy include the redistribution of subcutaneous fat, change in sweat and odor patterns, and hairline recession, including possible male pattern baldness. Patients also may experience increased libido, cessation of menses, vaginal atrophy, and increased clitoral size. Although testosterone generally causes temporary, and possibly permanent, decreased fertility, discussion about the possibility of continued ovulation is important for those patients with sexual practices that leave them with the potential for pregnancy. Patients should be counseled on current contraception options and their future reproductive life plan. The only absolute contraindications to masculinizing hormone therapy are current pregnancy, unstable coronary artery disease, and polycythemia (hematocrit greater than 55%) (15). Lipid profiles should be monitored in transmasculine patients receiving testosterone therapy (23). High-density lipoprotein levels decrease and triglycerides increase in transmasculine individuals receiving testosterone therapy. Studies have not shown an increased risk of cardiovascular events despite these adverse changes in the lipid profile.

There are many testosterone preparations available in the United States, including injectables, gels, creams, patches, and implantable pellets. Injectable testosterone cypionate is most commonly used subcutaneously, which allows for use of a smaller, less painful needle, but other formulations may be used based on patient preferences or adverse effects. Target ranges for testosterone levels are in the normal physiologic male range (typically 320–1,000 ng/dL) (20). See Table 1 for details on formulations and dosing. In addition to standard health care screening, it is recommended that testosterone levels and hematocrit be monitored every 3 months for the first year and then once or twice a year thereafter.

Patients should be counseled that menses likely will cease within a few months after initiating hormone therapy. If bleeding continues, the obstetrician–gynecologist may consider adding progesterone therapy to facilitate

Table 1. Hormone Preparations and Dosage: Masculinizing Hormone Therapy*

Route	Formulation	Dosage
Oral†	Testosterone undecanoate	160–240 mg/day
Parental (subcutaneous, intramuscular)	Testosterone enanthate, cypionate	50–200 mg/week 100–200 mg/10–14 days
Implant (subcutaneous)	Testosterone pellets, 75 mg	75 mg/pellet
Transdermal	Testosterone gel (1%) Testosterone patch	2.5–10 g/day 2.5–7.5 mg/day

*Dosages should be individualized according to the needs, preferences, and potential contraindications for each patient. Health care professionals also should have knowledge about generics and what medications will be covered by different payers.

†Requires participation in manufacturer monitored program.

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amenorrhea for patients who wish to avoid hysterectomy or endometrial ablation. Testosterone commonly will cause vaginal tissues to atrophy, similar to what is experienced by postmenopausal cisgender women. These tissues may be more susceptible to small amounts of tearing and changes in microbial environment, resulting in increased risk of bacterial vaginosis, cystitis, cervicitis, or dyspareunia (4). In these situations, obstetrician–gynecologists should consider topical treatments such as lubricants, vaginal moisturizers, and topical estrogen. Patients can be counseled that topical estrogen will have minimal systemic absorption and will not interfere with testosterone therapy.

Feminizing Therapy

Feminizing effects of hormone therapy include decreased erectile function, decreased testicular size, breast growth, and increased body fat percentage. Although there are no absolute contraindications to feminizing therapy, risks include venous thromboembolic embolism (VTE), hypertriglyceridemia, development of gallstones, and elevated liver enzymes. Patients on feminizing hormone therapy should be counseled to decrease risk factors for cardiovascular disease, such as smoking. Ethinyl estradiol, which provides better cycle control, may increase the risk of VTE; therefore, because cycle control is unnecessary for transgender women, its use is not indicated. Transdermal preparations of estradiol typically used for hormone replacement therapy are recommended for those with risk factors. If using oral estrogens, 17-β estradiol preparations are preferred (23). In general, prescribing the smallest dose possible to achieve desired effects is recommended. See Table 2 for preparation and dosing suggestions.

Antiandrogens, such as spironolactone, cyproterone acetate, gonadotropin-releasing hormone agonists, and 5-α reductase inhibitors, are used to reduce endogenous testosterone levels, which will decrease masculine characteristics and the amount of estrogen needed (15). Cyproterone is not available in the United States because of concern for hepatotoxicity. Gonadotropin-releasing hormone agonists are often expensive, so are not widely used. Spironolactone, which directly inhibits secretion of testosterone and androgen receptor binding, is the most commonly used antiandrogen in the United States. Because of the risk of hyperkalemia with these medications, it is important to monitor patients' blood pressure and potassium levels (23).

Although currently available data do not provide clear guidance on titration of dosing, it generally should be based on patient goals. Doses should be titrated to physiologic effects, while adjusting estrogen and antiandrogen dosing until in female physiologic range; then, dosing can be modified to focus on further increasing androgen blocking. The goals are to maintain estradiol levels at the mean daily levels for premenopausal women (less than 200 ng/ml) and testosterone in female range (less than 55 ng/dl) (20). Progestins may increase breast development as well as improve libido and mood in some patients. Recommended laboratory surveillance includes estradiol and total testosterone levels, sex hormone binding globulin, and albumin levels every 3 months in the first year to titrate estrogen dosing. After the first year, laboratory tests are necessary only if there are patient or health care professional concerns about adverse effects or after a change in dosage. Patients taking spironolactone also should be tested for potassium and creatinine levels every 3 months for first year and then yearly.

Notably, feminizing hormones do not result in substantial changes to voice. Vocal pitch is secondary to the size and mass of folds of the vocal cords, which are not reversed by the addition of estrogen. Patients with concerns that their voice is incongruent with their gender can be referred to a speech language pathologist who has specific training in this area. If speech therapy does not adequately help, surgical procedures can be considered.

Table 2. Hormone Preparations and Dosage: Feminizing Hormone Therapy*

Route	Formulation	Dosage
Oral	Estradiol	2–4 mg daily
Parental (subcutaneous, intramuscular)	Estradiol valerate	5–30 mg every 2 weeks
Transdermal	Estradiol	0.1–0.4 mg twice weekly
Antiandrogens	Progesterone	20–60 mg by mouth daily
	Medroxyprogesterone acetate	150 mg intramuscularly every 3 months
	GnRH agonist (leuprolide)	3.75–7.5 mg intramuscularly monthly
	Histrelin implant	50 mg implanted every 12 months
	Spironolactone	100–200 mg by mouth daily
	Finasteride	1 mg by mouth daily

*Dosages should be individualized according to the needs, preferences, and potential contraindications for each patient. Health care professionals also should have knowledge about generics and what medications will be covered by different payers.

Abbreviation: GnRH, gonadotropin-releasing hormone.

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Surgical Transition

Some of the surgical procedures described here may not be considered within the scope of practice for an obstetrician–gynecologist, but this section may provide education for clinicians who care for transgender patients before and after surgery. As with any surgical procedure, the quality of care provided before, during, and after surgery greatly affects patient outcomes. Many insurance companies that cover gender affirmation procedures will require a mental health assessment letter before authorization for surgery. Box 4 provides an overview of surgical procedures. For additional information on postoperative care for patients who have had gender-affirming surgery, obstetrician–gynecologists can see resources from the University of San Francisco's Center of Excellence for Transgender Health (4).

Masculinizing Surgery

Transmasculine individuals may choose chest reconstruction, hysterectomy with or without salpingo-oophorectomy, or metoidioplasty, phalloplasty, or both. The U.S. Transgender Survey reported that the majority (97%) of patients had or wanted masculinizing chest surgery; similarly, a majority (79%) of patients had undergone or wanted a hysterectomy. When asked about genital surgeries, only 4% had had metoidioplasty and 53% wanted the procedure in the future; for phalloplasty, 2% had had the procedure and 27% desired it in the future (10). The lower percentage of patients wanting these surgeries is likely multifactorial; limited insurance coverage is one issue. Masculinizing chest surgery, sometimes referred to as "top surgery," generally includes a subcutaneous mastectomy and recontouring to develop a masculine-appearing chest. Factors such as surgeon

Box 4. Surgical Procedures for Transgender Individuals

Masculinizing Surgical Procedures May Include the Following:

- Breast or chest surgery: subcutaneous mastectomy, creation of a male chest
- Genital surgery: hysterectomy with or without salpingo-oophorectomy, reconstruction of the fixed part of the urethra, which can be combined with a metoidioplasty or with a phalloplasty (employing a pedicled or free vascularized flap), vaginectomy, scrotoplasty, and implantation of erection or testicular prostheses
- Nongenital, nonbreast surgical interventions: voice surgery (rare), liposuction, lipofilling, pectoral implants, and various aesthetic procedures

Feminizing Surgical Procedures May Include the Following:

- Breast or chest surgery: augmentation mammoplasty (implants/lipofilling)
- Genital surgery: penectomy, orchiectomy, vaginoplasty, clitoroplasty, vulvoplasty
- Nongenital, nonbreast surgical interventions: facial feminization surgery, liposuction, lipofilling, voice surgery, thyroid cartilage reduction, gluteal augmentation (implants/lipofilling), hair reconstruction, and various aesthetic procedures

Reprinted from World Professional Association for Transgender Health. Standards of care for the health of transsexual, transgender, and gender nonconforming people. 7th version. Minneapolis (MN): WPATH; 2012.

expertise, body habitus, skin quality, and breast shape and size will influence the surgical approach.

Metoidioplasty to create a neophallus is generally chosen by patients who want genital surgery but are not interested in phalloplasty. Metoidioplasty involves releasing the clitoris, lengthening the urethra to the tip of the phallus, and covering the phallus with neighboring skin. It is possible to have concurrent vaginectomy and scrotoplasty. Patients who choose urethral lengthening will be able to void when standing if they are close to ideal body weight. If a patient desires scrotoplasty, rotational flaps of the labia majora are used to place the scrotum in an anatomic male position. Implants can be placed approximately 6 months later. Phalloplasty generally takes tissue from a donor site, which is shaped into a phallus, allowing for later penile implant to facilitate penetrative intercourse. Most commonly, tissue is taken from the radial forearm, latissimus dorsi, or anterolateral thigh. The decision on the location of the tissue donor site is based on surgeon technique and desired patient outcomes.

Hysterectomy with or without bilateral salpingo-oophorectomy is medically necessary for patients with gender dysphoria who desire this procedure. The route of hysterectomy should be based on clinical findings as well as surgeon and patient preference. Although vaginal hysterectomy will allow for recovery without abdominal scarring, some surgeons may find it to be technically difficult given likely lack of uterine descent and severe vaginal atrophy with a narrow introitus; however, it can be accomplished if desired (24). A genital examination may be challenging and worsen dysphoria for some patients. In these cases, it may be appropriate to conduct the examination under anesthesia before initiating the surgical procedure. Whether the ovaries are removed at the time of hysterectomy will be informed by the patient's fertility desires, long-term plans for hormonal use, and personal preferences and should be considered within a shared decision-making model. Patients should be offered consultation with a fertility specialist before surgical removal of ovaries. Counseling about bone health and cardiovascular protection is challenging because of limited data. Testosterone may have an anabolic effect on cortical bone, and if provided in adequate doses will prevent bone demineralization. No studies have found an increase in the occurrence of cardiovascular events in transmasculine individuals (23), so unless the patient is planning to stop taking testosterone in the future, it is unlikely that the ovaries are necessary to maintain bone or cardiovascular health. More research is needed in this area. Notably while some patients may not plan to stop testosterone, they may do so because of issues such as lack of access. Engaging in shared decision making and counseling regarding the risks and benefits of ovarian preservation before hysterectomy is important.

Feminizing Surgery

Although desire for surgical transition varies depending on the individual, the U.S. Transgender Survey reported that 74% of respondents had either undergone breast augmentation or wanted it in the future. One quarter had undergone orchiectomy and 61% desired it in the future; 87% had undergone vaginoplasty or wanted to do so in the future (10). Potential procedures for transfeminine individuals include breast augmentation, orchiectomy, vaginoplasty, and facial feminization surgeries. It generally is recommended that patients wait at least 6 months after initiating feminizing hormone therapy before undergoing breast augmentation; other experts suggest waiting 2–3 years to maximize hormonal effects (4). Breast augmentation typically is performed with implants, either subglandular or subpectoral depending on a patient's body habitus and desire.

Vaginoplasty involves penile inversion and the creation of a vaginal vault between the rectum and urethra. The vagina is lined with penile skin and labia are created using scrotal skin after orchiectomy is completed. The glans penis is used to create the clitoris. If there is not enough skin available to provide adequate depth, a skin graft is performed. Preoperative electrolysis of the scrotum is recommended to prevent hair from growing in the neovagina.

Successful recovery from this procedure requires patient commitment to a dilation regimen (up to three times per day) to maintain depth and width of the neovagina. Given the limited number of centers providing these procedures, it is not uncommon for a patient to present to their local obstetrician–gynecologist for ongoing postoperative care. The vagina is lined by skin, not mucosa; therefore, it will not lubricate naturally. For patients who are struggling with dilation, they should be counseled to increase the amount of lubricant used and to consider using a smaller-sized dilator to allow for more frequent and deeper dilation; patients can then gradually increase the size of the dilator. Individuals with persistent pain or discomfort with dilation may benefit from a referral to a pelvic floor physical therapist. For individuals presenting with vaginal discharge and odor, sources are most likely sebum, dead skin, or retained semen or lubricant. Those patients should be counseled to clean or douche with soap and water; the addition of vinegar may be considered if strong odor is noted. Patients may present with bleeding or discharge consistent with granulation tissue; this often can be easily treated with silver nitrate.

Cancer Screening

There are insufficient data to determine whether transgender individuals are at increased risk of malignancy compared with the general population. To guide preventive medical care, any anatomical structure present that warrants screening should be screened regardless of gender identity. It may be useful to comprehensively

label laboratory specimens (eg, "male with cervix") to ensure they are appropriately processed.

Transmasculine Individuals

For transmasculine individuals, screening includes breast cancer screening for patients who have breast tissue and cervical cancer screening for those who have a cervix. Before ceasing breast cancer screening, it is important to review operative reports to ensure that mastectomy was performed and not just breast reduction. For those individuals who have undergone mastectomy and reconstruction, there are limited data to support clinical chest examinations in the absence of patient concern (4). The American College of Obstetricians and Gynecologists recommends genetic counseling before surgery for those with a personal or family history of breast cancer or ovarian cancer (25).

Cervical cancer screening should be performed according to age-related guidelines (26–28). Self-collected human papillomavirus (HPV) specimens may be appropriate for those patients who otherwise may not access screening or for whom speculum insertion may be physically difficult or emotionally traumatic; though, to date, there is no patient-collected HPV test approved by the U.S. Food and Drug Administration. Atrophy secondary to testosterone may make cervical cancer screening more challenging. Transmasculine individuals have a 10-fold higher rate of unsatisfactory Pap tests (samples that cannot be evaluated by the laboratory due to a lack of sufficient cells or obscuring factors such as blood) compared with cisgender individuals (29). A 2018 study of transmasculine patients aged 21–64 years reported a high patient preference for self-collected vaginal HPV swabs (greater than 90% preference over swabs collected by health care professionals) and accurate self-collected results consistent with previous studies in cisgender female patients. There was a 71.4% concordance of self-collected samples compared with samples collected by health care professionals (15 of 21 cases detected) (30).

Similar to cisgender women, routine screening for endometrial cancer is not recommended for transmasculine individuals who still have a uterus. Although for transmasculine individuals there is a theoretical concern for increased risk of hyperplasia or malignancy because of the aromatization of exogenous testosterone to estrogen with anovulation leading to unopposed estrogen, there are no data to support this. In fact, most studies demonstrate that the endometrium is atrophic secondary to testosterone use. Therefore, on the basis of limited data, recommendations for screening for endometrial cancer for transmasculine individuals are no different than for cisgender women. Additionally, evaluation of transmasculine individuals with abnormal uterine bleeding are the same as those for cisgender women (31).

Transfeminine Individuals

A neovagina does not require routine cytologic screening. Prostate cancer screening for transfeminine individuals should follow the recommendations for cisgender men (32). Although there are some case reports of prostate cancer in transfeminine individuals, most of these were in individuals who started hormone therapy after 50 years of age; these individuals likely had preexisting lesions before initiating hormone therapy (33). It is likely that transfeminine individuals have a lower risk of breast cancer than cisgender women. A retrospective study of Dutch transfeminine individuals found an estimated breast cancer incidence of 4.1 in 100,000 person-years in comparison with 155 in 100,000 person-years in the cisgender female population (34). This decreased risk is likely because of a substantially decreased length of lifetime exposure to estrogen. However, it is notable that a study of 50 transfeminine individuals found 60% had dense or very dense breasts on mammography, leading to increased rates of false-negative mammogram results (35). General consensus is that screening should begin after 50 years of age and a minimum of 5 years of feminizing hormone use, with a health care professional-patient discussion about the potential harms of over screening (4).

Additional Considerations for Preventive Care

As for all patients, transgender individuals should be counseled about the importance of routine preventive health care. All individuals should be routinely screened for intimate partner violence, depression, substance use, cancer, and other health care needs and should be screened for sexually transmitted infections and counseled about appropriate immunizations based on age and risk factors, including HPV vaccination. As with the general population, screening for intimate partner violence in transgender patients is important and should be performed. A 2017 study found a higher report rate of intimate partner violence in transfeminine individuals (12.1%) when compared with cisgender women (2.7%), transmasculine individuals (6.6%), nonbinary individuals (8.2%), and transgender or gender diverse individuals who did not report a gender identity (9.1%) (36). Screening for mental health issues should be part of standard practice. Forty percent of transgender individuals have attempted suicide at some point during their lifetime (10).

Obstetrician–gynecologists should take a careful and thoughtful medical, family, and surgical history for all patients. Risk assessment for sexually transmitted infections should be based on a patient's behaviors and present anatomy. When performing the physical examination, it is important to remember that patients may have had traumatic examinations in the past. Self-collected vaginal and rectal swabs as well as the option for urine specimens may be appropriate alternatives to physical examination. Obstetrician–gynecologists should follow guidance for transgender individuals in the Centers for Disease Control and Prevention's 2015 STD Treatment Guidelines,

endorsed by the American College of Obstetricians and Gynecologists (37). Screening for human immunodeficiency virus (HIV) in at-risk individuals is of high importance. Among those respondents to the Transgender Discrimination Survey, 1.4% were living with HIV; this is five times higher than the rate of the general U.S. population. The rate in transfeminine individuals was 3.4%, and 19% of Black transfeminine individuals reported living with HIV (10). Obstetrician–gynecologists should counsel patients at high risk of HIV infection on safer sex practices and other prevention methods, as well as the option of preexposure prophylaxis (38).

Conclusion

Accessing health care as a transgender individual often is challenging. Obstetrician–gynecologists may provide comprehensive care for transgender patients at various times in their lives. Obstetrician–gynecologists should make their offices inclusive and inviting to all individuals who need obstetric or gynecologic health care. They should take steps to educate themselves and their medical teams about appropriate language and the health care needs of transgender patients. Putting the patient in the role of educator of the health care professional diminishes the patient-physician relationship. In order to provide the best care for patients, it is useful to know which health care professionals to include in a referral network for primary care and to have many clinician and surgeon options given the many different therapies available and the different sites at which these therapies are offered. Connecting with trans-friendly colleagues is a way to expand access to care for the transgender individuals in the community.

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TAB 175-40

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Attacks on Gender-Affirming and Transgender Health Care

Published: May 3, 2022

In 2021, Arkansas became the first state in the country to ban gender-affirming health care for transgender minors. Since then, Tennessee, Arizona, and Alabama have also enacted laws restricting access to gender-affirming care, and 11 other states are considering such bans as of March 2022. Alabama's ban included the harshest penalties of any legislation passed thus far, making the provision of gender-affirming care a felony punishable by up to 10 years in prison. Though legal challenges have so far kept these laws on hold, these health care bans are part of an increasing trend of anti-LGBTQ+ legislation proliferating at the state level, with a record of nearly 240 anti-LGBTQ+ bills already introduced this year.

The Office of Population Affairs at the U.S. Department of Health and Human Services (HHS) defines gender affirming care as "an array of services that may include medical, surgical, mental health, and non-medical services for transgender and nonbinary people. For transgender and nonbinary children and adolescents, early gender-affirming care is crucial to overall health and well-being as it allows the child or adolescent to focus on social transitions and can increase their confidence while navigating the healthcare system." Gender-affirming care is evidence-based medicine supported by many prestigious medical organizations, and study after study shows that gender-affirming care reduces depression and suicide among transgender youth. ACP and other leading medical organizations have condemned efforts to criminalize gender-affirming care and any care that interferes with the physician-patient relationship.

While restrictions have primarily focused on preventing minors from accessing gender-affirming care, some have also targeted transgender health care for older individuals. In four states, these laws extend bans to adults – applying to those under the age of 19 in Alabama, those under the age of 21 in North Carolina and Oklahoma, and those under 25 in Missouri. Additionally, Arkansas' law has banned insurance coverage of gender-affirming care overall for both public and private insurance plans, as would about half the bills being considered by other states.

The Williams Institute at the UCLA School of Law found that over 58,000 transgender youth and young adults are at risk of losing access to care in states that have restricted access to gender-affirming care or are considering doing so. Beyond immediate impacts, these laws drive stigma and endanger the wellbeing

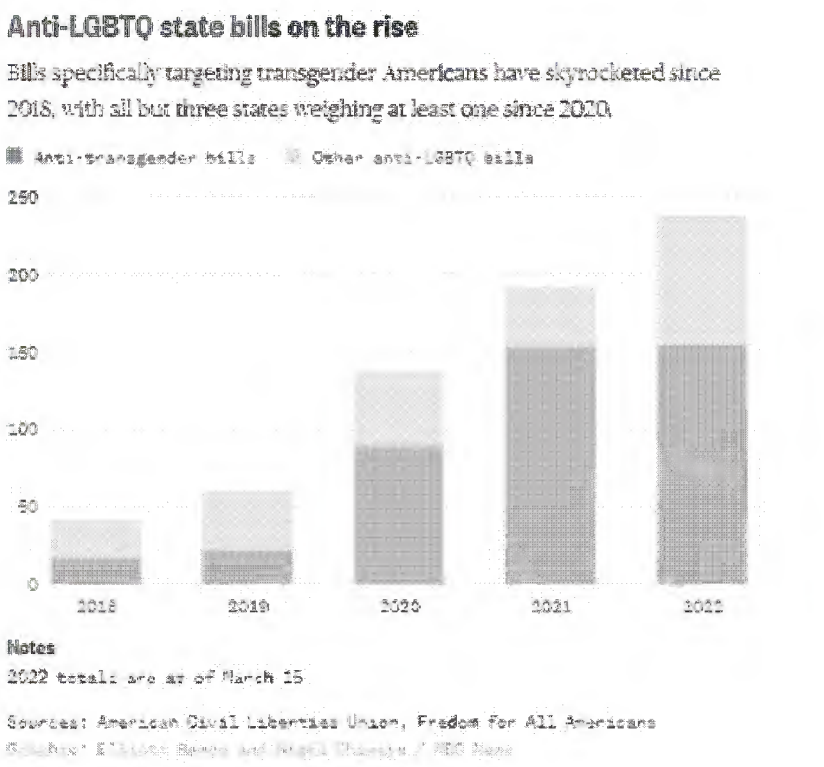
of LGBTQ+ youth. According to the Trevor Project's 2021 National Survey on LGBTQ Youth Mental Health, 94 percent of LGBTQ+ youth reported that recent politics have negatively impacted their mental health.

Most gender-affirming care restrictions either criminalize physicians – sometimes with extreme penalties, such as the bill passed by Idaho's House of Representatives carrying up to a life sentence for those who provide a minor with gender-affirming care – or make them subject to civil penalties or professional discipline through state licensing boards. Bills in multiple states (Alabama, Idaho, Kansas, North Carolina, Oklahoma, South Carolina, and Tennessee) would also establish penalties for parents who facilitate their children's access to gender-affirming care, including by designating this health care as abuse.

While Texas bills to ban gender-affirming care for transgender minors have not passed, the state has used administrative means to restrict access. After Texas Attorney General Ken Paxton issued an opinion describing gender-affirming care as child abuse, Governor Greg Abbott instructed the Texas Department of Family and Protective Services to investigate families with transgender children. This directive, which is currently blocked by a Texas appeals court, would have also imposed criminal penalties on physicians and other licensed professionals who did not report families who provide gender-affirming care to their children.

Florida has also moved to restrict gender-affirming care administratively. The state's Surgeon General released a memo contradicting HHS guidance on gender-affirming care for minors and setting "guidelines" prohibiting gender-affirming care, going as far to say that even social gender transition – such as a change in haircut or name – "should not be a treatment option."

While most of the nearly 240 anti-LGBTQ+ bills introduced so far this year propose restrictions on the lives of transgender children in medical and educational settings, they are part of a growing wave of anti-LGBTQ+ legislation overall. Notable in this trend have been efforts to limit school employees from discussing gender identity, sexual orientation, and race – such as Florida's recently passed "Don't Say Gay" law – and to ban libraries from carrying books related to those topics.



As a result of these initiatives that challenge or deny access to critical health care, criminalize parents, and threaten the removal of children from their homes, some families with the means to do so have fled their states for other jurisdictions. Removing a child from loving parents solely for providing evidence-based and oftentimes life-affirming care is wrong. Alarmingly, these laws have also fueled misinformation that has led to increasing harassment and violence against physicians and other health care workers who provide gender-affirming health care services.

ACP has decried these discriminatory policies against LGBTQ+ people and objected in particular to the interference with the physician-patient relationship and penalization of evidence-based care. ACP believes that physicians and other health care professionals should not fear criminal punishment for providing the medical standard of care, nor should the government attempt to force disclosure of patient information related to gender-affirming care. ACP policy also calls for coverage of comprehensive transgender health care in private and public insurance plans, which about half of these bills would ban. In addition to speaking out against these harmful laws, ACP has joined amicus briefs in legal challenges to the Texas directive and other policies discriminating against transgender people and will continue to support legal and legislative efforts protecting against these medically unsound and dangerous restrictions.

Federal Actions to Address Discrimination against Transgender People

The Biden Administration has taken multiple actions to address this legislative trend. On March 2, 2022, HHS clarified that physicians and other health care personnel are not required to disclose patient information regarding gender-affirming care and that denials of care based on gender identity are illegal.

On March 31, the U.S. Department of Justice wrote to state attorneys general warning that bans on gender-affirming care are unconstitutional and violate multiple federal laws. HHS has also called for physicians and patients who believe they have been discriminated against on the basis of gender identity or disability in seeking to access gender-affirming care to file a complaint with the department's Office of Civil Rights.

HHS also proposed a new rule in December 2021 banning health coverage-related discrimination based on gender identity or sexual orientation. While the new rule has not been finalized, ACP has expressed support.

State Actions to Support Gender-Affirming Care

In response to these bans, at least eight states have introduced legislation this year to prevent discrimination against transgender people in health care or otherwise protect access to gender- affirming care.

- The Hawaii's legislature passed a bill requiring insurers to cover gender-affirming care services if they also cover those treatments for purposes other than gender transition and to provide clear information about coverage of gender-affirming care.
- A Georgia bill would prohibit public insurance plans from discriminating on the basis of gender identity, including through denial of gender-affirming hormone therapy, and would repeal conflicting laws.
- A bill in Vermont would allow minors to consent to non-surgical gender-affirming care.
- A Maryland bill would ensure Medicaid coverage of comprehensive transgender health care.
- Washington state proposed legislation addressing the need to ensure access to gender- affirming care and other forms of health care in mergers, acquisitions, and contracting affiliations.
- California, Minnesota, and New York have responded to efforts in Texas and other states that designate gender-affirming care as abuse by introducing legislation that would block officials in their states from complying with out-of-state laws or judgments penalizing parents for providing gender-affirming care.

Resources

- Prohibiting Gender-Affirming Medical Care for Youth – Williams Institute at UCLA School of Law
- Lesbian, Gay, Bisexual, and Transgender Health Disparities: Executive Summary of a Policy Position Paper From the American College of Physicians (2015)
- ACP Statement of Principles on the Role of Governments in Regulating the Patient-Physician Relationship (2012)
- *Annals of Internal Medicine* Care of the Transgender Patient (2019)
- *Medical News Today* The "Life-Saving" Science Behind Gender Affirming Care for Youth
- HHS guidance on Gender-Affirming Care and Young People and statement in support of LGBTQ+ youth
- Amicus Brief filed by ACP and other medical organizations to Texas Supreme Court

- ACP Statements
  - On Alabama law
  - On Texas directive
  - On Texas, Florida, and Idaho laws

TAB 176-1

ACP Journals

Position Papers | 21 July 2015

Annals of Internal Medicine

Lesbian, Gay, Bisexual, and Transgender Health Disparities: Executive Summary of a Policy Position Paper From the American College of Physicians

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Hilary Daniel, BS and Renee Butkus, BA, ... View all authors

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https://doi.org/10.7326/M14-2482

Abstract

In this position paper, the American College of Physicians examines the health disparities experienced by the lesbian, gay, bisexual, and transgender (LGBT) community and makes a series of recommendations to achieve equity for LGBT individuals in the health care system. These recommendations include enhancing physician understanding of how to provide culturally and clinically competent care for LGBT individuals, addressing environmental and social factors that can affect their mental and physical well-being, and supporting further research into understanding their unique health needs.

The lesbian, gay, bisexual, and transgender (LGBT) community is diverse, comprising persons from various races, ethnicities, and socioeconomic

backgrounds; however, LGBT persons face a common set of challenges within the health care system. These challenges range from access to health care coverage and culturally competent care to state and federal policies that reinforce social stigma, marginalization, or discrimination. Recent years have brought about reliable data collection, research, and a greater understanding of the health care needs of the LGBT community and the challenges they face in accessing care. Although great strides have been taken in reducing health disparities in the LGBT community, much more needs to be done to achieve equity for LGBT persons in the health care system.

Although members of the LGBT community face similar health concerns as the general population, certain disparities are reported at a higher rate among LGBT persons than the heterosexual population (1). These disparities experienced by LGBT persons may be compounded if they are also part of a racial or ethnic minority (1). Of note, LGBT persons are more likely to identify themselves as being in poor health than heterosexual individuals, and different segments of the LGBT population have individual health risks and needs. For example, gay and bisexual men are at increased risk fo certain sexually transmitted infections and account for more than half of all persons living with HIV or AIDS in the United States (1); lesbian women are less likely to have mammography or Papanicolaou test screening for cancer (2); lesbian and bisexual women are more likely to be overweight or obese (3); and lesbian, gay, and bisexual persons are more likely to become disabled at a younger age than heterosexual individuals (4).

Various state or federal laws may affect the quality of life of LGBT persons and can affect their physical and mental health. Same-sex marriage bans may cause psychological distress (5), prohibitive hospital visitation policies may prevent a same-sex parent from seeing a minor while the child is ill or participating in medical decision making for the child, and exclusions on transgender health care in private and public health plans may cause a transgender patient to seek treatment options through illegal channels (6). These laws and policies, along with others that reinforce marginalization, discrimination, social stigma, or rejection of LGBT persons by their families or communities or that simply keep LGBT persons from accessing health care, have been associated with increased rates of anxiety, suicide, and substance or alcohol abuse (7).

Addressing these disparities will require changes in the way LGBT persons and their families are regarded in society and by the health care system. Policies that are discriminatory toward the LGBT community, or are no longer supported by empirical research, continue to reinforce the environmental and social factors that can affect the mental and physical well-being of LGBT persons. The American College of Physicians (ACP) has a long-standing commitment to improving the health of all Americans and opposes any form of discrimination in the delivery of health care services. ACP is dedicated to eliminating disparities in the quality of or access to health care and is committed to working toward fully understanding the unique needs of the LGBT community and eliminating health disparities for LGBT persons.

This Executive Summary provides a synopsis of the full position paper, which is available in Appendix.

Methods

The ACP Health and Public Policy Committee, which is charged with addressing issues affecting the health care of the U.S. public and the practice of internal medicine and its subspecialties, developed these recommendations. The committee reviewed numerous studies, reports, and surveys on LGBT health care and related health policy. The committee also reviewed information on how state and federal policies may affect the physical and mental health of the LGBT population. Draft recommendations were reviewed by the ACP Board of Regents, Board of Governors, Council of Early Career Physicians, Council of Resident/Fellow Members, Council of Student Members, and Council of Subspecialty Societies. The position paper and recommendations were reviewed by the ACP Board of Regents and approved on 27 April 2015.

ACP Position Statements and Recommendations

The following statements represent the official policy positions and recommendations of the ACP. The rationale for each is provided in the full position paper (Appendix).

A glossary of LGBT terminology used throughout this paper can be found at https://lgbt.ucsf.edu/glossary-terms.

1. The American College of Physicians recommends that gender identity, independent and fundamentally different from sexual orientation, be included as part of nondiscrimination and antiharassment policies. The College encourages medical schools, hospitals, physicians' offices, and other medical facilities to adopt gender identity as part of their nondiscrimination and antiharassment policies.

2. The American College of Physicians recommends that public and private health benefit plans include comprehensive transgender health care services and provide all covered services to transgender persons as they would all other beneficiaries.

3. The definition of "family" should be inclusive of those who maintain an ongoing emotional relationship with a person, regardless of their legal or biological relationship.

4. The American College of Physicians encourages all hospitals and medical facilities to allow all patients to determine who may visit and who may act on their behalf during their stay, regardless of their sexual orientation, gender identity, or marital status, and ensure visitation policies are consisten

the Centers for Medicare & Medicaid Services Conditions of Participation and The Joint Commission standards for Medicare-funded hospitals and critical-access hospitals.

5. The American College of Physicians supports civil marriage rights for same-sex couples. The denial of such rights can have a negative impact on

the physical and mental health of these persons and contribute to ongoing stigma and discrimination for LGBT persons and their families.

6. The American College of Physicians supports data collection and research into understanding the demographics of the LGBT population, potential causes of LGBT health disparities, and best practices in reducing these disparities.

7. Medical schools, residency programs, and continuing medical education programs should incorporate LGBT health issues into their curricula. The College supports programs that would help recruit LGBT persons into the practice of medicine and programs that offer support to LGBT medical students, residents, and practicing physicians.

8. The College opposes the use of "conversion," "reorientation," or "reparative' therapy for the treatment of LGBT persons.

9. The American College of Physicians supports continued reviews of blood donation deferral policies for men who have sex with men. The College supports evidence-based deferral policies that take into account a comprehensive assessment of the risk level of all individuals seeking to donate, which may result in varying deferral periods or a lengthened or permanent deferral on blood donation.

Conclusion

The ACP recognizes that reducing health disparities in the LGBT population will take concerted efforts not only by those in the medical community but

also from society as a whole. Training future physicians to be culturally and clinically competent in LGBT health care, working with practicing physicians to increase their understanding of the LGBT population and their health needs, advocating for practical health policies supported by empirical research, and working to eliminate laws that discriminate against the LGBT community and their families are all important steps to reducing and ultimately eliminating the health disparities experienced by the LGBT community.

Appendix: Lesbian, Gay, Bisexual, and Transgender Health Disparities: A Policy Position Paper From The American College of Physicians

Understanding the LGBT Community

The LGBT community is a highly diverse and multifaceted group of persons encompassing all cultures, ethnicities, and walks of life. Under the LGBT umbrella, each individual group faces unique cultural and health-related needs but shares common challenges, such as social stigma, discrimi and disparities in health care, that unite them.

Research into LGBT health has been expanding as the community has become more visible and outspoken about engaging the health care system in developing a knowledge base on the distinctive challenges and health disparities they face. However, gaps in the medical community's understanding of the overall makeup of the LGBT community and the environmental and social factors that may influence the needs of those

persons present an obstacle to addressing challenges in a meaningful way. In 2011, the Institute of Medicine issued a report outlining a research agenda targeting several areas that could affect how the health care system approaches LGBT health, including demographics, social influences, disparities and inequalities, intervention that includes increasing access to care and addressing physical or mental conditions, and transgender-specific needs. The report also recommended the inclusion of the LGBT community in national health surveys and emphasized a need for scientific rigor and a respectful environment when gathering data (8).

One important obstacle to identifying health issues within the LGBT population is a lack of reliable data and the exclusion of sexual and gender minorities' identification on federal health surveys. Recent efforts have been made to gather population data on persons who identify as lesbian, gay, bisexual, or transgender and those who identify as being in a same-sex marriage or partnership. For the first time in 2010, the U.S. Census Bureau did not change the data reporting the number of same-sex couples that identified as being married. Before that, the 2000 U.S. Census changed the relationship status of same-sex partners identifying as being the spou
the head of household to an "unmarried partner" because there were no states in which same-sex marriage was legal. In the 1990 U.S. Census, if a same-sex couple identified themselves as married, the sex of 1 of the respondents was automatically changed to the opposite sex and the couple was enumerated as an opposite-sex married couple (9). The Patient Protection and Affordable Care Act allows the Department of Health and Human Services (HHS) to collect "additional demographic data to further

improve our understanding of health disparities," and in 2013, the National Health Interview Survey—an annual study of health care access, use, and behaviors—included sexual orientation as part of its data collection system (10). Recent estimates put the number of persons who identify as lesbian, gay, bisexual, or transgender at more than 9 million or approximately 3.4% of the U.S. population, which some analysts believe may be an underestimate (1). Individuals who may have same-sex attractions or experiences but do not self-identify as LGBT may still fall into the category of sexual minorities and face health disparities associated with LGBT persons.

Access to Care in the LGBT Population

The LGBT community has often been overlooked when discussing health care disparities and continues to face barriers to equitable care. Barriers to care are multidimensional and include stigma and discrimination, poverty, lack of education, racial or ethnic minority status, and other psychological health determinants (11). Studies show that persons who identify as LGBT have greater economic disadvantages and are more vulnerable to poverty than those who do not. Using available information from national sur the Williams Institute reports higher overall poverty rates for persons identifying under the LGBT umbrella than heterosexual persons and higher rates of poverty in same-sex couples than heterosexual couples (7.6% vs. 5.7%) (12).

Research shows that LGBT adults and their children are more likely to be uninsured by public or private insurance and that they and their family

members continue to face difficulties in gaining access to care and face a higher risk for health disparities than the general population (2). Most Americans gain health insurance coverage through their employer; data are limited but suggest LGBT persons face higher unemployment rates than non-LGBT persons. A 2009 survey in California found a 14% unemployment rate among LGBT adult workers compared with 10% among non-LGBT adults (13).

The Affordable Care Act sought to increase access to care for low-income Americans by expanding Medicaid programs to all persons at or below 133% of the federal poverty level, providing financial subsidies to help those making between 100% and 400% of the federal poverty level purchase insurance on the federal and state marketplace exchanges, and including nondiscrimination protections in health plans sold on the exchanges. Although estimates suggested that the number of uninsured LGBT persons would be reduced as a result of Medicaid expansion, only about half of states have chosen to expand their Medicaid programs, which greatly diminishes its effect. This increases the number of LGBT persons who may fall into what has been dubbed the "coverage gap," in which persons may earn too m qualify for their state's Medicaid program but too little to qualify for subsidies (14).

Transgender individuals face additional challenges in gaining access to care. Not only are they more likely to be uninsured than the general population, they are more likely to be uninsured than lesbian, gay, or bisexual persons (1). They also face high out-of-pocket costs for transgender-specific medical

care if they lack insurance or their insurance coverage does not cover transgender health care. According to the American Congress of Obstetricians and Gynecologists, transgender youth who receive inadequate treatment are at an increased risk for engaging in self-mutilation or using illicit venues to obtain certain treatments; research shows more than 50% of persons who identify as transgender have obtained injected hormones through illegal means or outside of the traditional medical setting (6).

Mental and Physical Health Disparities

Existing research into the health of the LGBT population has found some health disparities that disproportionately affect the LGBT population. In 2000, the first federally funded research study on the health of LGBT persons assessed 5 major areas of concern for lesbian, gay, and bisexual persons (the report noted that transgender health concerns warranted an independent evaluation): cancer, family planning, HIV and AIDS, immunization and infectious diseases, and mental health (15). Research has shown that lesbian women are less likely to get preventive cancer screenings; lesbian and bisexual women are more likely to be overweight or obese (16); gay m
at higher risk for HIV and other sexually transmitted infections; and LGBT populations have the highest rates of tobacco, alcohol, and other drug use (17). Lesbian, gay, and bisexual persons are approximately 2.5 times more likely to have a mental health disorder than heterosexual men and women (18).

Transgender persons are also at a higher lifetime risk for suicide attempt and show higher incidence of social stressors, such as violence, discrimination, or childhood abuse, than nontransgender persons (19). A 2011 survey of transgender or gender-nonconforming persons found that 41% reported having attempted suicide, with the highest rates among those who faced job loss, harassment, poverty, and physical or sexual assault (20).

Positions

1. The American College of Physicians recommends that gender identity, independent and fundamentally different from sexual orientation, be included as part of nondiscrimination and antiharassment policies. The College encourages medical schools, hospitals, physicians' offices, and other medical facilities to adopt gender identity as part of their nondiscrimination and antiharassment policies.

Nondiscrimination policies are in place to prevent employment discrimination or harassment based on race, color, national or ethnic origin, age, religion, sex, disability, genetics, or other characteristics protecte under federal, state, or local law (21). However, state law varies consic on the inclusion of sexual orientation and gender identity in nondiscrimination policies and some policies based on sexual orientation alone may not include gender identity. Eighteen states have employment nondiscrimination or equal employment opportunity statutes that cover both gender identity and sexual orientation, and an additional 3 states have nondiscrimination statutes that cover sexual orientation only (22). The

Human Rights Campaign, an LGBT rights organization, estimated that as a result of these assorted laws, 3 of 5 U.S. citizens live in an area that does not provide protection for gender identity or sexual orientation (23).

Sexual orientation and gender identity are inherently different and should be considered as such when assessing whether nondiscrimination or harassment policies provide protection to all members of the LGBT community. According to the Institute of Medicine, "sexual orientation" refers to a person's enduring pattern of or disposition to have sexual or romantic desires for, and relationships with, persons of the same sex or both sexes (8). "Gender identity" refers to a person's basic sense of being a man or boy, a woman or girl, or another gender. Gender identity may or may not correspond to a person's anatomical sex assigned at birth. The term "transgender" is now widely used to refer to a diverse group of persons who depart significantly from traditional gender norms (24). Persons who have a "marked difference" between their anatomical sex at birth and their expressed or experienced gender may be diagnosed with gender dysphoria, which is a diagnosis under the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (25).

Evidence shows that individuals with gender identity variants face increased discrimination, threats of violence, and stigma. The National Gay and Lesbian Task Force and the National Center for Transgender Equality conducted a national survey of transgender and gender-nonidentifying persons and found high rates of harassment (78%), physical assault (35%), and sexual violence (12%) (20). More than 90% of survey participants

reported harassment or discrimination in the workplace, and they experience double the rate of unemployment than the general population (20). Therefore, LGBT persons are more likely to lose their job or not be hired (26).

Employers have the option to include gender identity as part of their company's nondiscrimination or antiharassment policies even if their state does not, and many companies have chosen to include comprehensive protections policies. To reduce the potential for discrimination, harassment, and physical and emotional harm toward persons who are not covered by current protections, the medical community should include both sexual orientation and gender identity as part of any comprehensive nondiscrimination or antiharassment policy.

2. The American College of Physicians recommends that public and private health benefit plans include comprehensive transgender health care services and provide all covered services to transgender persons as they would all other beneficiaries.

The LGBT community is at increased risk for physical and emotional l

resulting from discrimination or harassment, and transgender persons may face greater inequalities in the health care system than the general population. Of note, 19% of transgender persons lack any type of health insurance (20). A handful of states have laws about insurance coverage for transgender health care, such as hormone replacement therapy or sexual reassignment surgery, which may be considered medically necessary as part of the patient's care. Eight states and the District of Columbia have

prohibitions on insurance exclusion of treatments for sex reassignment surgery (27).

The World Professional Association for Transgender Health has developed health care standards for transgender persons who have been diagnosed with gender dysphoria. The standards emphasize treatments that will achieve "lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment" and may or may not include modification to a person's gender expression or how this individual appears or presents physically to others (28). Research shows that when transgender persons receive individual, medically appropriate care, they have improved mental health, reduction in suicide rates, and lower health care costs overall because of fewer mental health–related and substance abuse–related costs (29). However, not all health plans cover all services associated with transgender health or consider such services medically necessary; some plans may issue blanket exclusions on transgender health care, not cover certain services for a transgender person as they would for nontransgender persons, or only cover the cost of gender reassignment surgery if certain conditions are met. For example, an insurance company may cover posthysterectomy estrogenic hormone replacement therapy for biological women but will not cover a similar type of hormone therapy for a postoperative male-to-female transgender patient. Many professional medical organizations, including the American Medical Association, American Psychological Association, American Psychiatric Association, American Congress of Obstetricians and Gynecologists, and

American Academy of Family Physicians, consider gender transition–related medical services medically necessary (30).

The decision to institute a hormone therapy regimen or pursue sexual reassignment surgery for transgender individuals is not taken lightly. Transgender patients and their health care team, which may include primary care physicians, endocrinologists, mental health professionals, and others, are in the best position to determine the most appropriate care plan unique to the patient's needs. Throughout the course of treatment, patients and their physicians or health care team should discuss available options and the evidence base for those treatments in which such evidence exists. It is especially important that transgender patients whose health care team has determined that treatment should include cross-sex hormone therapy or sexual reassignment surgery and postoperative hormone therapy be well-informed about the potential health risks associated with the long-term use of some hormonal replacement therapies before treatment.

Without insurance coverage, the cost of treatment for persons with gender dysphoria may be prohibitively expensive. The most extensive and exp sexual reassignment surgeries may cost tens of thousands of dollars; t does not include associated costs, such as counseling, hormone replacement therapy, copays, or aftercare. The high costs of treatment can result in persons who cannot access the type of care they need, which can increase their levels of stress and discomfort and lead to more serious health conditions. In 2014, the HHS lifted the blanket ban on Medicare coverage for gender reassignment surgery (31) and the federal government announced it

would no longer prohibit health plans offered on the Federal Employees Health Benefits Program from offering gender reassignment as part of the plan (27). Transgender health advocates are hopeful this will result in wider coverage for transgender care in private health plans.

The cost of including transgender health care in employee health benefits plans is minimal and is unlikely to raise costs significantly, if at all. A survey of employers offering transition-related health care in their health benefit plans found that two thirds of employers that provided information on actual costs of employee utilization of transition-related coverage reported 0 costs (32). This is the result of a very small portion of the population identifying as transgender and a smaller portion of that group having the most expensive type of gender reassignment surgery as part of their treatment. An analysis of the utilization of transgender health services over 6 years after transgender discrimination was prohibited in one California health plan found a utilization rate of 0.062 per 1000 covered persons (33). The inclusion of transgender-related health care services within a health plan may also result in an overall reduction of health care costs over time because patients are less likely to engage in self-destructive behaviors, such alcohol or substance abuse.

3. The definition of "family" should be inclusive of those who maintain an ongoing emotional relationship with a person, regardless of their legal or biological relationship.

The term "family" as it is seen in society is changing and no longer means married heterosexual parents with children. An analysis shows only 22% of

families fall into this category (34). Stepparents, single parents, grandparents, same-sex couples, or foster or adoptive parents all make up the changing face of U.S. families. Across the country, LGBT persons are raising children, and demographic data shows that 110 000 same-sex couples are raising as many as 170 000 biological, adopted, or foster children and 37% of LGBT adults have had a child (35). This modern concept of family is no longer dependent on parental status and does not only include adult heads of household with minor children. Same-sex couples and different-sex couples who do not have children may nevertheless have persons in their lives that they consider family.

Despite research that shows a growing trend toward acceptance of LGBT individuals and families (36), there is no widely used standard definition of family inclusive of the diverse nature of the family structure and definitions vary widely: They can differ from state to state, within the Internal Revenue Service for tax purposes, by employers to determine eligibility for health plans, and by hospitals for the purposes of visitation or medical decision making. If LGBT spouses or partners are not legally considered a family member, they are at risk for reduced access to health care and restrict on caregiving and decision making; further, they are at increased risk for health disparities, and their children may not be eligible for health coverage (34). Therefore, LGBT persons and families may already be at a financial disadvantage, with single LGBT parents 3 times more likely to live near the poverty line than their non-LGBT counterparts and LGBT families twice as likely to live near the poverty threshold (35). These financial disadvantages can translate into lack of access to medical care and poorer health outcomes

similar to those experienced by non-LGBT persons and their families who are uninsured or underinsured, in addition to the health disparities that are already reported among the LGBT community.

The Human Rights Campaign's definition of family for health care organizations, developed with multistakeholder input, is inclusive of same- and different-sex married couples and families and is an example of a broad, comprehensive definition of family that includes a person's biological, legal, and chosen family:

> Family means any person(s) who plays a significant role in an individual's life. This may include a person(s) not legally related to the individual. Members of "family" include spouses, domestic partners, and both different-sex and same-sex significant others. "Family" includes a minor patient's parents, regardless of the gender of either parent. (37)

A definition of family inclusive of all types of families, including the LGBT population, is not only fundamental to reducing the disparities and inequalities that exist within the health care system, but also important for the equal treatment of LGBT patients and their visitors in the hospital setting. Countless accounts show loved ones being denied the right to visit; assist in the medical decision-making process for their partner, minor, or child; or be updated on the condition of a patient because hospital visitation policy broadly prohibits those who are not recognized family members from access to the patient. These policies are discriminatory against LGBT patients, their visitors, and the millions of others who are considered family,

such as friends, neighbors, or nonrelative caregivers who can offer support to the patient.

4. The American College of Physicians encourages all hospitals and medical facilities to allow all patients to determine who may visit and who may to act on their behalf during their stay, regardless of their sexual orientation, gender identity, or marital status, and ensure visitation policies are consistent with the Centers for Medicare & Medicaid Services Conditions of Participation and The Joint Commission standards for Medicare-funded hospitals and critical-access hospitals.

When persons or their loved ones need emergency care or extended inpatient stays in the hospital, they do not often immediately think about access to visitors or hospital visitation policies, the ability to assist in medical decision making, or their legal rights as patients or visitors. Hospital visitation policies are not always clear or consistent about who can visit or make medical decisions for a patient if they become incapacitated or cannot do so themselves. The absence or limited access of loved ones can cause uncertainty and anxiety for the patient. In contrast, the involvement c family and outside support systems can improve health outcomes, suc management of chronic illness and continuity of care (38).

A highly publicized incident of LGBT families facing discrimination and being denied hospital visitation occurred in Florida in 2007. A woman on vacation with her family had an aneurysm and was taken to the hospital. Her same-sex partner and their children were denied the right to see her or receive updates on her condition, and she eventually slipped into a coma

and died (39). In response to this incident, President Obama issued a presidential memorandum recommending that the HHS review and update hospital visitation policies for hospitals participating in Medicare or Medicaid and critical-access hospitals to prohibit discrimination based on such factors as sexual orientation or gender identity (40).

Throughout the rulemaking process, the HHS revised the Medicare Conditions of Participation to require that all hospitals explain to all patients their right to choose who may visit during an inpatient stay, including same-sex spouses, domestic partners, and other visitors, and the patients' right to choose a person to act on their behalf. The Joint Commission, the nation's largest organization for hospital accreditation, also updated its standards to include equal visitation for LGBT patients and visitors (41). As a result of these updated policies, most hospitals and long-term care facilities are required to allow equal visitation for LGBT persons and their families.

The presidential memorandum also recommended that the HHS instruct hospitals to disclose to their patients that patients have a right to designate a representative to make medical decisions on their behalf if they cann make those decisions themselves. The revised Conditions of Participa emphasized that hospitals "should give deference to patients' wishes about their representatives, whether expressed in writing, orally, or through other evidence, unless prohibited by state law" (42). With piecemeal regulations and policies governing the legal rights of LGBT persons and their families, some same-sex spouses or domestic partners choose to prepare advance directives, such as durable powers of attorney and health care proxies, in an

effort to ensure their access to family members and their ability to exert their right to medical decision making if necessary.

5. The American College of Physicians supports civil marriage rights for same-sex couples. The denial of such rights can have a negative impact on the physical and mental health of these persons and contribute to ongoing stigma and discrimination for LGBT persons and their families.

The health and financial benefits of marriage for different-sex couples are widely reported, and contemporary research supports similar benefits in same-sex marriage. On the other hand, denial of marriage rights for LGBT persons may lead to mental and physical health problems. Health benefits associated with same-sex marriage result from improved psychological health and a reinforced social environment with community support (43). Research suggests that being in a legally recognized same-sex marriage diminishes mental health differentials between LGBT and heterosexual persons (5). A comparison study on the utilization of public health services by gay and bisexual men before and after Massachusetts legalized same-sex marriage found a reduction in the number of visits for health problen mental health services. The study noted a 13% reduction in visits over after the legalization of same-sex marriage (44).

In contrast, denial of such rights can result in ongoing physical and psychological health issues. Thus, LGBT persons encountering negative societal attitudes and discrimination often internalize stressors and have poor health unseen to those around them; further, these stressors can lead to self-destructive behaviors (43). A study of LGBT individuals living in states

with a same-sex marriage ban found increases in general anxiety, mood disorders, and alcohol abuse (45). The denial of marriage rights to LGBT persons has also been found to reinforce stigmas of the LGBT population that may undermine health and social factors, which can affect young adults (46). The American Medical Association's broad policy supporting civil rights for LGBT persons acknowledges that denial of civil marriage rights can be harmful to LGBT persons and their families and contribute to ongoing health disparities (47).

Since 2003, the overall support for marriage equality has increased. The shift in attitudes toward acceptance of same-sex marriage has broad positive implications for the future of U.S. civil marriage rights. A 2013 survey by the Pew Research Center revealed that nearly half of U.S. adults expressed support for same-sex marriage. Of note, millennials (those born after 1980) showed the highest rate of support for same-sex marriage rights at 70%. Not only has overall opinion changed, but individually, 1 in 7 respondents reported they had changed their minds from opposing to supporting same-sex marriage. The Pew survey found that 32% of respondents changed their mind because they knew someone who identified as lesbian or gay (36

The legal landscape is also shifting in favor of inclusive civil marriage rights for same-sex couples. The American Bar Association has adopted a resolution recognizing "that lesbian, gay, bisexual and transgender (LGBT) persons have a human right to be free from discrimination, threats and violence based on their LGBT status and condemns all laws, regulations and rules or practices that discriminate on the basis that an individual is [an]

LGBT person" (48). In June 2013, the U.S. Supreme Court struck down a provision of the Defense of Marriage Act that defined marriage as a "union between a man and a woman." The decision allowed legally married same-sex couples to have the same federal benefits offered to heterosexual couples (49). Currently more than half of the states and the District of Columbia allow same-sex marriage, and several states have rulings in favor of same-sex marriage that are stayed pending legal appeals (50). In April 2015, the Supreme Court heard oral arguments in a case involving same-sex marriage bans in Michigan, Ohio, Kentucky, and Tennessee; this will ultimately determine the constitutionality of same-sex marriage bans, including whether states would be required to recognize same-sex marriages performed legally out of state (51).

6. The American College of Physicians supports data collection and research into understanding the demographics of the LGBT population, potential causes of LGBT health disparities, and best practices in reducing these disparities.

Previous efforts to understand the LGBT population by including sexu orientation or gender identity in health surveys and data collection ar good first step, but there is a long way to go to understand the unique health needs of all members of the LGBT community. Understanding the demographics of the persons who make up this community is a key first step to understanding how environmental and social determinants may contribute to the health disparities they face. Overwhelming evidence shows that racial and ethnic minorities experience greater health disparities than

the general population. In 2010, ACP published an updated position paper on racial and ethnic disparities in health care, which identified various statistics on health disparities in racial and ethnic minority groups, such as higher levels of uninsured Hispanics than white persons (34% vs. 13%) and lower rates of medication adherence in minority Medicare beneficiaries diagnosed with dementia (52). Persons who are part of both the LGBT community and a racial or ethnic minority group may face the highest levels of disparities. For example, data show that 30% of African American adults who identify as lesbian, gay, or bisexual are likely to delay getting a prescription compared with 19% of African American heterosexual adults (26).

Transgender persons may also face certain increased risk factors that can affect their health that are not included when discussing the LGBT population as a whole, which creates research gaps with the LGBT community. A survey study of transgender persons shows elevated reports of harassment, physical assault, and sexual violence (20). In addition, transgender persons are more likely to face discrimination in education, employment, housing, and public accommodations than other sexual, racial, or ethnic minority groups. The lack of and unfamiliarity with research focused on the physical health issues of transgender persons, such as hormone replacement therapy and cancer risk, limit the understanding or development of best practices that could reduce the disparities felt by this population. The dearth of such research is detrimental to physicians' understanding of issues unique to transgender patients and reduces their ability to care for these patients.

Data that have been gathered in the relatively short time since the inclusion of sexual orientation, gender identity, and same-sex marital status have revealed information that can be used to create tailored plans to decrease health disparities in in the LGBT community. For example, in 2009 the California Health Interview Survey collected information on certain health indicators and included sexual orientation along with racial and minority status. The survey found a higher rate of uninsured lesbian, gay, or bisexual Latino adults in the state than their African American counterparts (36% vs. 14%) (20).

In addition to obtaining information from population surveys, including gender identity and sexual orientation as a component of a patient's medical record (paper or electronic) may help a physician to better understand an LGBT patient's needs and provide more comprehensive care. This can be particularly useful in the care of transgender persons, whose gender identity and gender expression may differ from their sex assigned at birth and are not in line with the standard sex template on many forms. Including this information—especially in electronic health records that can standardize information, such as anatomy present and the preferred name/pronou can create a more comfortable experience for the patient and keep the physician up to date on the patient's transition history, if applicable (53). If a physician uses paper medical records, the patient's chart should be flagged using an indicator, such as a sticker, to alert staff to use the preferred name and pronoun of the patient (54).

7. Medical schools, residency programs, and continuing medical education programs should incorporate LGBT health issues into their curricula. The College supports programs that would help recruit LGBT persons into the practice of medicine and programs that offer support to LGBT medical students, residents, and practicing physicians.

Establishing understanding, trust, and communication between a physician and a patient is key to an ongoing and beneficial physician–patient relationship. However, reported instances of physician bias or denial of care to LGBT patients may influence patients to withhold information on their sexual orientation, gender identity, or medical conditions that could help the physician have a better understanding of the potential health needs of their patients. Physicians can play an integral role in helping an LGBT patient navigate through the medical system by providing respectful, culturally, and clinically competent care that underscores the overall health of the patient. In an article published in *The New England Journal of Medicine,* Makadon noted how physicians can create a welcoming and inclusive environment to LGBT patients:

> [G]uidelines for clinical practice can be very simple: ask the appropri[illegible] questions and be open and nonjudgmental about the answers. Few patients expect their providers to be experts on all aspects of gay and lesbian life. But it is important that providers inquire about life situations, be concerned about family and other important relationships, understand support systems, and make appropriate referrals for counseling and support when necessary. (55)

Providing clinically and culturally competent care for transgender persons in the primary care setting may present a challenge to physicians who are not knowledgeable about transgender health. Transgender persons have reported encounters with physicians who are unaware of how to approach treatment of a transgender person, and half of transgender patients reported having to "teach" their physician about transgender health (20). The National Transgender Survey found that 19% of participants had been denied medical care because of their transgender status (20). Resources for physicians on how to approach the treatment of transgender patients should emphasize respecting the patient's gender identity while providing prevention, treatment, and screening to the anatomy that is present (56).

To better understand the unique health needs of the LGBT community, physicians and medical professionals must develop a knowledge base in cultural and clinical competency and understand the factors that affect LGBT health; this should begin in the medical school setting and continue during practice. Assessment of LGBT-related content at medical schools found a median of 5 hours spent on LGBT-related issues over the course of the curriculum (57). Exposure to members of the LGBT population in medical school has been shown to increase the likelihood that a physician will take a more comprehensive patient history, have a better understanding of LGBT health issues, and have a more positive attitude toward LGBT patients (58). Studies show that undergraduate students pursuing a career in medicine are receptive to incorporating LGBT-related issues into their education and agree that it applies to their future work (59). The College recognizes the importance of incorporating LGBT health into the medical

school curriculum and publishes a comprehensive medical textbook on LGBT health, *The Fenway Guide to Lesbian, Gay, Bisexual, and Transgender Health, 2nd Edition* (60).

In November 2014, the Association of American Medical Colleges Advisory Committee on Sexual Orientation, Gender Identity, and Sex Development released a comprehensive report recommending strategies on how to implement changes in academic medical institutions to better address the needs of LGBT patients; further, the committee identified challenges and barriers to carrying out these changes. The report recognizes 3 methods of integrating LGBT health into the medical school curricula: full curriculum revision, the addition of a required class, or LGBT health study as a part of elective materials. The report also identifies barriers to curricular changes, including but not limited to a lack of material that has been shown to be effective, reluctance of faculty and staff to teach the new material, and a shortage of institutional time that would permit teachers to participate in continuing education on the topic (61).

For some LGBT persons interested in pursuing careers in medicine, th continues to be an underlying concern that their sexual orientation or gender identity may affect their selection into a medical school or residency program and acceptance by their peers. In 2012, Dr. Mark Schuster published his personal story about being gay in medicine starting in the 1980s when he entered medical school, through residency, and into practice. In his article, he spoke of a former attending physician he worked under who acted as an advisor and had indicated he would offer him a

recommendation for residency, only to find this physician later renege on that offer after Dr. Schuster shared that he was gay (62). Little research has been done on the recruitment of LGBT physicians into the practice of medicine or how disclosing sexual orientation may affect training. One survey measuring the perceptions and attitudes toward sexual orientation during training found that 30% of respondents did not reveal their sexual orientation when applying for residency positions for fear of rejection (63).

Academic medical institutions can make efforts to create a welcoming and inclusive environment for students and faculty. The University of California, San Francisco, LGBT Resource Center developed a checklist for medical schools to assess LGBT curriculum, admissions, and the working environment within their institution. The checklist includes inclusive application procedures, measurement of retention of LGBT students, and efforts and resources dedicated to student well-being (64). In a 2013 white paper, the Gay and Lesbian Medical Association made several recommendations to support an LGBT-inclusive climate at health professional schools in such areas as institutional equality, transgender services and support, diversity initiatives, admissions, staff and facult recruitment and retention, staff and faculty training, and other areas that underscore simple yet thoughtful ways to create an accepting environment for LGBT students, faculty, and employees (65). Tools such as these can assist in recruiting and retaining LGBT physicians.

8. The College opposes the use of "conversion," "reorientation," or "reparative' therapy for the treatment of LGBT persons.

Since 1973, the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* has not considered homosexuality an illness (66). All major medical and mental health organizations do not consider homosexuality as an illness but as a variation of human sexuality, and they denounce the practice of reparative therapy for treatment of LGBT persons (67). The core basis for "conversion," "reorientation," or "reparative" therapy, which is generally defined as therapy aiming at changing the sexual orientation of lesbian women and gay men, is mostly based on religious or moral objections to homosexuality or the belief that a homosexual person can be "cured" of their presumed illness.

In 2007, the American Psychological Association conducted a literature review of 83 studies on the efficacy of efforts to change sexual orientation. It found serious flaws in the research methods of most of the studies and identified only 1 study that met research standards for establishing safety or efficacy of conversion therapy and also compared persons who received a treatment with those who did not. In that study, intervention had no effect on the rates of same-sex behavior, so it is widely believed that there is no scientific evidence to support the use of reparative therapy (68). The I PDF Help American Health Organization, the regional office for the Americas of the larger World Health Organization, also supports the position that there is no medical basis for reparative therapy and that the practice may pose a threat to the overall health and well-being of an individual (69). Dr. Robert Spitzer, the author of a 2003 research study often cited by supporters of the reparative therapy movement to purport that persons may choose to change their sexual orientation, has denounced the research as flawed and

apologized to the LGBT community in a letter for misinterpretations or misrepresentations that arose from the study (70).

Available research does not support the use of reparative therapy as an effective method in the treatment of LGBT persons. Evidence shows that the practice may actually cause emotional or physical harm to LGBT individuals, particularly adolescents or young persons. Research done at San Francisco State University on the effect of familial attitudes and acceptance found that LGBT youth who were rejected by their families because of their identity were more likely than their LGBT peers who were not rejected or only mildly rejected by their families to attempt suicide, report high levels of depression, use illegal drugs, or be at risk for HIV and sexually transmitted illnesses (71). The American Psychological Association literature review found that reparative therapy is associated with the loss of sexual feeling, depression, anxiety, and suicidality (68).

States have delved into the debate over the use of reparative therapy for minor children given the potential for harm. California; New Jersey; and Washington, DC, have enacted laws banning the practice. Several othe legislatures, such as those in Washington state, Massachusetts, New Y and Oregon, have introduced or passed legislation through one chamber but failed to pass the bill into law (72). The New Jersey law was challenged on the grounds that the ban limited the free speech of mental health professionals, but the law was upheld by the Third U.S. Circuit Court of Appeals (73). In May 2015, the U.S. Supreme Court declined to hear a challenge to the law (74).

9. The American College of Physicians supports continued reviews of blood donation deferral policies for men who have sex with men. The College supports evidence-based deferral policies that take into account a comprehensive assessment of the risk level of all individuals seeking to donate, which may result in varying deferral periods or a lengthened or permanent deferral on blood donation.

Persons who are considered at increased or possible risk for certain infectious diseases, such as intravenous drug users, recipients of animal organs or tissues, and those who have traveled or lived abroad in certain countries, are prohibited by the U.S Food and Drug Administration from donating blood (75). Since the early 1980s, the policy has also included men who have sex with men (MSM) since 1977. This lifetime deferral of blood donation for MSM was instituted during a time when the incidence of HIV and AIDS increased to epidemic levels in the United States, and the disease and how it was transmitted were largely misunderstood by the scientific community. In the following years, concerted efforts by the medical community, patient advocates, and government officials and agencies resulted in advancements in blood screening technology and treatmei the virus. However, during that time of uncertainty, policies were implemented to balance the risk for contaminating the blood supply with what was known about the transmissibility of the disease.

Several medical organizations support deferral policy reform based on available scientific evidence and testing capabilities. The American Medical Association policy on blood donor criteria supports, "the use of rational,

scientifically based blood and tissue donation deferral periods that are fairly and consistently applied to donors according to their level of risk" (76). The American Association of Blood Banks, America's Blood Centers, and the American Red Cross have long advocated for a modification to deferral criteria to be "made comparable with criteria for other groups at increased risk for sexual transmission of transfusion-transmitted infections" and recommend a 12-month deferral for men who have had sex with another man since 1977, which is in line with deferral criteria for others who have exhibited high-risk behavior (77). The eligibility standards and policies on the donation of tissues or tissue products (5-year deferral since last sexual contact) (78) and vascular organs (risk assessed individually, disclosed to transplant team, and consent required) (79) by MSM also reflect a measured assessment of disease transmission risk to donor recipients.

Many countries, including the United Kingdom, Canada, Finland, Australia, and New Zealand, have successfully instituted deferral periods ranging from 12 months to 5 years in lieu of a lifetime ban on blood donation by MSM without measurable increased risk to the blood supply. A study of the risk of blood donations from MSM after the implementation of shorter defer periods in England and Wales 12 months after their last sexual encounter found only a marginal increase in the risk for transfusion-transmitted HIV (80). Australia changed the deferral policy for MSM from 5 years to 12 months over 1996 to 2000. A study that compared the prevalence of HIV among blood donors from the 5-year deferral period compared with the 12-month deferral period found no evidence that the 12-month period increased risk for HIV in recipients (81).

In late 2014, the HHS Advisory Committee on Blood and Tissue Safety and Availability voted in favor of recommending a 1-year deferral policy for MSM and increased surveillance of the blood supply. The U.S Food and Drug Administration announced it would be updating its policy on blood donation from MSM after considering recommendations made by the HHS, reviews of available scientific evidence, and recommendations from its own Blood Products Advisory Committee. The policy about indefinite deferral on blood donation from MSM is being updated to a 1-year deferral period from the last sexual contact, and the U.S. Food and Drug Administration will issue draft guidance on the policy change in 2015. In addition, the agency announced it has already taken steps to implement a national blood surveillance system to monitor what, if any, effects the new policy has on the nation's blood supply (82). Lifting the lifetime ban on blood donation by MSM is an important first step toward creating equity among those wishing to donate blood. The U.S Food and Drug Administration should continue to monitor the effects of a 1-year deferral and update its policy as information and data are gathered through surveillance to make further strides toward policies that assess donor eligibility on the basis of scientific data and individual risk fact such as the length of time since a high-risk behavior has occurred, typ sex that occurred, number of partners during a period of time, or a combination of factors (83).

Comments

6 Comments

Rex Moss, MD • Dallas, Texas • 27 May 2015

Comment

To the Editor: "ACP Takes a Stand against Health Disparities Affecting LGBT Individuals New policy paper aims to ensure high-quality health care for all" This is very disappointing. I love the Annals and very much enjoyed and learned a great deal at several ACP conferences. But I left the AMA as it stood up for abortion rights and I resign from ACP, now as you stand up for a number of foolish policies, more oriented to political ideology than medical care or logic. Your new policy states: For instance, health data related to marital status show a benefit for married heterosexual couples, but the committee found that the fact that LGBT partners and families live without the same protections and recognition appears to increase their risk for depression and other poor health outcomes. Does it really follow that societys protections and encouragement of heterosexual marriage has the power to prevent depression and poor health outcomes? Is it possible that heterosexual marriage is our natural state and that our minds and bodies work best when used in the appropriate way? ACP's Health and Public Policy Committee recommends: Including comprehensive transgender heath care services in public and private health benefit plans. You recommend public and private insurance pay for sexual reassignment surgery. Is there data of benefit? Perhaps a reduction in mortality, disability or morbidity? Do those who have sexual reassignment surgery live longer or commit suicide less often? Why should anyone outside the person determined to change their body pay for it? Expanding the definition of "family" to include all who maintain an emotional connection to the patient, regardless of legal or biological relationship. Do you have data that children raised in families other than with their biological parents do better or as well? In absence of data, would it not be logical to encourage keeping biological parents together or at least permit states to make the judgment for themselves how to regulate/ encourage marriage? (as opposed to having courts take over as the "determiners of all things not established by study or fact") Opposing the use of "conversion," "reorientation" or "reparative" therapies in the treatment of LGBT individuals. Do you have data that such therapies are harmful? If a deeply disturbed person is confused about his/ her sexual identity and wants to focus attention on the opposite sex and seeks counseling to do so, is that wrong or harmful? LGBT individuals have a high incidence of depression and suicide. Do you wish to oppose possible the may help if you have no alternative therapy that will help? Political trends come and go. Slavery, racial marriage, cocaine, smoking, breast self-exam, and epinephrine have been normal, encouraged, discouraged and tossed away. Allowing a popular political idea to lead to policy changes not supported by data, that costs a great deal of money and is very disruptive to a current healthy institution: heterosexual marriage is a poor plan. ACP think before you act. When you act wrongly think again and change. Good-bye, Rex Moss MD

Hilary Daniel, BS, Renee Butkus, BA • American College of Physicians • 11 September 2015

Response to Comments Made by Drs. Lacy and Ng

The two comments submitted by Drs. Lacy and Ng speak to the diversity of ACP's 143,000 internal medicine physicians and student members. ACP advocates on a wide variety of topics and the College

recognizes that not all ACP members will agree with our positions. The need to address the unique needs of the LGBT persons and their families is a based on ACP's long standing commitment to advocate for those being negatively affected by health care disparities. Ignoring or glossing over some topics that affect health because they are controversial would be inconsistent with ACP's mission "To enhance the quality and effectiveness of health care by fostering excellence and professionalism in the practice of medicine" including "to advocate responsible positions on individual health and on public policy relating to health care for the benefit of the public, our patients, the medical profession, and our members."

We appreciate Dr. Ng's support for our paper. As the paper was being developed, policies concerning same sex marriage, blood donation by men who have sex with men, and coverage for transgender health care services were undergoing change. The College recognizes the need for continued review of issues relating to LGBT health.

Dr. Lacy takes issue with our call for a more inclusive definition of family. As our paper points out, it's estimated that only 22% of U.S. families consist of married heterosexual parents with their own biological children. A modern definition of family that is inclusive of all types of families, including the LGBT population, is fundamental to reducing the disparities and inequalities that exist within the health care system and to equal treatment of LGBT patients and their visitors in the hospital setting. Our opposition to "therapy" to change the sexual orientation of an individual is based on the science that shows that sexual and gender orientation are not disability or disorder in need of treatment or cure, and that such "therapies" may be harmful to patients receiving them.

Hilary Daniel, BS
Renee Butkus, BA

1. Movement Advancement Project, Family Equality Council, Center for American Progress. All children matter: how legal and social inequalities hurt LGBT families: condensed version. Denver: Movement Advancement Project; 2011. Accessed at www.lgbtmap.org/file/all-children-matter-condensed-report.pdf on 11 February 2015

2. American Psychological Association Task Force. Report of the American Psychological Association Task Force on appropriate therapeutic responses to sexual orientation. Washington, DC: American Psychological Association; 2009. Accessed atwww.apa.org/pi/lgbt/resources/therapeutic-response.pdf on 11 February 2015.

Paul J Hudson, MD, MPH, FACP • SIM • 22 June 2015

The policy on LGBT reaches beyond evidence

Dear friends at ACP,

I too am disappointed at the lack of evidence for this very broad set of policy changes, which not only goes beyond the evidence but becomes an agent for changing institutions that have stood the test of millenia. For example, defining a family as something other than biological is a step in the wrong direction. The evidence shows that children need a father and they need a mother; this has something to do with biology, and cannot be socially constructed.

Please reconsider your over-reach and return to medical evidence.

Thank you,

Paul Hudson, MD, FACP, MPH

Mark D Lacy • Lubbock, Tx • 3 June 2015

Access for All but losing our way in the Process

To advocate for the elimination of health care disparities among Lesbian, Gay, Bisexual, and Transgender (LGBT) persons is a worthy objective not just for these populations but all patients facing obstacles to quality care. Sadly, the American College of Physicians Position Paper published May 12, 2015 addressing LGBT Health Disparities goes beyond advocating health care access by promoting a damaging sociopolitical ideology. The Paper re-defines the meaning of family, marriage, and calls for denying LGBT persons choices in behavioral health services.

While alleging the Position Paper was the product following review of "numerous studies, reports, and surveys on LGBT health care and related health policy" many cited references are based on research neither well executed nor widely corroborated. Further, it appears the reviewers fail to account for sound, copious evidence contradicting the cited sources.

To redefine family as "those who maintain an ongoing emotional relationship with a person, regardless of their legal or biological relationship" is to deny the reality of paternity and maternity, both integr most wholesome child-rearing environments. Dads contribute to the growth and development children much differently than moms do. Asserting family as whatever one wants it to be is to succumb to the solipsistic notion that the self is the final arbiter of reality, to substitute the real and immutable childhood need for mothers and fathers with the sexual-romantic mutable desires of adults. Will the next Position Paper call for endorsing the aims of the North American Man Boy Love Association or Peter Singer's call for granting civil rights to primates? Marriage is, and for millennia has been, rooted in the male-female complementarity that makes sexual reproduction possible and child-rearing wholistic. What is at play in this Statement are very imprudent mental maneuvres, "The moment you step into the world of facts, you step into a world of limits. You can free things from alien or accidental laws, but not from the laws of their own nature. You may, if you like, free a tiger from his bars, but not free him from his stripes. Do not free a camel from his hump; you may be freeing him from being a camel". In "re-inventing" family and the meaning of marriage is to engage in the same sort of casuistry.

With regard to the American Psychological Association (APA) being invoked as the authority to repudiate psychotherapy for unwanted sexual behaviours recall the APA Task Force unequivocally posits "Same-sex sexual attractions, behavior, and orientations per se are normal and positive variants of human sexuality." If that is the a priori assertion, can objective assessment of "sexual orientation change efforts" (SOCE) be realistically expected? Probably not. To satisfactorily debunk SOCE entails more than citing the APA. In the meantime, persons who opt for SOCE should be given the prerogative in the same way, for example, the transgender person is offered high- dose estrogens in spite of the increased risk of thrombosis.

The LGBT Position Papers unfortunately makes the Annals a mouthpiece for the post-modern notion that we can write our own narrative and call it true, regardless of the facts. Once the Annals becomes a purveyor of ideology and asserts a world view which doesn't comport with facts, it is no longer a reliable source of guidance for physicians.

Mark D Lacy, MD, MA, FACP

Henry Ng, MD, MPH, FAAP, FACP • **MetroHealth Medical Center, Case Western Reserve** University School of Medicine • 2 June 2015

In support of the American College of Physician's Policy Position Paper on Lesbian, Gay, Bisexual and Transgender Health Disparities

As an internist-pediatrician who has worked in LGBT health care for the last decade, I am invigorated that the American College of Physicians (ACP), one of my professional homes, has developed a set of LGBT health focused policy statements. From my perspective as an LGBT health advocate and clinical director of a hospital-based LGBT health service line, these policy statements were sorely needed to assist internists around the US and internationally to improve the health experiences and outcomes, and ultimately eliminate health disparities of LGBT patients. I am proud to see the American College of Physicians join a growing group of professional organizations with LGBT-inclusive policies or mi: statements including the American Academy of Family Physicians, the American Medical Assoc American Academy of Pediatrics, the American Academy of Physician Assistants, the American Academy of Nursing , the American College of Obstetrics and Gynecology, the American Psychological Association, the American Psychiatric Association, GLMA: Health Professionals Advancing LGBT Equality and others.

The nine policy statements developed by Daniel et al which compose the ACP's policy position paper are both bold and broad in their recommendations. Many of the recommendations are timely and remind internists to keep in-step with guidelines set forth by accrediting bodies such as the Joint Commission and the Centers for Medicare & Medicaid Services. This is especially important as more and more LGBT Americans enroll in health insurance through the Affordable Care Act and begin to routinely access the US health care system. However, the ACP's policy statements will only be as useful as they are complete and current and must be considered a living document with the capacity to grow and change based on

the best available data and knowledge regarding LGBT health. I encourage the members of the ACP Health and Public Policy Committee to revisit the policy statement on regular intervals for updates to fill the many gaps in our knowledge about LGBT health.

Future revisions of the policy statement should pay careful attention to details not necessarily called out in the current policy's executive summary. For example, policy statement 2 calls for the ACP to "recommend that all public and private health benefit plans include comprehensive transgender care services and provide all covered services to transgender persons as they would all other beneficiaries."1 The authors continue to describe the impact of arbitrary or blanket exclusions for transgender health services in their example of hysterectomy coverage for a cisgender patient, but exclusion for a transgender patient. Yet in the policy statement, the ACP falls short of stating that such hormonal and/or surgical care is medically necessary. Moreover, the term "comprehensive" is an unclear term in this context. For optimal health outcomes, comprehensive care would need to be inclusive of all medically necessary care including primary care, mental health care, transgender hormonal care, transgender-related and non-transgender-related surgical care, and HIV care.

The policy authors write in policy statement 6 that the ACP supports data collection and research into the understanding the demographics of the LGBT population, potential causes of LGBT health disparities, and best practices in reducing these disparities. This statement particularly important as there exist few nationally representative datasets describing LGBT population health. In fact, Healthy People 2020 still prioritizes collecting data on LGB and Transgender populations in their four objectives.2 To date, only the 2013 National Health Interview Survey has collected nationally representative data on lesbian, gay and bisexual people.3 Federal nationally representative surveys continue to exclude transgender respondents by not collecting gender identity/expression as part of the respondents' demographic variables. Unfortunately, the majority of electronic health records also fail to provide fields for collection of sexual orientation and gender identity (SOGI) data. Cahill et al found that integrating SOGI data collection into the meaningful use requirements was both acceptable to diverse samples of patients, including heterosexuals, and feasible.4 The ACP should consider supporting inclusion of SOGI data collection in Meaningful Use as another strategy to improve LGBT health data collection.

Daniel et al write in position statement 7 that "Medical Schools, residency programs, and continue medical education programs should incorporate LGBT health issues into their curriculum. The College supports programs that would help recruit LGBT persons into the practice of medicine and programs that offer support to other LGBT medical students, residents, and practicing physicians."1 Creating the next generation of culturally and clinically competent health professionals and internists is central to improving LGBT health. Nationally, few health organizations and hospitals have actively implemented comprehensive programs to create LGBT affirming environments, educate health professionals and staff on LGBT health, or create sustainable supportive infrastructure. There continues to be a great need for LGBT safe space programs, LGBT 101 cultural competency education, and inclusion of LGBT topics in academic discourse and mentorship. Homophobia, transphobia, few visible LGBT health professional

mentors and lack of institutional support for LGBT health scholarship serve as barriers to growing a cadre of academic internists adequately prepared to care for LGBT populations.5 The College can continue to champion LGBT health by supporting inclusion of LGBT health content in internal medicine certification examination questions, internal medicine in-training examination questions and promotion of additional LGBT health education resources like Fenway Guide to Lesbian, Gay, Bisexual, and Transgender Health.6

Finally, the ACP should consider adding an additional statement which addresses and acknowledges the intersectionality of our patients' identities as noted by IOM report.7 Sexual orientation and gender identity/expression do not exist within a vacuum and are part of the multidimensionality of our identities as people.

References:

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Disclosures: I am the President of GLMA: Health Professionals Advancing LGBT Equality

Hilary Daniel • American College of Physicians • 13 May 2015

FDA Releases Draft Guidance on Blood Donation by MSM

On Tuesday May 12, 2015 the Food and Drug Administration released the document "Revised Recommendations for Reducing the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products: Draft Guidance for Industry." The proposed recommendations would replace the lifetime deferral period on blood donation by men who have sex with men (MSM) with a 12-month deferral period from most recent sexual contact. The FDA is accepting public comment on the guidance for 60 days.

PREVIOUS ARTICLE NEXT ARTICLE

TAB 176-2

James L. Madara, MD
CEO, EXECUTIVE VICE PRESIDENT
jamo.madara@ama-assn.org

Pl. Trial Ex. 042

April 26, 2021

Mr. Bill McBride
Executive Director
National Governors Association
Hall of States
444 North Capitol Street NW, Suite 267
Washington, DC 20001

Dear Mr. McBride:

On behalf of the American Medical Association (AMA) and our physician and medical student members, I write to urge the National Governors Association (NGA) and its member governors to oppose state legislation that would prohibit the provision of medically necessary gender transition-related care to minor patients. We believe this legislation represents a dangerous governmental intrusion into the practice of medicine and will be detrimental to the health of transgender children across the country.

Empirical evidence has demonstrated that trans and non-binary gender identities are normal variations of human identity and expression. For gender diverse individuals, standards of care and accepted medically necessary services that affirm gender or treat gender dysphoria may include mental health counseling, non-medical social transition, gender-affirming hormone therapy, and/or gender-affirming surgeries. Clinical guidelines established by professional medical organizations for the care of minors promote these supportive interventions based on the current evidence and that enable young people to explore and live the gender that they choose. Every major medical association in the United States recognizes the medical necessity of transition-related care for improving the physical and mental health of transgender people.

Arkansas' recently enacted SAFE Act and similar bills pending in several other states would insert the government into clinical decision-making and force physicians to disregard clinical guidelines. Decisions about medical care belong within the sanctity of the patient-physician relationship. As with all medical interventions, physicians are guided by their ethical duty to act in the best interest of their patients and must tailor recommendations about specific interventions and the timing of those interventions to each patient's unique circumstances. Such decisions must be sensitive to the child's clinical situation, nurture the child's short and long-term development, and balance the need to preserve the child's opportunity to make important life choices autonomously in the future. We believe it is inappropriate and harmful for any state to legislatively dictate that certain transition-related services are never appropriate and limit the range of options physicians and families may consider when making decisions for pediatric patients.

In addition, evidence has demonstrated that forgoing gender-affirming care can have tragic consequences. Transgender individuals are up to three times more likely than the general population to report or be diagnosed with mental health disorders, with as many as 41.5 percent reporting at least one diagnosis of a mental health or substance use disorder.[1] The increased prevalence of these mental health conditions is widely thought to be a consequence of minority stress, the chronic stress from coping with societal

[1] Sari Reisner, et al., *Psychiatric Diagnoses and Comorbidities in a Diverse, Multicity Cohort of Young Transgender Women: Baseline Findings from Project LifeSkills*, 170 J. Am. Med. Ass'n Pediatrics 5, 481–86 (May 2016).

stigma, and discrimination because of one's gender identity and expression. Because of this stress, transgender minors also face a significantly heightened risk of suicide.

Transgender children, like all children, have the best chance to thrive when they are supported and can obtain the health care they need. Studies suggest that improved body satisfaction and self-esteem following the receipt of gender-affirming care is protective against poorer mental health and supports healthy relationships with parents and peers.[2] Studies also demonstrate dramatic reductions in suicide attempts, as well as decreased rates of depression and anxiety.[3] Other studies show that a majority of patients report improved mental health and function after receipt of gender-affirming care. Medically supervised care can also reduce rates of harmful self-prescribed hormones, use of construction-grade silicone injections, and other interventions that have potential to cause adverse events.[4]

It is imperative that transgender minors be given the opportunity to explore their gender identity under the safe and supportive care of a physician. Arkansas's law and others like it would forestall that opportunity. This is a dangerous intrusion into the practice of medicine and we strongly urge the NGA and its member governors to oppose these troubling bills.

We thank you for the opportunity to express our views on this important issue. Please contact Annalia Michelman, JD, Senior Legislative Attorney, AMA Advocacy Resource Center at annalia.michelman@ama-assn.org to discuss this issue further and how our two organizations can work together.

Sincerely,

James L. Madara, MD

[2] Ashli Owen-Smith, et al., *Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals*, 15 J Sexual Med 4, 591-600 (Apr. 2018); Michelle Marie Johns, et al., *Protective Factors Among Transgender and Gender Variant Youth: A Systematic Review by Socioecological Level*, 39 J Primary Prevention 3, 263-301 (Jun. 2018).

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TAB 176-3

ISSUE BRIEF

Health insurance coverage for gender-affirming care of transgender patients

Background

Gender identity refers to an individual's concept of self as male, female, a blend of both or neither. Approximately 1.4 million adults and 150,000 youth ages 13 to 17 in the United States identify as transgender, meaning those individuals' gender identity and/or expression is different from cultural expectations based on the sex they were assigned at birth.[1] Individuals may also identify as gender expansive, meaning they identify with neither traditional binary gender role nor a single gender narrative or experience.[2] In this document, the term transgender is used inclusive of patients with transgender or gender expansive identities.

Many but not all transgender people experience gender dysphoria, a medical condition defined by the American Psychiatric Association as a "conflict between a person's physical or assigned gender and the gender with which he/she/they identify."[3] Standards of care and accepted medically necessary services that affirm gender or treat gender dysphoria may include but are not limited to mental health counseling, non-medical social transition, gender-affirming hormone therapy, and/or gender-affirming surgeries.[4] Every major medical association in the United States recognizes the medical necessity of transition-related care for improving the physical and mental health of transgender people and has called for health insurance coverage for treatment of gender dysphoria.[5]

Barriers to care

As a population, transgender individuals are frequently subject to bias and discrimination in many aspects of their lives, including the provision of health care. The transgender population is less likely to be insured than both the lesbian, gay and bisexual (LGB) and general populations and often faces challenges in accessing needed healthcare services.[6] A national survey of transgender individuals found:

- 25 percent of respondents experienced a problem with their insurance in the past year related to being transgender, such as being denied coverage for care related to gender transition;
- 25 percent of those who sought coverage for hormones in the past year were denied;
- 55 percent of those who sought coverage for transition-related surgery in the past year were denied;

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5. Kellan Baker, *The Future of Transgender Coverage*, 376 New Eng. J. Med. 19, 1801-04 (May 2017).
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AMA AMERICAN MEDICAL ASSOCIATION

GLMA Health Professionals Advancing LGBTQ Equality

Pl. Trial Ex. 043

- 78 percent of respondents wanted hormone therapy related to gender transition, but only 49 percent had ever received it;
- 42 percent reported that insurance covered only some of the surgical care needed for transition; and
- 21 percent reported that insurance covered transition-related surgery, but had no in-network providers.[7]

Federal and state policies

Section 1557 of the Affordable Care Act (ACA) created specific protections barring insurance discrimination based on sexual orientation and gender identity.[8] Prior to enactment, medically necessary gender-affirming hormones and surgeries were often excluded from insurance coverage. Addressing this disparity, the US Department of Health and Human Services (HHS) promulgated final regulations in 2016 implementing section 1557 of the ACA to extend protections against sex discrimination to health coverage and care for the first time and including gender identity discrimination within the definition of sex discrimination.[9] However, a federal court stayed a legal challenge to the rule after the current Administration announced it would reconsider the rule's prohibition on discrimination based on gender identity. The timeline for HHS reconsideration is unknown and the current Administration has, to date, declined to defend the regulation.[10] Rulings by the Equal Employment Opportunity Commission remain intact, however, which found that employer-sponsored plans that exclude gender-affirming care violate Title VII.[11] Title VII of the Civil Rights Act prohibits employment discrimination based on race, color, religion, sex and national origin.

In addition to the ACA, the federal government has taken steps to bar discrimination against transgender individuals in federal health programs. In 2014, HHS invalidated a prior prohibition on Medicare coverage of gender-affirming surgery, citing evidence supporting its effectiveness in treating gender dysphoria and potential for improved health outcomes.[12] In 2016, the federal Office of Personnel Management barred exclusions for gender transition services from the Federal Employees Health Benefits Program. In 2018, the US Department of Veterans Affairs (VA) proposed to amend its medical regulations by removing a provision that excludes "gender alterations" from its medical benefits package, which would effectively authorize transition-related surgery as part of VA care when medically necessary. Final regulations, however, have not yet been issued by the VA.

State-wise, twenty states (CA, CT, CO, DE, HI, IL, MA, MD, MI, MN, NJ, NM, NV, NY, OR, PA, RI, VT and WA) and District of Columbia prohibit health insurers from excluding coverage for transgender health services.[13] California, for example, prohibits health plans from denying coverage or limiting coverage on the basis of sex, which is defined to include gender, gender identity and gender expression. In regulation, California specifies four prohibited practices:

- Denying or cancelling an insurance policy on the basis of gender identity;
- Using gender identity as a basis for determining premium;
- Considering gender identity as a pre-existing condition; and
- Denying coverage or claims for health care services to transgender people when coverage is provided to non-transgender people for the same services.[14]

7. Nat'l Ctr. Transgender Equality, The Report of the 2015 US Transgender Survey (2016)
8. 42 U.S.C. § 18116.
9. Nondiscrimination in Health Programs and Activities, 81 Fed. Reg. 31375 (May 18, 2016) (to be codified in 45 C.F.R. pt. 92).
10. *Franciscan Alliance, Inc. et al. v. Burwell et al.*, No. 7:16–cv-00108-o (N.D. Texas Dec. 31, 2016).
11. *Macy v. Holder*, No. 0120120821, 2012 WL 1435995 (E.E.O.C. Apr. 20, 2012); *EEOC v. Deluxe Financial Services Corp.*, (D. Minn., Civ. No. 0:15-cv-02646-ADM-SER, filed June 4, 2015, settled January 20, 2016).
12. U.S. Dep't Health & Human Servs., Departmental Appeals Bd., Appellate Div. NCD 140.3, Transsexual Surgery, Docket No. A-13–87, Decision No. 2576 (May 30, 2014).
13. Baker, *supra* note 5.
14. Cal. Ins. Code § 10140; Cal. Code Regs. Tit. 10 § 2561.2.

Cost savings

In promulgating the regulations, the California Department of Insurance issued an Economic Impact Assessment that determined that aggregate costs of the antidiscrimination rules would be "insignificant and immaterial" while yielding significant benefits to transgender individuals including suicide reduction, improvements in mental health, reduction in substance use rates, higher rates of adherence to HIV care and reduction in self-medication.[15] The Economic Impact Assessment also identified potential cost savings in the medium to long term due to lower costs associated with suicide, attempts at suicide, overall improvements in mental health and lower rates of substance abuse.[16] The assessment noted that the Centers for Disease Control and Prevention estimate the average acute medical costs of a single suicide completion or attempt in the United States is $2,596 and $7,234 respectively.[17]

Other studies have similarly demonstrated that transgender inclusive health coverage is cost-effective compared to the costs associated with untreated gender dysphoria.[18] A cost analysis of the City and County of San Francisco's coverage of transition-related surgeries found that costs in the first five years to both insurers and employers were low, averaging between $0.77 and $0.96 per year per enrollee, and resulted in no surcharge or premium increases.[19] The analysis also found no evidence of a "magnet effect" wherein transgender individuals would have deliberately sought employment in order to access services.

Health implications for transgender individuals

Transgender individuals in the US are up to three times more likely than the general population to report or be diagnosed with mental health disorders, with as many as 41.5 percent reporting at least one diagnosis of a mental health or substance use disorder:

- Over a third of transgender individuals suffer a major depressive episode in their lifetimes;
- 20.2 percent have been diagnosed with suicidality in the past 30 days;
- 7.9 percent have been diagnosed with an anxiety disorder in the past six months;
- 9.8 percent have been diagnosed with post-traumatic stress disorder in the past six months; and
- 15.2 percent have been diagnosed with a substance use disorder in the past year.[20]

The increased prevalence of these mental health conditions is widely thought to be a consequence of minority stress, the chronic stress from coping with societal stigma and discrimination because of one's gender identity and expression.[21] Indeed, gender based discrimination affecting access to services is a strong predictor of suicide risk among transgender persons.[22] Lack of access to gender-affirming care may directly contribute to poor mental

15. State of Cal., Dep't Ins., Economic Impact Assessment, Gender Nondiscrimination in Health Insurance, Reg-2011-00023 (Apr. 13, 2012).
16. *Id.*
17. *Id*, citing Ctrs. Disease Control & Prevention, Nat'l Ctr. Injury Prevention & Control, Fact Sheet: The Medical Cost Associated with Suicide in the United States, 2010.
18. State of Cal., supra note 15; William Padula, et al., *Societal Implications of Health Insurance Coverage for Medically Necessary Services in the U.S. Transgender Population: A Cost-Effectiveness Analysis*, 31 J Gen. Internal Med. 4, 394-401 (Apr. 2016).
19. Human Rights Campaign, San Francisco Transgender Benefit, available at http://www.hrc.org/resources/san-francisco-transgender-benefit
20. Sari Reisner, et al., *Psychiatric Diagnoses and Comorbidities in a Diverse, Multicity Cohort of Young Transgender Women: Baseline Findings from Project LifeSkills*, 170 J. Am. Med. Ass'n Pediatrics 5, 481–86 (May 2016).
21. Stephen Russell & Jessica Fish, *Mental Health in Lesbian, Gay, Bisexual, and Transgender (LGBT) Youth*, 12 Ann. Rev. Clinical Psychology 1, 465-87 (Mar. 2016).
22. Kristin Clements-Nolle, et al., *Attempted Suicide among Transgender Persons: The Influence of Gender-Based Discrimination and Victimization*, 53 J Homosexuality 3, 53-69 (Oct. 2008).

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health: individuals with gender dysphoria who have undergone no gender confirmation treatment are twice as likely to experience moderate to severe depression and four times more likely to experience anxiety than their surgically-affirmed peers.[23]

Improving access to gender-affirming care is an important means of improving health outcomes for the transgender population. Studies demonstrate dramatic reductions in rate of suicide attempts, with one meta-analysis finding that suicidality rates dropped from 30 percent pre-treatment to 8 percent post-treatment.[24] Studies have also demonstrated a decrease in depression and anxiety and that a majority of patients report improved mental health and function after receipt of gender-affirming care.[25] In addition, receipt of appropriate care is associated with decreased substance use and improved HIV medication adherence among the transgender population, reducing long term negative health outcomes and potential transmission rates. [26] Medically supervised care can also reduce rates of harmful self-prescribed hormones, use of construction grade silicone injections and other interventions that have potential to cause adverse events.[27]

Patients who receive gender-affirming care, including surgical care, feel more congruent in their bodies and report improved mental health. Specifically, one study found that facial feminization surgery improved mental health-related quality of life scores among transgender women to levels seen in the general female population.[28] Studies suggest that improved body satisfaction and self-esteem following medical and surgical therapies is protective against poorer mental health and also supports healthy relationships with parents and peers.[29]

Positive health effects from gender-affirming care extend to children and adolescents as well.[30] Recent research demonstrates that integrated affirmative models of care for youths, which include access to medications and surgeries, result in fewer mental health concerns than has been historically seen among transgender populations.[31] Importantly, rates of self-reported feelings of regret among adolescents following receipt of gender-affirming care are extremely low.[32]

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23. Ashli Owen-Smith, et al., *Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals*, 15 J Sexual Med 4, 591-600 (Apr. 2018).
24. M. Hassan Murad, et al., *Hormonal Therapy and Sex Reassignment: A Systematic Review and Meta-Analysis of Quality of Life and Psychosocial Outcomes*, 72 Clinical Endocrinology 2, 214-331 (Feb. 2010).
25. Yolanda Smith, et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adult and Adolescent Transsexuals*, 35 Psychological Med. 1, 89-99 (Jan. 2005); Tiffany Ainsworth & Jeffrey Spiegel, *Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery*, 19 Quality Life Res. 7, 1019-24 (Sep. 2010).
26. Jamil Rehman, et al., *The Reported Sex and Surgery Satisfactions of 28 Postoperative Male to-Female Transsexual Patients*, 28 Archives Sexual Behav. 1, 71-89; Jae Sevelius, Adam Carrico & Mallory Johnson, *Antiretroviral Therapy Adherence Among Transgender Women Living with HIV*, 21 J Ass'n Nurses AIDS Care 3, 256-64 (May 2010).
27. Jessica Xavier, Admin. HIV and AIDS, D.C. Gov't, The Washington Transgender Needs Assessment Survey (2000); Wendy Bostwick & Gretchen Kenagy, *Health and Social Service Needs of Transgendered People in Chicago*, 8 Int'l J Transgenderism 2-3, 57-66 (Oct. 2008); Cathy Reback, et al., Los Angeles Transgender Health Study: Community Report (2001).
28. Ainsworth & Spiegel, *supra* note 25.
29. Ashli Owen-Smith, et al., *Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals*, 15 J Sexual Med 4, 591-600 (Apr. 2018); Michelle Marie Johns, et al., *Protective Factors Among Transgender and Gender Variant Youth: A Systematic Review by Socioecological Level*, 39 J Primary Prevention 3, 263-301 (Jun. 2018).
30. Lily Durwood, Katie Mclaughlin & Kristina Olson, *Mental Health and Self-Worth in Socially Transitioned Transgender Youth*, 56 J Am Acad. Child Adolescent Psychiatry 2, 116-23 (Nov. 2016).
31. Laura Edwards-Leeper & Norman Spack, *Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center*, 59 J Homosexuality 3, 321-36 (Mar. 2012). Edgardo Menvielle, *A comprehensive program for children with gender variant behaviors and gender identity disorders*, 59 J Homosexuality 3, 357-68 (Mar. 2012); Darryl Hill, et al., *An affirmative intervention for families with gender variant children: parental ratings of child mental health and gender*, 36 J Sex & Marital Therapy 1, 6–23 (2010)
32. Johanna Olson-Kennedy, et al., *Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts*, 172 JAMA Pediatrics 5, 431-436 (May 2018).

Medical society opinions

The AMA opposes any discrimination based on an individual's sex, sexual orientation or gender identity, opposes the denial of health insurance on the basis of sexual orientation or gender identity, and supports public and private health insurance coverage for treatment of gender dysphoria as recommended by the patient's physician. GLMA: Health Professionals Advancing LGBTQ Equality recognizes that mental healthcare, hormone replacement therapy, and/or gender-affirming surgery are medically necessary for the treatment of transgender people who meet the criteria for gender dysphoria and advocates that these services not be excluded from any public or private insurance programs. In addition, other medical associations, including the American Academy of Family Physicians, American College of Obstetricians and Gynecologists and American Psychiatric Association have stated that medically necessary transition-related care should be covered by insurance.[33]

AMA policy

Removing Financial Barriers to Care for Transgender Patients H-185.950
Our AMA supports public and private health insurance coverage for treatment of gender dysphoria as recommended by the patient's physician. (Res. 122 A-08; Modified: Res. 05, A-16)

Sexual Orientation and/or Gender Identity as Health Insurance Criteria H-180.980
The AMA opposes the denial of health insurance on the basis of sexual orientation or gender identity. (Res. 178, A-88; Reaffirmed: Sub. Res. 101, I-97; Reaffirmed: CMS Rep. 9, A-07; Modified: BOT Rep. 11, A-07; Reaffirmed: CMS Rep. 01, A-17)

Military Medical Policies Affecting Transgender Individuals H-40.966
Our American Medical Association affirms that there is no medically valid reason to exclude transgender individuals from service in the US military and affirms transgender service members be provided care as determined by patient and physician according to the same medical standards that apply to non-transgender personnel. (Res. 11, A-15)

Reducing Suicide Risk Among Lesbian, Gay, Bisexual, Transgender, and Questioning Youth Through Collaboration with Allied Organizations H-60.927
Our AMA will partner with public and private organizations dedicated to public health and public policy to reduce lesbian, gay, bisexual, transgender, and questioning (LGBTQ) youth suicide and improve health among LGBTQ youth. (Res. 402, A-12)

GLMA policy

GLMA 127-18-101: Transgender Healthcare
Therapeutic treatment, including hormone therapy, mental health therapy and gender affirming surgeries, are medically necessary for the treatment of gender dysphoria. These gender-affirming medical and surgical treatments should be covered by all public and private insurance plans. (Approved 2018)

For additional information or assistance with advocacy to protect transgender individuals' access to medically necessary services, please visit the www.ama-assn.org/go/arc or contact Annalia Michelman, JD, Senior Legislative Attorney, AMA Advocacy Resource Center at annalia.michelman@ama-assn.org or (312) 464-4788.

33. See Am. Acad. Fam. Physicians, Coverage Equity for Drugs, Testing, Procedure, Preventive Services, and Reproductive Technologies (2017); Am. College Obstetricians & Gynecologists, Health Care for Transgender Individuals (2011); Am. Psychiatric Ass'n, Position Statement on Access to Care for Transgender and Gender Variant Individuals (2012).

TAB 176-5

Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

American Psychological Association

Transgender and gender nonconforming[1] (TGNC) people are those who have a gender identity that is not fully aligned with their sex assigned at birth. The existence of TGNC people has been documented in a range of historical cultures (Coleman, Colgan, & Gooren, 1992; Feinberg, 1996; Miller & Nichols, 2012; Schmidt, 2003). Current population estimates of TGNC people have ranged from 0.17 to 1,333 per 100,000 (Meier & Labuski, 2013). The Massachusetts Behavioral Risk Factor Surveillance Survey found 0.5% of the adult population aged 18 to 64 years identified as TGNC between 2009 and 2011 (Conron, Scott, Stowell, & Landers, 2012). However, population estimates likely underreport the true number of TGNC people, given difficulties in collecting comprehensive demographic information about this group (Meier & Labuski, 2013). Within the last two decades, there has been a significant increase in research about TGNC people. This increase in knowledge, informed by the TGNC community, has resulted in the development of progressively more trans-affirmative practice across the multiple health disciplines involved in the care of TGNC people (Bockting, Knudson, & Goldberg, 2006; Coleman et al., 2012). Research has documented the extensive experiences of stigma and discrimination reported by TGNC people (Grant et al., 2011) and the mental health consequences of these experiences across the life span (Bockting, Miner, Swinburne Romine, Hamilton, & Coleman, 2013), including increased rates of depression (Fredriksen-Goldsen et al., 2014) and suicidality (Clements-Nolle, Marx, & Katz, 2006). TGNC people's lack of access to trans-affirmative mental and physical health care is a common barrier (Fredriksen-Goldsen et al., 2014; Garofalo, Deleon, Osmer, Doll, & Harper, 2006; Grossman & D'Augelli, 2006), with TGNC people sometimes being denied care because of their gender identity (Xavier et al., 2012).

In 2009, the American Psychological Association (APA) Task Force on Gender Identity and Gender Variance (TFGIGV) survey found that less than 30% of psychologist and graduate student participants reported familiarity with issues that TGNC people experience (APA TFGIGV, 2009). Psychologists and other mental health professionals who have limited training and experience in TGNC-affirmative care may cause harm to TGNC people (Mikalson, Pardo, & Green, 2012; Xavier et al., 2012). The significant level of societal stigma and discrimination that TGNC people face, the associated mental health consequences, and psychologists' lack of familiarity with trans-affirmative care led the APA Task Force to recommend that psychological practice guidelines be developed to help psychologists maximize the effectiveness of services offered and avoid harm when working with TGNC people and their families.

Purpose

The purpose of the *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* (hereafter *Guidelines*) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people. Trans-affirmative practice is the provision

The American Psychological Association's (APA's) Task Force on Guidelines for Psychological Practice with Transgender and Gender Nonconforming People developed these guidelines. lore m. dickey, Louisiana Tech University, and Anneliese A. Singh, The University of Georgia, served as chairs of the Task Force. The members of the Task Force included Walter O. Bockting, Columbia University; Sand Chang, Independent Practice; Kelly Ducheny, Howard Brown Health Center; Laura Edwards-Leeper, Pacific University; Randall D. Ehrbar, Whitman Walker Health Center; Max Fuentes Fuhrmann, Independent Practice; Michael L. Hendricks, Washington Psychological Center, P.C.; and Ellen Magalhaes, Center for Psychological Studies at Nova Southeastern University and California School of Professional Psychology at Alliant International University.

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This document will expire as APA policy in 2022. After this date, users should contact the APA Public Interest Directorate to determine whether the guidelines in this document remain in effect as APA policy.

Correspondence concerning this article should be addressed to the Public Interest Directorate, American Psychological Association, 750 First Street, NE, Washington, DC 20002.

[1] For the purposes of these guidelines, we use the term *transgender and gender nonconforming* (TGNC). We intend for the term to be as broadly inclusive as possible, and recognize that some TGNC people do not ascribe to these terms. Readers are referred to Appendix A for a listing of terms that include various TGNC identity labels.

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of care that is respectful, aware, and supportive of the identities and life experiences of TGNC people (Korell & Lorah, 2007). The *Guidelines* are an introductory resource for psychologists who will encounter TGNC people in their practice, but can also be useful for psychologists with expertise in this area of practice to improve the care already offered to TGNC people. The *Guidelines* include a set of definitions for readers who may be less familiar with language used when discussing gender identity and TGNC populations (see Appendix A). Distinct from TGNC, the term "cisgender" is used to refer to people whose sex assigned at birth is aligned with their gender identity (E. R. Green, 2006; Serano, 2006).

Given the added complexity of working with TGNC and gender-questioning youth[2] and the limitations of the available research, the *Guidelines* focus primarily, though not exclusively, on TGNC adults. Future revisions of the *Guidelines* will deepen a focus on TGNC and gender-questioning children and adolescents. The *Guidelines* address the strengths of TGNC people, the challenges they face, ethical and legal issues, life span considerations, research, education, training, and health care. Because issues of gender identity are often conflated with issues of gender expression or sexual orientation, psychological practice with the TGNC population warrants the acquisition of specific knowledge about concerns unique to TGNC people that are not addressed by other practice guidelines (APA, 2012). It is important to note that these *Guidelines* are not intended to address some of the conflicts that cisgender people may experience due to societal expectations regarding gender roles (Butler, 1990), nor are they intended to address intersex people (Dreger, 1999; Preves, 2003).

Documentation of Need

In 2005, the APA Council of Representatives authorized the creation of the Task Force on Gender Identity and Gender Variance (TFGIGV), charging the Task Force to review APA policies related to TGNC people and to offer recommendations for APA to best meet the needs of TGNC people (APA TFGIGV, 2009). In 2009, the APA Council of Representatives adopted the Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination, which calls upon psychologists in their professional roles to provide appropriate, nondiscriminatory treatment; encourages psychologists to take a leadership role in working against discrimination; supports the provision of adequate and necessary mental and medical health care; recognizes the efficacy, benefit, and medical necessity of gender transition; supports access to appropriate treatment in institutional settings; and supports the creation of educational resources for all psychologists (Anton, 2009). In 2009, in an extensive report on the current state of psychological practice with TGNC people, the TFGIGV determined that there was sufficient knowledge and expertise in the field to warrant the development of practice guidelines for TGNC populations (APA TFGIGV, 2009). The report identified that TGNC people constituted a population with unique needs and that the creation of practice guidelines would be a valuable resource for the field (APA TFGIGV, 2009). Psychologists' relative lack of knowledge about TGNC people and trans-affirmative care, the level of societal stigma and discrimination that TGNC people face, and the significant mental health consequences that TGNC people experience as a result offer a compelling need for psychological practice guidelines for this population.

Users

The intended audience for these *Guidelines* includes psychologists who provide clinical care, conduct research, or provide education or training. Given that gender identity issues can arise at any stage in a TGNC person's life (Lev, 2004), clinicians can encounter a TGNC person in practice or have a client's presenting problem evolve into an issue related to gender identity and gender expression. Researchers, educators, and trainers will benefit from use of these *Guidelines* to inform their work, even when not specifically focused on TGNC populations. Psychologists who focus on TGNC populations in their clinical practice, research, or educational and training activities will also benefit from the use of these *Guidelines*.

Distinction Between Standards and Guidelines

When using these *Guidelines*, psychologists should be aware that APA has made an important distinction between *standards* and *guidelines* (Reed, McLaughlin, & Newman, 2002). Standards are mandates to which all psychologists must adhere (e.g., the *Ethical Principles of Psychologists and Code of Conduct*; APA, 2010), whereas guidelines are aspirational. Psychologists are encouraged to use these *Guidelines* in tandem with the *Ethical Principles of Psychologists and Code of Conduct*, and should be aware that state and federal laws may override these *Guidelines* (APA, 2010).

In addition, these *Guidelines* refer to psychological practice (e.g., clinical work, consultation, education, research, and training) rather than treatment. Practice guidelines are practitioner-focused and provide guidance for professionals regarding "conduct and the issues to be considered in particular areas of clinical practice" (Reed et al., 2002, p. 1044). Treatment guidelines are client-focused and address intervention-specific recommendations for a clinical population or condition (Reed et al., 2002). The current *Guidelines* are intended to complement treatment guidelines for TGNC people seeking mental health services, such as those set forth by the World Professional Association for Transgender Health Standards of Care (Coleman et al., 2012) and the Endocrine Society (Hembree et al., 2009).

[2] For the purposes of these guidelines, "youth" refers to both children and adolescents under the age of 18.

Compatibility

These *Guidelines* are consistent with the APA *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010), the *Standards of Accreditation for Health Service Psychology* (APA, 2015), the APA TFGIGV (2009) report, and the APA Council of Representatives Resolution on Transgender, Gender Identity, & Gender Expression Non-Discrimination (Anton, 2009).

Practice Guidelines Development Process

To address one of the recommendations of the APA TFGIGV (2009), the APA Committee on Sexual Orientation and Gender Diversity (CSOGD; then the Committee on Lesbian, Gay, Bisexual, and Transgender Concerns) and Division 44 (the Society for the Psychological Study of Lesbian, Gay, Bisexual and Transgender Issues) initiated a joint Task Force on Psychological Practice Guidelines with Transgender and Gender Nonconforming People in 2011. Task Force members were selected through an application and review process conducted by the leadership of CSOGD and Division 44. The Task Force included 10 members who had substantial psychological practice expertise with TGNC people. Of the 10 task force members, five individuals identified as TGNC with a range of gender identities and five identified as cisgender. In terms of race/ethnicity, six of the task force members identified as White and four identified as people of color (one Indian American, one Chinese American, one Latina American, and one mixed race).

The Task Force conducted a comprehensive review of the extant scholarship, identified content most pertinent to the practice of psychology with TGNC people, and evaluated the level of evidence to support guidance within each guideline. To ensure the accuracy and comprehensiveness of these *Guidelines*, Task Force members met with TGNC community members and groups and consulted with subject matter experts within and outside of psychology. When the Task Force discovered a lack of professional consensus, every effort was made to include divergent opinions in the field relevant to that issue. When this occurred, the Task Force described the various approaches documented in the literature. Additionally, these *Guidelines* were informed by comments received at multiple presentations held at professional conferences and comments obtained through two cycles of open public comment on earlier *Guideline* drafts.

This document contains 16 guidelines for TGNC psychological practice. Each guideline includes a Rationale section, which reviews relevant scholarship supporting the need for the guideline, and an Application section, which describes how the particular guideline may be applied in psychological practice. The *Guidelines* are organized into five clusters: (a) foundational knowledge and awareness; (b) stigma, discrimination, and barriers to care; (c) life span development; (d) assessment, therapy, and intervention; and (e) research, education, and training.

Funding for this project was provided by Division 44 (Society for the Psychological Study of LGBT Issues); the APA Office on Lesbian, Gay, Bisexual, and Transgender (LGBT) Concerns; a grant from the Committee on Division/APA Relations (CODAPAR); and donations from Randall Ehrbar and Pamela St. Amand. Some members of the Task Force have received compensation through presentations (e.g., honoraria) or royalties (e.g., book contracts) based in part on information contained in these *Guidelines*.

Selection of Evidence

Although the number of publications on the topic of TGNC-affirmative practice has been increasing, this is still an emerging area of scholarly literature and research. When possible, the Task Force relied on peer-reviewed publications, but books, chapters, and reports that do not typically receive a high level of peer review have also been cited when appropriate. These sources are from a diverse range of fields addressing mental health, including psychology, counseling, social work, and psychiatry. Some studies of TGNC people utilize small sample sizes, which limits the generalizability of results. Few studies of TGNC people utilize probability samples or randomized control groups (e.g., Conron et al., 2012; Dhejne et al., 2011). As a result, the Task Force relied primarily on studies using convenience samples, which limits the generalizability of results to the population as a whole, but can be adequate for describing issues and situations that arise within the population.

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth.

Rationale. Gender identity is defined as a person's deeply felt, inherent sense of being a girl, woman, or female; a boy, a man, or male; a blend of male or female; or an alternative gender (Bethea & McCollum, 2013; Institute of Medicine [IOM], 2011). In many cultures and religious traditions, gender has been perceived as a binary construct, with mutually exclusive categories of male or female, boy or girl, man or woman (Benjamin, 1966; Mollenkott, 2001; Tanis, 2003). These mutually exclusive categories include an assumption that gender identity is always in alignment with sex assigned at birth (Bethea & McCollum, 2013). For TGNC people, gender identity differs from sex assigned at birth to varying degrees, and may be experienced and expressed outside of the gender binary (Harrison, Grant, & Herman, 2012; Kuper, Nussbaum, & Mustanski, 2012).

Gender as a nonbinary construct has been described and studied for decades (Benjamin, 1966; Herdt, 1994; Kulick, 1998). There is historical evidence of recognition, societal acceptance, and sometimes reverence of diversity in gender identity and gender expression in several different cultures (Coleman et al., 1992; Feinberg, 1996; Miller

& Nichols, 2012; Schmidt, 2003). Many cultures in which gender nonconforming persons and groups were visible were diminished by westernization, colonialism, and systemic inequity (Nanda, 1999). In the 20th century, TGNC expression became medicalized (Hirschfeld, 1910/1991), and medical interventions to treat discordance between a person's sex assigned at birth, secondary sex characteristics, and gender identity became available (Meyerowitz, 2002).

As early as the 1950s, research found variability in how an individual described their[3] gender, with some participants reporting a gender identity different from the culturally defined, mutually exclusive categories of "man" or "woman" (Benjamin, 1966). In several recent large online studies of the TGNC population in the United States, 30% to 40% of participants identified their gender identity as other than man or woman (Harrison et al., 2012; Kuper et al., 2012). Although some studies have cultivated a broader understanding of gender (Conron, Scout, & Austin, 2008), the majority of research has required a forced choice between man and woman, thus failing to represent or depict those with different gender identities (IOM, 2011). Research over the last two decades has demonstrated the existence of a wide spectrum of gender identity and gender expression (Bockting, 2008; Harrison et al., 2012; Kuper et al., 2012), which includes people who identify as either man or woman, neither man nor woman, a blend of man and woman, or a unique gender identity. A person's identification as TGNC can be healthy and self-affirming, and is not inherently pathological (Coleman et al., 2012). However, people may experience distress associated with discordance between their gender identity and their body or sex assigned at birth, as well as societal stigma and discrimination (Coleman et al., 2012).

Between the late 1960s and the early 1990s, health care to alleviate gender dysphoria largely reinforced a binary conceptualization of gender (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). At that time, it was considered an ideal outcome for TGNC people to conform to an identity that aligned with either sex assigned at birth or, if not possible, with the "opposite" sex, with a heavy emphasis on blending into the cisgender population or "passing" (APA TFGIGV, 2009; Bolin, 1994; Hastings, 1974). Variance from these options could raise concern for health care providers about a TGNC person's ability to transition successfully. These concerns could act as a barrier to accessing surgery or hormone therapy because medical and mental health care provider endorsement was required before surgery or hormones could be accessed (Berger et al., 1979). Largely because of self-advocacy of TGNC individuals and communities in the 1990s, combined with advances in research and models of trans-affirmative care, there is greater recognition and acknowledgment of a spectrum of gender diversity and corresponding individualized, TGNC-specific health care (Bockting et al., 2006; Coleman et al., 2012).

Application. A nonbinary understanding of gender is fundamental to the provision of affirmative care for TGNC people. Psychologists are encouraged to adapt or modify their understanding of gender, broadening the range of variation viewed as healthy and normative. By understanding the spectrum of gender identities and gender expressions that exist, and that a person's gender identity may not be in full alignment with sex assigned at birth, psychologists can increase their capacity to assist TGNC people, their families, and their communities (Lev, 2004). Respecting and supporting TGNC people in authentically articulating their gender identity and gender expression, as well as their lived experience, can improve TGNC people's health, well-being, and quality of life (Witten, 2003).

Some TGNC people may have limited access to visible, positive TGNC role models. As a result, many TGNC people are isolated and must cope with the stigma of gender nonconformity without guidance or support, worsening the negative effect of stigma on mental health (Fredriksen-Goldsen et al., 2014; Singh, Hays, & Watson, 2011). Psychologists may assist TGNC people in challenging gender norms and stereotypes, and in exploring their unique gender identity and gender expression. TGNC people, partners, families, friends, and communities can benefit from education about the healthy variation of gender identity and gender expression, and the incorrect assumption that gender identity automatically aligns with sex assigned at birth.

Psychologists may model an acceptance of ambiguity as TGNC people develop and explore aspects of their gender, especially in childhood and adolescence. A nonjudgmental stance toward gender nonconformity can help to counteract the pervasive stigma faced by many TGNC people and provide a safe environment to explore gender identity and make informed decisions about gender expression.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Rationale. The constructs of gender identity and sexual orientation are theoretically and clinically distinct, even though professionals and nonprofessionals frequently conflate them. Although some research suggests a potential link in the development of gender identity and sexual orientation, the mechanisms of such a relationship are unknown (Adelson & American Academy of Child and Adolescent Psychiatry [AACAP] Committee on Quality Issues [CQI], 2012; APA TFGIGV, 2009; A. H. Devor, 2004; Drescher & Byne, 2013). *Sexual orientation* is defined as a person's sexual and/or emotional attraction to another person (Shively & De Cecco, 1977), compared with *gender identity*, which is defined by a person's felt, inherent sense of gender. For most people, gender identity develops earlier than sexual orientation. Gender identity is often established in young toddlerhood (Adelson & AACAP CQI, 2012; Kohlberg, 1966), compared with aware-

[3] The third person plural pronouns "they," "them," and "their" in some instances function in these guidelines as third-person singular pronouns to model a common technique used to avoid the use of gendered pronouns when speaking to or about TGNC people.

ness of same-sex attraction, which often emerges in early adolescence (Adelson & AACAP CQI, 2012; D'Augelli & Hershberger, 1993; Herdt & Boxer, 1993; Ryan, 2009; Savin-Williams & Diamond, 2000). Although gender identity is usually established in childhood, individuals may become aware that their gender identity is not in full alignment with sex assigned at birth in childhood, adolescence, or adulthood. The developmental pathway of gender identity typically includes a progression through multiple stages of awareness, exploration, expression, and identity integration (Bockting & Coleman, 2007; A. H. Devor, 2004; Vanderburgh, 2007). Similarly, a person's sexual orientation may progress through multiple stages of awareness, exploration, and identity through adolescence and into adulthood (Bilodeau & Renn, 2005). Just as some people experience their sexual orientation as being fluid or variable (L. M. Diamond, 2013), some people also experience their gender identity as fluid (Lev, 2004).

The experience of questioning one's gender can create significant confusion for some TGNC people, especially for those who are unfamiliar with the range of gender identities that exist. To explain any discordance they may experience between their sex assigned at birth, related societal expectations, patterns of sexual and romantic attraction, and/or gender role nonconformity and gender identity, some TGNC people may assume that they must be gay, lesbian, bisexual, or queer (Bockting, Benner, & Coleman, 2009). Focusing solely on sexual orientation as the cause for discordance may obscure awareness of a TGNC identity. It can be very important to include sexual orientation and gender identity in the process of identity exploration as well as in the associated decisions about which options will work best for any particular person. In addition, many TGNC adults have disguised or rejected their experience of gender incongruence in childhood or adolescence to conform to societal expectations and minimize their fear of difference (Bockting & Coleman, 2007; Byne et al., 2012).

Because gender and patterns of attraction are used to identify a person's sexual orientation, the articulation of sexual orientation is made more complex when sex assigned at birth is not aligned with gender identity. A person's sexual orientation identity cannot be determined by simply examining external appearance or behavior, but must incorporate a person's identity and self-identification (Broido, 2000).

Application. Psychologists may assist people in differentiating gender identity and sexual orientation. As clients become aware of previously hidden or constrained aspects of their gender identity or sexuality, psychologists may provide acceptance, support, and understanding without making assumptions or imposing a specific sexual orientation or gender identity outcome (APA TFGIGV, 2009). Because of their roles in assessment, treatment, and prevention, psychologists are in a unique position to help TGNC people better understand and integrate the various aspects of their identities. Psychologists may assist TGNC people by introducing and normalizing differences in gender identity and expression. As a TGNC person finds a comfortable way to actualize and express their gender identity, psychologists may notice that previously incongruent aspects of their sexual orientation may become more salient, better integrated, or increasingly egosyntonic (Bockting et al., 2009; H. Devor, 1993; Schleifer, 2006). This process may allow TGNC people the comfort and opportunity to explore attractions or aspects of their sexual orientation that previously had been repressed, hidden, or in conflict with their identity. TGNC people may experience a renewed exploration of their sexual orientation, a widened spectrum of attraction, or a shift in how they identify their sexual orientation in the context of a developing TGNC identity (Coleman, Bockting, & Gooren, 1993; Meier, Pardo, Labuski, & Babcock, 2013; Samons, 2008).

Psychologists may need to provide TGNC people with information about TGNC identities, offering language to describe the discordance and confusion TGNC people may be experiencing. To facilitate TGNC people's learning, psychologists may introduce some of the narratives written by TGNC people that reflect a range of outcomes and developmental processes in exploring and affirming gender identity (e.g., Bornstein & Bergman, 2010; Boylan, 2013; J. Green, 2004; Krieger, 2011; Lawrence, 2014). These resources may potentially aid TGNC people in distinguishing between issues of sexual orientation and gender identity and in locating themselves on the gender spectrum. Psychologists may also educate families and broader community systems (e.g., schools, medical systems) to better understand how gender identity and sexual orientation are different but related; this may be particularly useful when working with youth (Singh & Burnes, 2009; Whitman, 2013). Because gender identity and sexual orientation are often conflated, even by professionals, psychologists are encouraged to carefully examine resources that claim to provide affirmative services for lesbian, gay, bisexual, transgender, and queer (LGBTQ) people, and to confirm which are knowledgeable about and inclusive of the needs of TGNC people before offering referrals or recommendations to TGNC people and their families.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Rationale. Gender identity and gender expression may have profound intersections with other aspects of identity (Collins, 2000; Warner, 2008). These aspects may include, but are not limited to, race/ethnicity, age, education, socioeconomic status, immigration status, occupation, disability status, HIV status, sexual orientation, relational status, and religion and/or spiritual affiliation. Whereas some of these aspects of identity may afford privilege, others may create stigma and hinder empowerment (Burnes & Chen, 2012; K. M. de Vries, 2015). In addition, TGNC people who transition may not be prepared for changes in privilege or societal treatment based on gender identity and gender expression. To illustrate, an African American trans man may gain male privilege, but may face racism and

societal stigma particular to African American men. An Asian American/Pacific Islander trans woman may experience the benefit of being perceived as a cisgender woman, but may also experience sexism, misogyny, and objectification particular to Asian American/Pacific Islander cisgender women.

The intersection of multiple identities within TGNC people's lives is complex and may obstruct or facilitate access to necessary support (A. Daley, Solomon, Newman, & Mishna, 2008). TGNC people with less privilege and/or multiple oppressed identities may experience greater stress and restricted access to resources. They may also develop resilience and strength in coping with disadvantages, or may locate community-based resources available to specific groups (e.g., for people living with HIV; Singh et al., 2011). Gender identity affirmation may conflict with religious beliefs or traditions (Bockting & Cesaretti, 2001). Finding an affirmative expression of their religious and spiritual beliefs and traditions, including positive relationships with religious leaders, can be an important resource for TGNC people (Glaser, 2008; Porter, Ronneberg, & Witten, 2013; Xavier, 2000).

Application. In practice, psychologists strive to recognize the salient multiple and intersecting identities of TGNC people that influence coping, discrimination, and resilience (Burnes & Chen, 2012). Improved rapport and therapeutic alliance are likely to develop when psychologists avoid overemphasizing gender identity and gender expression when not directly relevant to TGNC people's needs and concerns. Even when gender identity is the main focus of care, psychologists are encouraged to understand that a TGNC person's experience of gender may also be shaped by other important aspects of identity (e.g., age, race/ethnicity, sexual orientation), and that the salience of different aspects of identity may evolve as the person continues psychosocial development across the life span, regardless of whether they complete a social or medical transition.

At times, a TGNC person's intersection of identities may result in conflict, such as a person's struggle to integrate gender identity with religious and/or spiritual upbringing and beliefs (Kidd & Witten, 2008; Levy & Lo, 2013; Rodriguez & Follins, 2012). Psychologists may aid TGNC people in understanding and integrating identities that may be differently privileged within systems of power and systemic inequity (Burnes & Chen, 2012). Psychologists may also highlight and strengthen the development of TGNC people's competencies and resilience as they learn to manage the intersection of stigmatized identities (Singh, 2012).

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gender expression may affect the quality of care they provide to TGNC people and their families.

Rationale. Psychologists, like other members of society, come to their personal understanding and acceptance of different aspects of human diversity through a process of socialization. Psychologists' cultural biases, as well as the cultural differences between psychologists and their clients, have a clinical impact (Israel, Gorcheva, Burnes, & Walther, 2008; Vasquez, 2007). The assumptions, biases, and attitudes psychologists hold regarding TGNC people and gender identity and/or gender expression can affect the quality of services psychologists provide and their ability to develop an effective therapeutic alliance (Bess & Stabb, 2009; Rachlin, 2002). In addition, a lack of knowledge or training in providing affirmative care to TGNC people can limit a psychologist's effectiveness and perpetuate barriers to care (Bess & Stabb, 2009; Rachlin, 2002). Psychologists experienced with lesbian, gay, or bisexual (LGB) people may not be familiar with the unique needs of TGNC people (Israel, 2005; Israel et al., 2008). In community surveys, TGNC people have reported that many mental health care providers lack basic knowledge and skills relevant to care of TGNC people (Bradford, Xavier, Hendricks, Rives, & Honnold, 2007; Xavier, Bobbin, Singer, & Budd, 2005) and receive little training to prepare them to work with TGNC people (APA TFGIGV, 2009; Lurie, 2005). The National Transgender Discrimination Survey (Grant et al., 2011) reported that 50% of TGNC respondents shared that they had to educate their health care providers about TGNC care, 28% postponed seeking medical care due to antitrans bias, and 19% were refused care due to discrimination.

The APA ethics code (APA, 2010) specifies that psychologists practice in areas only within the boundaries of their competence (Standard 2.01), participate in proactive and consistent ways to enhance their competence (Standard 2.03), and base their work upon established scientific and professional knowledge (Standard 2.04). Competence in working with TGNC people can be developed through a range of activities, such as education, training, supervised experience, consultation, study, or professional experience.

Application. Psychologists may engage in practice with TGNC people in various ways; therefore, the depth and level of knowledge and competence required by a psychologist depends on the type and complexity of service offered to TGNC people. Services that psychologists provide to TGNC people require a basic understanding of the population and its needs, as well as the ability to respectfully interact in a trans-affirmative manner (L. Carroll, 2010).

APA emphasizes the use of evidence-based practice (APA Presidential Task Force on Evidence-Based Practice, 2006). Given how easily assumptions or stereotypes could influence treatment, evidence-based practice may be especially relevant to psychological practice with TGNC people. Until evidence-based practices are developed specifically for TGNC people, psychologists are encouraged to utilize existing evidence-based practices in the care they provide. APA also promotes collaboration with clients concerning clinical decisions, including issues related to costs, potential benefits, and the existing options and resources related to treatment (APA Presidential Task Force on Evidence-Based Practice, 2006). TGNC people could benefit from such collaboration and active engagement in decision

making, given the historical disenfranchisement and disempowerment of TGNC people in health care.

In an effort to develop competence in working with TGNC people, psychologists are encouraged to examine their personal beliefs regarding gender and sexuality, gender stereotypes, and TGNC identities, in addition to identifying gaps in their own knowledge, understanding, and acceptance (American Counseling Association [ACA], 2010). This examination may include exploring one's own gender identity and gendered experiences related to privilege, power, or marginalization, as well as seeking consultation and training with psychologists who have expertise in working with TGNC people and communities.

Psychologists are further encouraged to develop competence in working with TGNC people and their families by seeking up-to-date basic knowledge and understanding of gender identity and expression, and learning how to interact with TGNC people and their families respectfully and without judgment. Competence in working with TGNC people may be achieved and maintained in formal and informal ways, ranging from exposure in the curriculum of training programs for future psychologists and continuing education at professional conferences, to affirmative involvement as allies in the TGNC community. Beyond acquiring general competence, psychologists who choose to specialize in working with TGNC people presenting with gender-identity-related concerns are strongly encouraged to obtain advanced training, consultation, and professional experience (ACA, 2010; Coleman et al., 2012).

Psychologists may gain knowledge about the TGNC community and become more familiar with the complex social issues that affect the lives of TGNC people through first-hand experiences (e.g., attending community meetings and conferences, reading narratives written by TGNC people). If psychologists have not yet developed competence in working with TGNC people, it is recommended that they refer TGNC people to other psychologists or providers who are knowledgeable and able to provide trans-affirmative care.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Rationale. Many TGNC people experience discrimination, ranging from subtle to severe, when accessing housing, health care, employment, education, public assistance, and other social services (Bazargan & Galvan, 2012; Bradford, Reisner, Honnold, & Xavier, 2013; Dispenza, Watson, Chung, & Brack, 2012; Grant et al., 2011). Discrimination can include assuming a person's assigned sex at birth is fully aligned with that person's gender identity, not using a person's preferred name or pronoun, asking TGNC people inappropriate questions about their bodies, or making the assumption that psychopathology exists given a specific gender identity or gender expression (Nadal, Rivera, & Corpus, 2010; Nadal, Skolnik, & Wong, 2012). Discrimination may also include refusing access to housing or employment or extreme acts of violence (e.g., sexual assault, murder). TGNC people who hold multiple marginalized identities are more vulnerable to discrimination and violence. TGNC women and people of color disproportionately experience severe forms of violence and discrimination, including police violence, and are less likely to receive help from law enforcement (Edelman, 2011; National Coalition of Anti-Violence Programs, 2011; Saffin, 2011).

TGNC people are at risk of experiencing antitrans prejudice and discrimination in educational settings. In a national representative sample of 7,898 LGBT youth in K-12 settings, 55.2% of participants reported verbal harassment, 22.7% reported physical harassment, and 11.4% reported physical assault based on their gender expression (Kosciw, Greytak, Palmer, & Boesen, 2014). In a national community survey of TGNC adults, 15% reported prematurely leaving educational settings ranging from kindergarten through college as a result of harassment (Grant et al., 2011). Many schools do not include gender identity and gender expression in their school nondiscrimination policies; this leaves TGNC youth without needed protections from bullying and aggression in schools (Singh & Jackson, 2012). TGNC youth in rural settings may be even more vulnerable to bullying and hostility in their school environments due to antitrans prejudice (Kosciw et al., 2014).

Inequities in educational settings and other forms of TGNC-related discrimination may contribute to the significant economic disparities TGNC people have reported. Grant and colleagues (2011) found that TGNC people were four times more likely to have a household income of less than $10,000 compared with cisgender people, and almost half of a sample of TGNC older adults reported a household income at or below 200% of poverty (Fredriksen-Goldsen et al., 2014). TGNC people often face workplace discrimination both when seeking and maintaining employment (Brewster, Velez, Mennicke, & Tebbe, 2014; Dispenza et al., 2012; Mizock & Mueser, 2014). In a nonrepresentative national study of TGNC people, 90% reported having "directly experienced harassment or mistreatment at work and felt forced to take protective actions that negatively impacted their careers or their well-being, such as hiding who they were to avoid workplace repercussions" (Grant et al., 2011, p. 56). In addition, 78% of respondents reported experiencing some kind of direct mistreatment or discrimination at work (Grant et al., 2011). Employment discrimination may be related to stigma based on a TGNC person's appearance, discrepancies in identity documentation, or being unable to provide job references linked to that person's pretransition name or gender presentation (Bender-Baird, 2011).

Issues of employment discrimination and workplace harassment are particularly salient for TGNC military personnel and veterans. Currently, TGNC people cannot serve openly in the U.S. military. Military regulations cite "transsexualism" as a medical exclusion from service (Department of Defense, 2011; Elders & Steinman, 2014). When

enlisted, TGNC military personnel are faced with very difficult decisions related to coming out, transition, and seeking appropriate medical and mental health care, which may significantly impact or end their military careers. Not surprisingly, research documents very high rates of suicidal ideation and behavior among TGNC military and veteran populations (Blosnich et al., 2013; Matarazzo et al., 2014). Being open about their TGNC identity with health care providers can carry risk for TGNC military personnel (OutServe-Servicemembers Legal Defense Network, n.d.). Barriers to accessing health care noted by TGNC veterans include viewing the VA health care system as an extension of the military, perceiving the VA as an unwelcoming environment, and fearing providers' negative reactions to their identity (Sherman, Kauth, Shipherd, & Street, 2014; Shipherd, Mizock, Maguen, & Green, 2012). A recent study shows 28% of LGBT veterans perceived their VA as welcoming and one third as unwelcoming (Sherman et al., 2014). Multiple initiatives are underway throughout the VA system to improve the quality and sensitivity of services to LGBT veterans.

Given widespread workplace discrimination and possible dismissal following transition, TGNC people may engage in sex work or survival sex (e.g., trading sex for food), or sell drugs to generate income (Grant et al., 2011; Hwahng & Nuttbrock, 2007; Operario, Soma, & Underhill, 2008; Stanley, 2011). This increases the potential for negative interactions with the legal system, such as harassment by the police, bribery, extortion, and arrest (Edelman, 2011; Testa et al., 2012), as well as increased likelihood of mental health symptoms and greater health risks, such as higher incidence of sexually transmitted infections, including HIV (Nemoto, Operario, Keatley, & Villegas, 2004).

Incarcerated TGNC people report harassment, isolation, forced sex, and physical assault, both by prison personnel and other inmates (American Civil Liberties Union National Prison Project, 2005; Brotheim, 2013; C. Daley, 2005). In sex-segregated facilities, TGNC people may be subjected to involuntary solitary confinement (also called "administrative segregation"), which can lead to severe negative mental and physical health consequences and may block access to services (Gallagher, 2014; National Center for Transgender Equality, 2012). Another area of concern is for TGNC immigrants and refugees. TGNC people in detention centers may not be granted access to necessary care and experience significant rates of assault and violence in these facilities (Gruberg, 2013). TGNC people may seek asylum in the United States to escape danger as a direct result of lack of protections in their country of origin (APA Presidential Task Force on Immigration, 2012; Cerezo, Morales, Quintero, & Rothman, 2014; Morales, 2013).

TGNC people have difficulty accessing necessary health care (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012) and often feel unsafe sharing their gender identity or their experiences of antitrans prejudice and discrimination due to historical and current discrimination from health care providers (Grant et al., 2011; Lurie, 2005; Singh & McKleroy, 2011). Even when TGNC people have health insurance, plans may explicitly exclude coverage related to gender transition (e.g., hormone therapy, surgery). TGNC people may also have difficulty accessing trans-affirmative primary health care if coverage for procedures is denied based on gender. For example, trans men may be excluded from necessary gynecological care based on the assumption that men do not need these services. These barriers often lead to a lack of preventive health care for TGNC people (Fredriksen-Goldsen et al., 2014; Lambda Legal, 2012). Although the landscape is beginning to change with the recent revision of Medicare policy (National Center for Transgender Equality, 2014) and changes to state laws (Transgender Law Center, n.d.), many TGNC people are still likely to have little to no access to TGNC-related health care as a result of the exclusions in their insurance.

Application. Awareness of and sensitivity to the effects of antitrans prejudice and discrimination can assist psychologists in assessing, treating, and advocating for their TGNC clients. When a TGNC person faces discrimination based on gender identity or gender expression, psychologists may facilitate emotional processing of these experiences and work with the person to identify supportive resources and possible courses of action. Specific needs of TGNC people might vary from developing self-advocacy strategies, to navigating public spaces, to seeking legal recourse for harassment and discrimination in social services and other systems. Additionally, TGNC people who have been traumatized by physical or emotional violence may need therapeutic support.

Psychologists may be able to assist TGNC people in accessing relevant social service systems. For example, psychologists may be able to assist in identifying health care providers and housing resources that are affirming and affordable, or locating affirming religious and spiritual communities (Glaser, 2008; Porter et al., 2013). Psychologists may also assist in furnishing documentation or official correspondence that affirms gender identity for the purpose of accessing appropriate public accommodations, such as bathroom use or housing (Lev, 2009; W. J. Meyer, 2009).

Additionally, psychologists may identify appropriate resources, information, and services to help TGNC people in addressing workplace discrimination, including strategies during a social and/or medical transition for identity disclosure at work. For those who are seeking employment, psychologists may help strategize about how and whether to share information about gender history. Psychologists may also work with employers to develop supportive policies for workplace gender transition or to develop training to help employees adjust to the transition of a coworker.

For TGNC military and veteran populations, psychologists may help to address the emotional impact of navigating TGNC identity development in the military system. Psychologists are encouraged to be aware that issues of confidentiality may be particularly sensitive with active duty or reserve status service members, as the consequences of being identified as TGNC may prevent the client's disclosure of gender identity in treatment.

In educational settings, psychologists may advocate for TGNC youth on a number of levels (APA & National

Association of School Psychologists, 2014; Boulder Valley School District, 2012). Psychologists may consult with administrators, teachers, and school counselors to provide resources and trainings on antitrans prejudice and developing safer school environments for TGNC students (Singh & Burnes, 2009). Peer support from other TGNC people has been shown to buffer the negative effect of stigma on mental health (Bockting et al., 2013). As such, psychologists may consider and develop peer-based interventions to facilitate greater understanding and respectful treatment of TGNC youth by cisgender peers (Case & Meier, 2014). Psychologists may work with TGNC youth and their families to identify relevant resources, such as school policies that protect gender identity and gender expression (APA & National Association of School Psychologists, 2014; Gonzalez & McNulty, 2010), referrals to TGNC-affirmative organizations, and online resources, which may be especially helpful for TGNC youth in rural settings.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Rationale. Antitrans prejudice and the adherence of mainstream society to the gender binary adversely affect TGNC people within their families, schools, health care, legal systems, workplaces, religious traditions, and communities (American Civil Liberties Union National Prison Project, 2005; Bradford et al., 2013; Brewster et al., 2014; Levy & Lo, 2013; McGuire, Anderson, & Toomey, 2010). TGNC people face challenges accessing gender-inclusive restrooms, which may result in discomfort when being forced to use a men's or women's restroom (Transgender Law Center, 2005). In addition to the emotional distress the forced binary choice that public restrooms may create for some, TGNC people are frequently concerned with others' reactions to their presence in public restrooms, including potential discrimination, harassment, and violence (Herman, 2013).

Many TGNC people may be distrustful of care providers due to previous experiences of being pathologized (Benson, 2013). Experiences of discrimination and prejudice with health care providers may be complicated by power differentials within the therapeutic relationship that may greatly affect or complicate the care that TGNC people experience. TGNC people have routinely been asked to obtain an endorsement letter from a psychologist attesting to the stability of their gender identity as a prerequisite to access an endocrinologist, surgeon, or legal institution (e.g., driver's license bureau; Lev, 2009). The need for such required documentation from a psychologist may influence rapport, resulting in TGNC people fearing prejudicial treatment in which this documentation is withheld or delayed by the treating provider (Bouman et al., 2014). Whether a TGNC person has personally experienced interactions with providers as disempowering or has learned from community members to expect such a dynamic, psychologists are encouraged to be prepared for TGNC people to be very cautious when entering into a therapeutic relationship. When TGNC people feel validated and empowered within the environment in which a psychologist practices, the therapeutic relationship will benefit and the person may be more willing to explore their authentic selves and share uncertainties and ambiguities that are a common part of TGNC identity development.

Application. Because many TGNC people experience antitrans prejudice or discrimination, psychologists are encouraged to ensure that their work settings are welcoming and respectful of TGNC people, and to be mindful of what TGNC people may perceive as unwelcoming. To do so, psychologists may educate themselves about the many ways that cisgender privilege and antitrans prejudice may be expressed. Psychologists may also have specific conversations with TGNC people about their experiences of the mental health system and implement feedback to foster TGNC-affirmative environments. As a result, when TGNC people access various treatment settings and public spaces, they may experience less harm, disempowerment, or pathologization, and thus will be more likely to avail themselves of resources and support.

Psychologists are encouraged to be proactive in considering how overt or subtle cues in their workplaces and other environments may affect the comfort and safety of TGNC people. To increase the comfort of TGNC people, psychologists are encouraged to display TGNC-affirmative resources in waiting areas and to avoid the display of items that reflect antitrans attitudes (Lev, 2009). Psychologists are encouraged to examine how their language (e.g., use of incorrect pronouns and names) may reinforce the gender binary in overt or subtle and unintentional ways (Smith, Shin, & Officer, 2012). It may be helpful for psychologists to provide training for support staff on how to respectfully interact with TGNC people. A psychologist may consider making changes to paperwork, forms, or outreach materials to ensure that these materials are more inclusive of TGNC people (Spade, 2011b). For example, demographic questionnaires can communicate respect through the use of inclusive language and the inclusion of a range of gender identities. In addition, psychologists may also work within their institutions to advocate for restrooms that are inclusive and accessible for people of all gender identities and/or gender expressions.

When working with TGNC people in a variety of care and institutional settings (e.g., inpatient medical and psychiatric hospitals, substance abuse treatment settings, nursing homes, foster care, religious communities, military and VA health care settings, and prisons), psychologists may become liaisons and advocates for TGNC people's mental health needs and for respectful treatment that addresses their gender identity in an affirming manner. In playing this role, psychologists may find guidance and best practices that have been published for particular institutional contexts to be helpful (e.g., Department of Veterans Affairs, Veterans' Health Administration, 2013; Glezer, McNiel, & Binder, 2013; Merksamer, 2011).

Guideline 7: Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

Rationale. The lack of public policy that addresses the needs of TGNC people creates significant hardships for them (Taylor, 2007). Although there have been major advances in legal protections for TGNC people in recent years (Buzuvis, 2013; Harvard Law Review Association, 2013), many TGNC people are still not afforded protections from discrimination on the basis of gender identity or expression (National LGBTQ Task Force, 2013; Taylor, 2007). For instance, in many states, TGNC people do not have employment or housing protections and may be fired or lose their housing based on their gender identity. Many policies that protect the rights of cisgender people, including LGB people, do not protect the rights of TGNC people (Currah, & Minter, 2000; Spade, 2011a).

TGNC people can experience challenges obtaining gender-affirming identity documentation (e.g., birth certificate, passport, social security card, driver's license). For TGNC people experiencing poverty or economic hardship, requirements for obtaining this documentation may be impossible to meet, in part due to the difficulty of securing employment without identity documentation that aligns with their gender identity and gender expression (Sheridan, 2009). Additionally, systemic barriers related to binary gender identification systems prevent some TGNC people from changing their documents, including those who are incarcerated, undocumented immigrants, and people who live in jurisdictions that explicitly forbid such changes (Spade, 2006). Documentation requirements can also assume a universal TGNC experience that marginalizes some TGNC people, especially those who do not undergo a medical transition. This may affect a TGNC person's social and psychological well-being and interfere with accessing employment, education, housing and shelter, health care, public benefits, and basic life management resources (e.g., opening a bank account).

Application. Psychologists are encouraged to inform public policy to reduce negative systemic impact on TGNC people and to promote positive social change. Psychologists are encouraged to identify and improve systems that permit violence; educational, employment, and housing discrimination; lack of access to health care; unequal access to other vital resources; and other instances of systemic inequity that TGNC people experience (ACA, 2010). Many TGNC people experience stressors from constant barriers, inequitable treatment, and forced release of sensitive and private information about their bodies and their lives (Hendricks & Testa, 2012). To obtain proper identity documentation, TGNC people may be required to provide court orders, proof of having had surgery, and documentation of psychotherapy or a psychiatric diagnosis. Psychologists may assist TGNC people by normalizing their reactions of fatigue and traumatization while interacting with legal systems and requirements; TGNC people may also benefit from guidance about alternate avenues of recourse, self-advocacy, or appeal. When TGNC people feel that it is unsafe to advocate for themselves, psychologists may work with their clients to access appropriate resources in the community.

Psychologists are encouraged to be sensitive to the challenges of attaining gender-affirming identity documentation and how the receipt or denial of such documentation may affect social and psychological well-being, the person's ability to obtain education and employment, find safe housing, access public benefits, obtain student loans, and access health insurance. It may be of significant assistance for psychologists to understand and offer information about the process of a legal name change, gender marker change on identification, or the process for accessing other gender-affirming documents. Psychologists may consult the National Center for Transgender Equality, the Sylvia Rivera Law Project, or the Transgender Law Center for additional information on identity documentation for TGNC people.

Psychologists may choose to become involved with an organization that seeks to revise law and public policy to better protect the rights and dignities of TGNC people. Psychologists may participate at the local, state, or national level to support TGNC-affirmative health care accessibility, human rights in sex-segregated facilities, or policy change regarding gender-affirming identity documentation. Psychologists working in institutional settings may also expand their roles to work as collaborative advocates for TGNC people (Gonzalez & McNulty, 2010). Psychologists are encouraged to provide written affirmations supporting TGNC people and their gender identity so that they may access necessary services (e.g., hormone therapy).

Life Span Development

Guideline 8. Psychologists working with gender-questioning [4] and TGNC youth understand the different developmental needs of children and adolescents, and that not all youth will persist in a TGNC identity into adulthood.

Rationale. Many children develop stability (constancy across time) in their gender identity between Ages 3 to 4 (Kohlberg, 1966), although gender consistency (recognition that gender remains the same across situations) often does not occur until Ages 4 to 7 (Siegal & Robinson, 1987). Children who demonstrate gender nonconformity in preschool and early elementary years may not follow this trajectory (Zucker & Bradley, 1995). Existing research suggests that between 12% and 50% of children diagnosed with gender dysphoria may persist in their identification with a gender different than sex assigned at birth into late adolescence and young adulthood (Drummond, Bradley,

[4] Gender-questioning youth are differentiated from TGNC youth in this section of the guidelines. Gender-questioning youth may be questioning or exploring their gender identity but have not yet developed a TGNC identity. As such, they may not be eligible for some services that would be offered to TGNC youth. Gender-questioning youth are included here because gender questioning may lead to a TGNC identity.

Peterson-Badaali, & Zucker, 2008; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008). However, several research studies categorized 30% to 62% of youth who did not return to the clinic for medical intervention after initial assessment, and whose gender identity may be unknown, as "desisters" who no longer identified with a gender different than sex assigned at birth (Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008a). As a result, this research runs a strong risk of inflating estimates of the number of youth who do not persist with a TGNC identity. Research has suggested that children who identify more intensely with a gender different than sex assigned at birth are more likely to persist in this gender identification into adolescence (Steensma et al., 2013), and that when gender dysphoria persists through childhood and intensifies into adolescence, the likelihood of long-term TGNC identification increases (A. L. de Vries, Steensma, Doreleijers, & Cohen-Kettenis, 2011; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008; Zucker, 2008b). Gender-questioning children who do not persist may be more likely to later identify as gay or lesbian than non-gender-questioning children (Bailey & Zucker, 1995; Drescher, 2014; Wallien & Cohen-Kettenis, 2008).

A clear distinction between care of TGNC and gender-questioning children and adolescents exists in the literature. Due to the evidence that not all children persist in a TGNC identity into adolescence or adulthood, and because no approach to working with TGNC children has been adequately, empirically validated, consensus does not exist regarding best practice with prepubertal children. Lack of consensus about the preferred approach to treatment may be due in part to divergent ideas regarding what constitutes optimal treatment outcomes for TGNC and gender-questioning youth (Hembree et al., 2009). Two distinct approaches exist to address gender identity concerns in children (Hill, Menvielle, Sica, & Johnson, 2010; Wallace & Russell, 2013), with some authors subdividing one of the approaches to suggest three (Byne et al., 2012; Drescher, 2014; Stein, 2012).

One approach encourages an affirmation and acceptance of children's expressed gender identity. This may include assisting children to socially transition and to begin medical transition when their bodies have physically developed, or allowing a child's gender identity to unfold without expectation of a specific outcome (A. L. de Vries & Cohen-Kettenis, 2012; Edwards-Leeper & Spack, 2012; Ehrensaft, 2012; Hidalgo et al., 2013; Tishelman et al., 2015). Clinicians using this approach believe that an open exploration and affirmation will assist children to develop coping strategies and emotional tools to integrate a positive TGNC identity should gender questioning persist (Edwards-Leeper & Spack, 2012).

In the second approach, children are encouraged to embrace their given bodies and to align with their assigned gender roles. This includes endorsing and supporting behaviors and attitudes that align with the child's sex assigned at birth prior to the onset of puberty (Zucker, 2008a; Zucker, Wood, Singh, & Bradley, 2012). Clinicians using this approach believe that undergoing multiple medical interventions and living as a TGNC person in a world that stigmatizes gender nonconformity is a less desirable outcome than one in which children may be assisted to happily align with their sex assigned at birth (Zucker et al., 2012). Consensus does not exist regarding whether this approach may provide benefit (Zucker, 2008a; Zucker et al., 2012) or may cause harm or lead to psychosocial adversities (Hill et al., 2010; Pyne, 2014; Travers et al., 2012; Wallace & Russell, 2013). When addressing psychological interventions for children and adolescents, the World Professional Association for Transgender Health Standards of Care identify interventions "aimed at trying to change gender identity and expression to become more congruent with sex assigned at birth" as unethical (Coleman et al., 2012, p. 175). It is hoped that future research will offer improved guidance in this area of practice (Adelson & AACAP CQI, 2012; Malpas, 2011).

Much greater consensus exists regarding practice with adolescents. Adolescents presenting with gender identity concerns bring their own set of unique challenges. This may include having a late-onset (i.e., postpubertal) presentation of gender nonconforming identification, with no history of gender role nonconformity or gender questioning in childhood (Edwards-Leeper & Spack, 2012). Complicating their clinical presentation, many gender-questioning adolescents also present with co-occurring psychological concerns, such as suicidal ideation, self-injurious behaviors (Liu & Mustanski, 2012; Mustanski, Garofalo, & Emerson, 2010), drug and alcohol use (Garofalo et al., 2006), and autism spectrum disorders (A. L. de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Jones et al., 2012). Additionally, adolescents can become intensely focused on their immediate desires, resulting in outward displays of frustration and resentment when faced with any delay in receiving the medical treatment from which they feel they would benefit and to which they feel entitled (Angello, 2013; Edwards-Leeper & Spack, 2012). This intense focus on immediate needs may create challenges in assuring that adolescents are cognitively and emotionally able to make life-altering decisions to change their name or gender marker, begin hormone therapy (which may affect fertility), or pursue surgery.

Nonetheless, there is greater consensus that treatment approaches for adolescents affirm an adolescents' gender identity (Coleman et al., 2012). Treatment options for adolescents extend beyond social approaches to include medical approaches. One particular medical intervention involves the use of puberty-suppressing medication or "blockers" (GnRH analogue), which is a reversible medical intervention used to delay puberty for appropriately screened adolescents with gender dysphoria (Coleman et al., 2012; A. L. C. de Vries et al., 2014; Edwards-Leeper, & Spack, 2012). Because of their age, other medical interventions may also become available to adolescents, and psychologists are frequently consulted to provide an assessment of whether such procedures would be advisable (Coleman et al., 2012).

Application. Psychologists working with TGNC and gender-questioning youth are encouraged to regularly review the most current literature in this area, recognizing the limited available research regarding the potential benefits and risks of different treatment approaches for children and for adolescents. Psychologists are encouraged to offer parents and guardians clear information about available treatment approaches, regardless of the specific approach chosen by the psychologist. Psychologists are encouraged to provide psychological service to TGNC and gender-questioning children and adolescents that draws from empirically validated literature when available, recognizing the influence psychologists' values and beliefs may have on the treatment approaches they select (Ehrbar & Gorton, 2010). Psychologists are also encouraged to remain aware that what one youth and/or parent may be seeking in a therapeutic relationship may not coincide with a clinician's approach (Brill & Pepper, 2008). In cases in which a youth and/or parent identify different preferred treatment outcomes than a clinician, it may not be clinically appropriate for the clinician to continue working with the youth and family, and alternative options, including referral, might be considered. Psychologists may also find themselves navigating family systems in which youth and their caregivers are seeking different treatment outcomes (Edwards-Leeper & Spack, 2012). Psychologists are encouraged to carefully reflect on their personal values and beliefs about gender identity development in conjunction with the available research, and to keep the best interest of the child or adolescent at the forefront of their clinical decisions at all times.

Because gender nonconformity may be transient for younger children in particular, the psychologist's role may be to help support children and their families through the process of exploration and self-identification (Ehrensaft, 2012). Additionally, psychologists may provide parents with information about possible long-term trajectories children may take in regard to their gender identity, along with the available medical interventions for adolescents whose TGNC identification persists (Edwards-Leeper & Spack, 2012).

When working with adolescents, psychologists are encouraged to recognize that some TGNC adolescents will not have a strong history of childhood gender role nonconformity or gender dysphoria either by self-report or family observation (Edwards-Leeper & Spack, 2012). Some of these adolescents may have withheld their feelings of gender nonconformity out of a fear of rejection, confusion, conflating gender identity and sexual orientation, or a lack of awareness of the option to identify as TGNC. Parents of these adolescents may need additional assistance in understanding and supporting their youth, given that late-onset gender dysphoria and TGNC identification may come as a significant surprise. Moving more slowly and cautiously in these cases is often advisable (Edwards-Leeper & Spack, 2012). Given the possibility of adolescents' intense focus on immediate desires and strong reactions to perceived delays or barriers, psychologists are encouraged to validate these concerns and the desire to move through the process quickly while also remaining thoughtful and deliberate in treatment. Adolescents and their families may need support in tolerating ambiguity and uncertainty with regard to gender identity and its development (Brill & Pepper, 2008). It is encouraged that care should be taken not to foreclose this process.

For adolescents who exhibit a long history of gender nonconformity, psychologists may inform parents that the adolescent's self-affirmed gender identity is most likely stable (A. L. de Vries et al., 2011). The clinical needs of these adolescents may be different than those who are in the initial phases of exploring or questioning their gender identity. Psychologists are encouraged to complete a comprehensive evaluation and ensure the adolescent's and family's readiness to progress while also avoiding unnecessary delay for those who are ready to move forward.

Psychologists working with TGNC and gender-questioning youth are encouraged to become familiar with medical treatment options for adolescents (e.g., puberty-suppressing medication, hormone therapy) and work collaboratively with medical providers to provide appropriate care to clients. Because the ongoing involvement of a knowledgeable mental health provider is encouraged due to the psychosocial implications, and is often also a required part of the medical treatment regimen that may be offered to TGNC adolescents (Coleman et al., 2012; Hembree et al., 2009), psychologists often play an essential role in assisting in this process.

Psychologists may encourage parents and caregivers to involve youth in developmentally appropriate decision making about their education, health care, and peer networks, as these relate to children's and adolescents' gender identity and gender expression (Ryan, Russell, Huebner, Diaz, & Sanchez, 2010). Psychologists are also encouraged to educate themselves about the advantages and disadvantages of social transition during childhood and adolescence, and to discuss these factors with both their young clients and clients' parents. Emphasizing to parents the importance of allowing their child the freedom to return to a gender identity that aligns with sex assigned at birth or another gender identity at any point cannot be overstated, particularly given the research that suggests that not all young gender nonconforming children will ultimately express a gender identity different from that assigned at birth (Wallien, & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Psychologists are encouraged to acknowledge and explore the fear and burden of responsibility that parents and caregivers may feel as they make decisions about the health of their child or adolescent (Grossman, D'Augelli, Howell, & Hubbard, 2006). Parents and caregivers may benefit from a supportive environment to discuss feelings of isolation, explore loss and grief they may experience, vent anger and frustration at systems that disrespect or discriminate against them and their youth, and learn how to communicate with others about their child's or adolescent's gender identity or gender expression (Brill & Pepper, 2008).

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Rationale. Little research has been conducted about TGNC elders, leaving much to be discovered about this life stage for TGNC people (Auldridge, Tamar-Mattis, Kennedy, Ames, & Tobin, 2012). Socialization into gender role behaviors and expectations based on sex assigned at birth, as well as the extent to which TGNC people adhere to these societal standards, is influenced by the chronological age at which a person self-identifies as TGNC, the age at which a person comes out or socially and/or medically transitions (Birren & Schaie, 2006; Bockting & Coleman, 2007; Cavanaugh & Blanchard-Fields, 2010; Nuttbrock et al., 2010; Wahl, Iwarsson, & Oswald, 2012), and a person's generational cohort (e.g., 1950 vs. 2010; Fredriksen-Goldsen et al., 2011).

Even decades after a medical or social transition, TGNC elders may still subscribe to the predominant gender role expectations that existed at the time of their transition (Knochel, Croghan, Moore, & Quam, 2011). Prior to the 1980s, TGNC people who transitioned were strongly encouraged by providers to pass in society as cisgender and heterosexual and to avoid associating with other TGNC people (Benjamin, 1966; R. Green & Money, 1969; Hastings, 1974; Hastings & Markland, 1978). Even TGNC elders who were comfortable telling others about their TGNC identity when they were younger may choose not to reveal their identity at a later stage of life (Ekins & King, 2005; Ippolito & Witten, 2014). Elders' unwillingness to disclose their TGNC identity can result from feelings of physical vulnerability or increased reliance on others who may discriminate against them or treat them poorly as a result of their gender identity (Bockting & Coleman, 2007), especially if the elder resides in an institutionalized setting (i.e., nursing home, assisted living facility) and relies on others for many daily needs (Auldridge et al., 2012). TGNC elders are also at a heightened risk for depression, suicidal ideation, and loneliness compared with LGB elders (Auldridge et al., 2012; Fredriksen-Goldsen et al., 2011).

A Transgender Law Center survey found that TGNC and LGB elders had less financial well-being than their younger cohorts, despite having a higher than average educational level for their age group compared with the general population (Hartzell, Frazer, Wertz, & Davis, 2009). Survey research has also revealed that TGNC elders experience underemployment and gaps in employment, often due to discrimination (Auldridge et al., 2012; Beemyn & Rankin, 2011; Factor & Rothblum, 2007). In the past, some TGNC people with established careers may have been encouraged by service providers to find new careers or jobs to avoid undergoing a gender transition at work or being identified as TGNC, potentially leading to a significant loss of income and occupational identity (Cook-Daniels, 2006). Obstacles to employment can increase economic disparities that result in increased needs for supportive housing and other social services (National Center for Transgender Equality, 2012; Services and Advocacy for GLBT Elders & National Center for Transgender Equality, 2012).

TGNC elders may face obstacles to seeking or accessing resources that support their physical, financial, or emotional well-being. For instance, they may be concerned about applying for social security benefits, fearing that their TGNC identity may become known (Hartzell et al., 2009). A TGNC elder may avoid medical care, increasing the likelihood of later needing a higher level of medical care (e.g., home-based care, assisted living, or nursing home) than their same-age cisgender peers (Hartzell et al., 2009; Ippolito & Witten, 2014; Mikalson et al., 2012). Nursing homes and assisted living facilities are rarely sensitive to the unique medical needs of TGNC elders (National Senior Citizens Law Center, 2011). Some TGNC individuals who enter congregate housing, assisted living, or long-term care settings may feel the need to reverse their transition to align with sex assigned at birth to avoid discrimination and persecution by other residents and staff (Ippolito & Witten, 2014).

Older age may both facilitate and complicate medical treatment related to gender transition. TGNC people who begin hormone therapy later in life may have a smoother transition due to waning hormone levels that are a natural part of aging (Witten & Eyler, 2012). Age may also influence the decisions TGNC elders make regarding sex-affirmation surgeries, especially if physical conditions exist that could significantly increase risks associated with surgery or recovery.

Much has been written about the resilience of elders who have endured trauma (Fuhrmann & Shevlowitz, 2006; Hardy, Concato, & Gill, 2004; Mlinac, Sheeran, Blissmer, Lees, & Martins, 2011; Rodin & Stewart, 2012). Although some TGNC elders have experienced significant psychological trauma related to their gender identity, some also have developed resilience and effective ways of coping with adversity (Fruhauf & Orel, 2015). Despite the limited availability of LGBTQ-affirmative religious organizations in many local communities, TGNC elders make greater use of these resources than their cisgender peers (Porter et al., 2013).

Application. Psychologists are encouraged to seek information about the biopsychosocial needs of TGNC elders to inform case conceptualization and treatment planning to address psychological, social, and medical concerns. Many TGNC elders are socially isolated. Isolation can occur as a result of a loss of social networks through death or through disclosure of a TGNC identity. Psychologists may assist TGNC elders in establishing new social networks that support and value their TGNC identity, while also working to strengthen existing family and friend networks after a TGNC identity has been disclosed. TGNC elders may find special value in relationships with others in their generational cohort or those who may have similar coming-out experiences. Psychologists may encourage TGNC elders to identify ways they can mentor and improve the resilience of younger TGNC generations, creating a sense of generativity (Erikson, 1968) and contribu-

tion while building new supportive relationships. Psychologists working with TGNC elders may help them recognize the sources of their resilience and encourage them to connect with and be active in their communities (Fuhrmann & Craffey, 2014).

For TGNC elders who have chosen not to disclose their gender identity, psychologists may provide support to address shame, guilt, or internalized antitrans prejudice, and validate each person's freedom to choose their pattern of disclosure. Clinicians may also provide validation and empathy when TGNC elders have chosen a model of transition that avoids any disclosure of gender identity and is heavily focused on passing as cisgender.

TGNC elders who choose to undergo a medical or social transition in older adulthood may experience antitrans prejudice from people who question the value of transition at an older age or who believe that these elders are not truly invested in their transition or in a TGNC identity given the length of time they have waited (Auldridge et al., 2012). Some TGNC elders may also grieve lost time and missed opportunities. Psychologists may validate elders' choices to come out, transition, or evolve their gender identity or gender expression at any age, recognizing that such choices may have been much less accessible or viable at earlier stages of TGNC elders' lives.

Psychologists may assist congregate housing, assisted living, or long-term care settings to best meet TGNC elders' needs through respectful communication and affirmation of each person's gender identity and gender expression. Psychologists may work with TGNC people in hospice care systems to develop an end-of-life plan that respects the person's wishes about disclosure of gender identity during and after death.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Rationale. TGNC people may seek assistance from psychologists in addressing gender-related concerns, other mental health issues, or both. Mental health problems experienced by a TGNC person may or may not be related to that person's gender identity and/or may complicate assessment and intervention of gender-related concerns. In some cases, there may not be a relationship between a person's gender identity and a co-occurring condition (e.g., depression, PTSD, substance abuse). In other cases, having a TGNC identity may lead or contribute to a co-occurring mental health condition, either directly by way of gender dysphoria, or indirectly by way of minority stress and oppression (Hendricks & Testa, 2012; I. H. Meyer, 1995, 2003). In extremely rare cases, a co-occurring condition can mimic gender dysphoria (i.e., a psychotic process that distorts the perception of one's gender; Baltieri & De Andrade, 2009; Hepp, Kraemer, Schnyder, Miller, & Delsignore, 2004).

Regardless of the presence or absence of an etiological link, gender identity may affect how a TGNC person experiences a co-occurring mental health condition, and/or a co-occurring mental health condition may complicate the person's gender expression or gender identity. For example, an eating disorder may be influenced by a TGNC person's gender expression (e.g., rigid eating patterns used to manage body shape or menstruation may be related to gender identity or gender dysphoria; Ålgars, Alanko, Santtila, & Sandnabba, 2012; Murray, Boon, & Touyz, 2013). In addition, the presence of autism spectrum disorder may complicate a TGNC person's articulation and exploration of gender identity (Jones et al., 2012). In cases in which gender dysphoria is contributing to other mental health concerns, treatment of gender dysphoria may be helpful in alleviating those concerns as well (Keo-Meier et al., 2015).

A relationship also exists between mental health conditions and the psychological sequelae of minority stress that TGNC people can experience. Given that TGNC people experience physical and sexual violence (Clements-Nolle et al., 2006; Kenagy & Bostwick, 2005; Lombardi, Wilchins, Priesing, & Malouf, 2001; Xavier et al., 2005), general harassment and discrimination (Beemyn & Rankin, 2011; Factor & Rothblum, 2007), and employment and housing discrimination (Bradford et al., 2007), they are likely to experience significant levels of minority stress. Studies have demonstrated the disproportionately high levels of negative psychological sequelae related to minority stress, including suicidal ideation and suicide attempts (Center for Substance Abuse Treatment, 2012; Clements-Nolle et al., 2006; Cochran & Cauce, 2006; Nuttbrock et al., 2010; Xavier et al., 2005) and completed suicides (Dhejne et al., 2011; van Kesteren, Asscheman, Megens, & Gooren, 1997). Recent studies have begun to demonstrate an association between sources of external stress and psychological distress (Bockting et al., 2013; Nuttbrock et al., 2010), including suicidal ideation and attempts and self-injurious behavior (dickey, Reisner, & Juntunen, 2015; Goldblum et al., 2012; Testa et al., 2012).

The minority stress model accounts for both the negative mental health effects of stigma-related stress and the processes by which members of the minority group may develop resilience and resistance to the negative effects of stress (I. H. Meyer, 1995, 2003). Although the minority stress model was developed as a theory of the relationship between sexual orientation and mental disorders, the model has been adapted to TGNC populations (Hendricks & Testa, 2012).

Application. Because of the increased risk of stress-related mental health conditions, psychologists are encouraged to conduct a careful diagnostic assessment, including a differential diagnosis, when working with TGNC people (Coleman et al., 2012). Taking into account the intricate interplay between the effects of mental health symptoms and gender identity and gender expression, psychologists are encouraged to neither ignore mental health problems a TGNC person is experiencing, nor erroneously

assume that those mental health problems are a result of the person's gender identity or gender expression. Psychologists are strongly encouraged to be cautious before determining that gender nonconformity or dysphoria is due to an underlying psychotic process, as this type of causal relationship is rare.

When TGNC people seek to access transition-related health care, a psychosocial assessment is often part of this process (Coleman et al., 2012). A comprehensive and balanced assessment typically includes not only information about a person's past experiences of antitrans prejudice or discrimination, internalized messages related to these experiences, and anticipation of future victimization or rejection (Coolhart, Provancher, Hager, & Wang, 2008), but also coping strategies and sources of resilience (Hendricks & Testa, 2012; Singh et al., 2011). Gathering information about negative life events directly related to a TGNC person's gender identity and gender expression may assist psychologists in understanding the sequelae of stress and discrimination, distinguishing them from concurrent and potentially unrelated mental health problems. Similarly, when a TGNC person has a primary presenting concern that is not gender focused, a comprehensive assessment takes into account that person's experience relative to gender identity and gender expression, including any discrimination, just as it would include assessing other potential trauma history, medical concerns, previous experience with helping professionals, important future goals, and important aspects of identity. Strategies a TGNC person uses to navigate antitrans discrimination could be sources of strength to deal with life challenges or sources of distress that increase challenges and barriers.

Psychologists are encouraged to help TGNC people understand the pervasive influence of minority stress and discrimination that may exist in their lives, potentially including internalized negative attitudes about themselves and their TGNC identity (Hendricks & Testa, 2012). With this support, clients can better understand the origins of their mental health symptoms and normalize their reactions when faced with TGNC-related inequities and discrimination. Minority stress models also identify potentially important sources of resilience. TGNC people can develop resilience when they connect with other TGNC people who provide information on how to navigate antitrans prejudice and increase access to necessary care and resources (Singh et al., 2011). TGNC people may need help developing social support systems to nurture their resilience and bolster their ability to cope with the adverse effects of antitrans prejudice and/or discrimination (Singh & McKleroy, 2011).

Feminizing or masculinizing hormone therapy can positively or negatively affect existing mood disorders (Coleman et al., 2012). Psychologists may also help TGNC people who are in the initial stages of hormone therapy adjust to normal changes in how they experience emotions. For example, trans women who begin estrogens and antiandrogens may experience a broader range of emotions than they are accustomed to, or trans men beginning testosterone might be faced with adjusting to a higher libido and feeling more emotionally reactive in stressful situations. These changes can be normalized as similar to the emotional adjustments that cisgender women and men experience during puberty. Some TGNC people will be able to adapt existing coping strategies, whereas others may need help developing additional skills (e.g., emotional regulation or assertiveness). Readers are encouraged to refer to the World Professional Association for Transgender Health Standards of Care for discussion of the possible effects of hormone therapy on a TGNC person's mood, affect, and behavior (Coleman et al., 2012).

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Rationale. Research has primarily shown positive treatment outcomes when TGNC adults and adolescents receive TGNC-affirmative medical and psychological services (i.e., psychotherapy, hormones, surgery; Byne et al., 2012; R. Carroll, 1999; Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; Davis & Meier, 2014; De Cuypere et al., 2006; Gooren, Giltay, & Bunck, 2008; Kuhn et al., 2009), although sample sizes are frequently small with no population-based studies. In a meta-analysis of the hormone therapy treatment literature with TGNC adults and adolescents, researchers reported that 80% of participants receiving trans-affirmative care experienced an improved quality of life, decreased gender dysphoria, and a reduction in negative psychological symptoms (Murad et al., 2010).

In addition, TGNC people who receive social support about their gender identity and gender expression have improved outcomes and quality of life (Brill & Pepper, 2008; Pinto, Melendez, & Spector, 2008). Several studies indicate that family acceptance of TGNC adolescents and adults is associated with decreased rates of negative outcomes, such as depression, suicide, and HIV risk behaviors and infection (Bockting et al., 2013; Dhejne et al., 2011; Grant et al., 2011; Liu & Mustanski, 2012; Ryan, 2009). Family support is also a strong protective factor for TGNC adults and adolescents (Bockting et al., 2013; Moody & Smith, 2013; Ryan et al., 2010). TGNC people, however, frequently experience blatant or subtle antitrans prejudice, discrimination, and even violence within their families (Bradford et al., 2007). Such family rejection is associated with higher rates of HIV infection, suicide, incarceration, and homelessness for TGNC adults and adolescents (Grant et al., 2011; Liu & Mustanski, 2012). Family rejection and lower levels of social support are significantly correlated with depression (Clements-Nolle et al., 2006; Ryan, 2009). Many TGNC people seek support through peer relationships, chosen families, and communities in which they may be more likely to experience acceptance (Gonzalez & McNulty, 2010; Nuttbrock et al., 2009). Peer support from other TGNC people has been found to be a moderator between antitrans discrimination and mental health, with higher levels of peer support associated with better mental health (Bockting et al., 2013). For some TGNC people, support from religious and spiritual communities provides

an important source of resilience (Glaser, 2008; Kidd & Witten, 2008; Porter et al., 2013).

Application. Given the strong evidence for the positive influence of affirmative care, psychologists are encouraged to facilitate access to and provide trans-affirmative care to TGNC people. Whether through the provision of assessment and psychotherapy, or through assisting clients to access hormone therapy or surgery, psychologists may play a critical role in empowering and validating TGNC adults' and adolescents' experiences and increasing TGNC people's positive life outcomes (Bess & Stabb, 2009; Rachlin, 2002).

Psychologists are also encouraged to be aware of the importance of affirmative social support and assist TGNC adults and adolescents in building social support networks in which their gender identity is accepted and affirmed. Psychologists may assist TGNC people in negotiating family dynamics that may arise in the course of exploring and establishing gender identity. Depending on the context of psychological practice, these issues might be addressed in individual work with TGNC clients, conjoint sessions including members of their support system, family therapy, or group therapy. Psychologists may help TGNC people decide how and when to reveal their gender identity at work or school, in religious communities, and to friends and contacts in other settings. TGNC people who decide not to come out in all aspects of their lives can still benefit from TGNC-affirmative in-person or online peer support groups.

Clients may ask psychologists to assist family members in exploring feelings about their loved one's gender identity and gender expression. Published models of family adjustment (Emerson & Rosenfeld, 1996) may be useful to help normalize family members' reactions upon learning that they have a TGNC family member, and to reduce feelings of isolation. When working with family members or significant others, it may be helpful to normalize feelings of loss or fear of what may happen to current relationships as TGNC people disclose their gender identity and expression to others. Psychologists may help significant others adjust to changing relationships and consider how to talk to extended family, friends, and other community members about TGNC loved ones. Providing significant others with referrals to TGNC-affirmative providers, educational resources, and support groups can have a profound impact on their understanding of gender identity and their communication with TGNC loved ones. Psychologists working with couples and families may also help TGNC people identify ways to include significant others in their social or medical transition.

Psychologists working with TGNC people in rural settings may provide clients with resources to connect with other TGNC people online or provide information about in-person support groups in which they can explore the unique challenges of being TGNC in these geographic areas (Walinsky & Whitcomb, 2010). Psychologists serving TGNC military and veteran populations are encouraged to be sensitive to the barriers these individuals face, especially for people who are on active duty in the U.S. military (OutServe-Servicemembers Legal Defense Network, n.d.). Psychologists may help TGNC military members and veterans establish specific systems of support that create a safe and affirming space to reduce isolation and to create a network of peers with a shared military experience. Psychologists who work with veterans are encouraged to educate themselves on recent changes to VA policy that support equal access to VA medical and mental health services (Department of Veterans Affairs, Veterans' Health Administration, 2013).

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Rationale. Relationships involving TGNC people can be healthy and successful (Kins, Hoebeke, Heylens, Rubens, & De Cuyprere, 2008; Meier, Sharp, Michonski, Babcock, & Fitzgerald, 2013) as well as challenging (Brown, 2007; Iantaffi & Bockting, 2011). A study of successful relationships between TGNC men and cisgender women found that these couples attributed the success of their relationship to respect, honesty, trust, love, understanding, and open communication (Kins et al., 2008). Just as relationships between cisgender people can involve abuse, so can relationships between TGNC people and their partners (Brown, 2007), with some violent partners threatening to disclose a TGNC person's identity to exact control in the relationship (FORGE, n.d.).

In the early decades of medical and social transition for TGNC people, only those whose sexual orientations would be heterosexual posttransition (e.g., trans woman with a cisgender man) were deemed eligible for medical and social transition (Meyerowitz, 2002). This restriction prescribed only certain relationship partners (American Psychiatric Association, 1980; Benjamin, 1966; Chivers & Bailey, 2000), denied access to surgery for trans men identifying as gay or bisexual (Coleman & Bockting, 1988), or trans women identifying as lesbian or bisexual, and even required that TGNC people's existing legal marriages be dissolved before they could gain access to transition care (Lev, 2004).

Disclosure of a TGNC identity can have an important impact on the relationship between TGNC people and their partners. Disclosure of TGNC status earlier in the relationship tends to be associated with better relationship outcomes, whereas disclosure of TGNC status many years into an existing relationship may be perceived as a betrayal (Erhardt, 2007). When a TGNC person comes out in the context of an existing relationship, it can also be helpful if both partners are involved in decision making about the use of shared resources (i.e., how to balance the financial costs of transition with other family needs) and how to share this news with shared supports (i.e., friends and family). Sometimes relationship roles are renegotiated in the context of a TGNC person coming out to their partner (Samons, 2008). Assumptions about what it means to be a "husband" or a "wife" can shift if the gender identity of one's spouse shifts

(Erhardt, 2007). Depending on when gender issues are disclosed and how much of a change this creates in the relationship, partners may grieve the loss of aspects of their partner and the way the relationship used to be (Lev, 2004).

Although increasing alignment between gender identity and gender expression, whether it be through dress, behavior, or through medical interventions (i.e., hormones, surgery), does not necessarily affect to whom a TGNC person is attracted (Coleman et al., 1993), TGNC people may become more open to exploring their sexual orientation, may redefine sexual orientation as they move through transition, or both (Daskalos, 1998; H. Devor, 1993; Schleifer, 2006). Through increased comfort with their body and gender identity, TGNC people may explore aspects of their sexual orientation that were previously hidden or that felt discordant with their sex assigned at birth. Following a medical and/or social transition, a TGNC person's sexual orientation may remain constant or shift, either temporarily or permanently (e.g., renewed exploration of sexual orientation in the context of TGNC identity, shift in attraction or choice of sexual partners, widened spectrum of attraction, shift in sexual orientation identity; Meier, Sharp et al., 2013; Samons, 2008). For example, a trans man previously identified as a lesbian may later be attracted to men (Coleman et al., 1993; dickey, Burnes, & Singh, 2012), and a trans woman attracted to women pretransition may remain attracted to women posttransition (Lev, 2004).

Some TGNC people and their partners may fear the loss of mutual sexual attraction and other potential effects of shifting gender identities in the relationship. Lesbian-identified partners of trans men may struggle with the idea that being in a relationship with a man may cause others to perceive them as a heterosexual couple (Califia, 1997). Similarly, women in heterosexual relationships who later learn that their partners are trans women may be unfamiliar with navigating stigma associated with sexual minority status when viewed as a lesbian couple (Erhardt, 2007). Additionally, partners may find they are not attracted to a partner after transition. As an example, a lesbian whose partner transitions to a male identity may find that she is no longer attracted to this person because she is not sexually attracted to men. Partners of TGNC people may also experience grief and loss as their partners engage in social and/or medical transitions.

Application. Psychologists may help foster resilience in relationships by addressing issues specific to partners of TGNC people. Psychologists may provide support to partners of TGNC people who are having difficulty with their partner's evolving gender identity or transition, or are experiencing others having difficulty with the partner's transition. Partner peer support groups may be especially helpful in navigating internalized antitrans prejudice, shame, resentment, and relationship concerns related to a partner's gender transition. Meeting or knowing other TGNC people, other partners of TGNC people, and couples who have successfully navigated transition may also help TGNC people and their partners and serve as a protective factor (Brown, 2007). When TGNC status is disclosed during an existing relationship, psychologists may help couples explore which relationship dynamics they want to preserve and which they might like to change.

In working with psychologists, TGNC people may explore a range of issues in their relationships and sexuality (dickey et al., 2012), including when and how to come out to current or potential romantic and sexual partners, communicating their sexual desires, renegotiating intimacy that may be lost during the TGNC partner's transition, adapting to bodily changes caused by hormone use or surgery, and exploring boundaries regarding touch, affection, and safer sex practices (Iantaffi & Bockting, 2011; Sevelius, 2009). TGNC people may experience increased sexual self-efficacy through transition. Although psychologists may aid partners in understanding a TGNC person's transition decisions, TGNC people may also benefit from help in cultivating awareness of the ways in which these decisions influence the lives of loved ones.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Rationale. Psychologists work with TGNC people across the life span to address parenting and family issues (Kenagy & Hsieh, 2005). There is evidence that many TGNC people have and want children (Wierckx et al., 2012). Some TGNC people conceive a child through sexual intercourse, whereas others may foster, adopt, pursue surrogacy, or employ assisted reproductive technologies, such as sperm or egg donation, to build or expand a family (De Sutter, Kira, Verschoor, & Hotimsky, 2002). Based on a small body of research to date, there is no indication that children of TGNC parents suffer long-term negative impacts directly related to parental gender change (R. Green, 1978, 1988; White & Ettner, 2004). TGNC people may find it both challenging to find medical providers who are willing to offer them reproductive treatment and to afford the cost (Coleman et al., 2012). Similarly, adoption can be quite costly, and some TGNC people may find it challenging to find foster care or adoption agencies that will work with them in a nondiscriminatory manner. Current or past use of hormone therapy may limit fertility and restrict a TGNC person's reproductive options (Darnery, 2008; Wierckx et al., 2012). Other TGNC people may have children or families before coming out as TGNC or beginning a gender transition.

TGNC people may present with a range of parenting and family-building concerns. Some will seek support to address issues within preexisting family systems, some will explore the creation or expansion of a family, and some will need to make decisions regarding potential fertility issues related to hormone therapy, pubertal suppression, or surgical transition. The medical and/or social transition of a TGNC parent may shift family dynamics, creating challenges and opportunities for partners, children, and other family members. One study of therapists' reflections on their experiences with TGNC clients suggested that family constellation and the parental relationship was more significant for children than the parent's social and/or medical

transition itself (White & Ettner, 2004). Although research has not documented that the transitions of TGNC people have an effect on their parenting abilities, preexisting partnerships or marriages may not survive the disclosure of a TGNC identity or a subsequent transition (dickey et al., 2012). This may result in divorce or separation, which may affect the children in the family. A positive relationship between parents, regardless of marital status, has been suggested to be an important protective factor for children (Amato, 2001; White & Ettner, 2007). This seems to be the case especially when children are reminded of the parent's love and assured of the parent's continued presence in their life (White & Ettner, 2007). Based on a small body of literature available, it is generally the case that younger children are best able to incorporate the transition of a parent, followed by adult children, with adolescents generally having the most difficulty (White & Ettner, 2007). If separated or divorced from their partners or spouses, TGNC parents may be at risk for loss of custody or visitation rights because some courts presume that there is a nexus between their gender identity or gender expression and parental fitness (Flynn, 2006). This type of prejudice is especially common for TGNC people of color (Grant et al., 2011).

Application. Psychologists are encouraged to attend to the parenting and family-building concerns of TGNC people. When working with TGNC people who have previous parenting experience, psychologists may help TGNC people identify how being a parent may influence decisions to come out as TGNC or to begin a transition (Freeman, Tasker, & Di Ceglie, 2002; Grant et al., 2011; Wierckx et al., 2012). Some TGNC people may choose to delay disclosure until their children have grown and left home (Bethea & McCollum, 2013). Clinical guidelines jointly developed by a Vancouver, British Columbia, TGNC community organization and a health care provider organization encourage psychologists and other mental health providers working with TGNC people to plan for disclosure to a partner, previous partner, or children, and to pay particular attention to resources that assist TGNC people to discuss their identity with children of various ages in developmentally appropriate ways (Bockting et al., 2006). Lev (2004) uses a developmental stage framework for the process that family members are likely to go through in coming to terms with a TGNC family member's identity that some psychologists may find helpful. Awareness of peer support networks for spouses and children of TGNC people can also be helpful (e.g., PFLAG, TransYouth Family Allies). Psychologists may provide family counseling to assist a family in managing disclosure, improve family functioning, and maintain family involvement of the TGNC person, as well as aiding the TGNC person in attending to the ways that their transition process has affected their family members (Samons, 2008). Helping parents to continue to work together to focus on the needs of their children and to maintain family bonds is likely to lead to the best results for the children (White & Ettner, 2007).

For TGNC people with existing families, psychologists may support TGNC people in seeking legal counsel regarding parental rights in adoption or custody. Depending on the situation, this may be desirable even if the TGNC parent is biologically related to the child (Minter & Wald, 2012). Although being TGNC is not a legal impediment to adoption in the United States, there is the potential for overt and covert discrimination and barriers, given the widespread prejudice against TGNC people. The question of whether to disclose TGNC status on an adoption application is a personal one, and a prospective TGNC parent would benefit from consulting a lawyer for legal advice, including what the laws in their jurisdiction say about disclosure. Given the extensive background investigation frequently conducted, it may be difficult to avoid disclosure. Many lawyers favor disclosure to avoid any potential legal challenges during the adoption process (Minter & Wald, 2012).

In discussing family-building options with TGNC people, psychologists are encouraged to remain aware that some of these options require medical intervention and are not available everywhere, in addition to being quite costly (Coleman et al., 2012). Psychologists may work with clients to manage feelings of loss, grief, anger, and resentment that may arise if TGNC people are unable to access or afford the services they need for building a family (Bockting et al., 2006; De Sutter et al., 2002).

When TGNC people consider beginning hormone therapy, psychologists may engage them in a conversation about the possibly permanent effects on fertility to better prepare TGNC people to make a fully informed decision. This may be of special importance with TGNC adolescents and young adults who often feel that family planning or loss of fertility is not a significant concern in their current daily lives, and therefore disregard the long-term reproductive implications of hormone therapy or surgery (Coleman et al., 2012). Psychologists are encouraged to discuss contraception and safer sex practices with TGNC people, given that they may still have the ability to conceive even when undergoing hormone therapy (Bockting, Robinson, & Rosser, 1998). Psychologists may play a critical role in educating TGNC adolescents and young adults and their parents about the long-term effects of medical interventions on fertility and assist them in offering informed consent prior to pursuing such interventions. Although hormone therapy may limit fertility (Coleman et al., 2012), psychologists may encourage TGNC people to refrain from relying on hormone therapy as the sole means of birth control, even when a person has amenorrhea (Gorton & Grubb, 2014). Education on safer sex practices may also be important, as some segments of the TGNC community (e.g., trans women and people of color) are especially vulnerable to sexually transmitted infections and have been shown to have high prevalence and incidence rates of HIV infection (Kellogg, Clements-Nolle, Dilley, Katz, & McFarland, 2001; Nemoto, Operario, Keatley, Han, & Soma, 2004).

Depending on the timing and type of options selected, psychologists may explore the physical, social, and emotional implications should TGNC people choose to delay or

stop hormone therapy, undergo fertility treatment, or become pregnant. Psychological effects of stopping hormone therapy may include depression, mood swings, and reactions to the loss of physical masculinization or feminization facilitated by hormone therapy (Coleman et al., 2012). TGNC people who choose to halt hormone therapy during attempts to conceive or during a pregnancy may need additional psychological support. For example, TGNC people and their families may need help in managing the additional antitrans prejudice and scrutiny that may result when a TGNC person with stereotypically masculine features becomes visibly pregnant. Psychologists may also assist TGNC people in addressing their loss when they cannot engage in reproductive activities that are consistent with their gender identity, or when they encounter barriers to conceiving, adopting, or fostering children not typically faced by other people (Vanderburgh, 2007). Psychologists are encouraged to assess the degree to which reproductive health services are TGNC-affirmative prior to referring TGNC people to them. Psychologists are also encouraged to provide TGNC-affirmative information to reproductive health service personnel when there is a lack of trans-affirmative knowledge.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Rationale. Collaboration across disciplines can be crucial when working with TGNC people because of the potential interplay of biological, psychological, and social factors in diagnosis and treatment (Hendricks & Testa, 2012). The challenges of living with a stigmatized identity and the need of many TGNC people to transition, socially and/or medically, may call for the involvement of health professionals from various disciplines, including psychologists, psychiatrists, social workers, primary health care providers, endocrinologists, nurses, pharmacists, surgeons, gynecologists, urologists, electrologists, speech therapists, physical therapists, pastoral counselors and chaplains, and career or educational counselors. Communication, cooperation, and collaboration will ensure optimal coordination and quality of care. Just as psychologists often refer TGNC people to medical providers for assessment and treatment of medical issues, medical providers may rely on psychologists to assess readiness and assist TGNC clients to prepare for the psychological and social aspects of transition before, during, and after medical interventions (Coleman et al., 2012; Hembree et al., 2009; Lev, 2009). Outcome research to date supports the value and effectiveness of an interdisciplinary, collaborative approach to TGNC-specific care (see Coleman et al., 2012 for a review).

Application. Psychologists' collaboration with colleagues in medical and associated health disciplines involved in TGNC clients' care (e.g., hormonal and surgical treatment, primary health care; Coleman et al., 2012; Lev, 2009) may take many forms and should occur in a timely manner that does not complicate access to needed services (e.g., considerations of wait time). For example, a psychologist working with a trans man who has a diagnosis of bipolar disorder may need to coordinate with his primary care provider and psychiatrist to adjust his hormone levels and psychiatric medications, given that testosterone can have an activating effect, in addition to treating gender dysphoria. At a basic level, collaboration may entail the creation of required documentation that TGNC people present to surgeons or medical providers to access gender-affirming medical interventions (e.g., surgery, hormone therapy; Coleman et al., 2012). Psychologists may offer support, information, and education to interdisciplinary colleagues who are unfamiliar with issues of gender identity and gender expression to assist TGNC people in obtaining TGNC-affirmative care (Holman & Goldberg, 2006; Lev, 2009). For example, a psychologist who is assisting a trans woman with obtaining gender-affirming surgery may, with her consent, contact her new gynecologist in preparation for her first medical visit. This contact could include sharing general information about her gender history and discussing how both providers could most affirmatively support appropriate health checks to ensure her best physical health (Holman & Goldberg, 2006).

Psychologists in interdisciplinary settings could also collaborate with medical professionals prescribing hormone therapy by educating TGNC people and ensuring TGNC people are able to make fully informed decisions prior to starting hormone treatment (Coleman et al., 2012; Deutsch, 2012; Lev, 2009). Psychologists working with children and adolescents play a particularly important role on the interdisciplinary team due to considerations of cognitive and social development, family dynamics, and degree of parental support. This role is especially crucial when providing psychological evaluation to determine the appropriateness and timeliness of a medical intervention. When psychologists are not part of an interdisciplinary setting, especially in isolated or rural communities, they can identify interdisciplinary colleagues with whom they may collaborate and/or refer (Walinsky & Whitcomb, 2010). For example, a rural psychologist could identify a trans-affirmative pediatrician in a surrounding area and collaborate with the pediatrician to work with parents raising concerns about their TGNC and questioning children and adolescents.

In addition to working collaboratively with other providers, psychologists who obtain additional training to specialize in work with TGNC people may also serve as consultants in the field (e.g., providing additional support to providers working with TGNC people or assisting school and workplaces with diversity training). Psychologists who have expertise in working with TGNC people may play a consultative role with providers in inpatient settings seeking to provide affirmative care to TGNC clients. Psychologists may also collaborate with social service colleagues to provide TGNC people with affirmative referrals related to housing, financial support, vocational/educational counseling and training, TGNC-affirming religious or spiritual communities, peer support, and other community resources (Gehi & Arkles, 2007). This collaboration might also in-

clude assuring that TGNC people who are minors in the care of the state have access to culturally appropriate care.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Rationale. Historically, in a set of demographic questions, psychological research has included one item on either sex or gender, with two response options—male and female. This approach wastes an opportunity to increase knowledge about TGNC people for whom neither option may fit their identity, and runs the risk of alienating TGNC research participants (IOM, 2011). For example, there is little knowledge about HIV prevalence, risks, and prevention needs of TGNC people because most of the research on HIV has not included demographic questions to identify TGNC participants within their samples. Instead, TGNC people have been historically subsumed within larger demographic categories (e.g., men who have sex with men, women of color), rendering the impact of the HIV epidemic on the TGNC population invisible (Herbst et al., 2008). Scholars have noted that this invisibility fails to draw attention to the needs of TGNC populations that experience the greatest health disparities, including TGNC people who are of color, immigrants, low income, homeless, veterans, incarcerated, live in rural areas, or have disabilities (Bauer et al., 2009; Hanssmann, Morrison, Russian, Shiu-Thornton, & Bowen, 2010; Shipherd et al., 2012; Walinsky & Whitcomb, 2010).

There is a great need for more research to inform practice, including affirmative treatment approaches with TGNC people. Although sufficient evidence exists to support current standards of care (Byne et al., 2012; Coleman et al., 2012), much is yet to be learned to optimize quality of care and outcome for TGNC clients, especially as it relates to the treatment of children (IOM, 2011; Mikalson et al., 2012). In addition, some research with TGNC populations has been misused and misinterpreted, negatively affecting TGNC people's access to health services to address issues of gender identity and gender expression (Namaste, 2000). This has resulted in justifiable skepticism and suspicion in the TGNC community when invited to participate in research initiatives. In accordance with the APA ethics code (APA, 2010), psychologists conduct research and distribute research findings with integrity and respect for their research participants. As TGNC research increases, some TGNC communities may experience being oversampled in particular geographic areas and/or TGNC people of color may not be well-represented in TGNC studies (Hwahng & Lin, 2009; Namaste, 2000).

Application. All psychologists conducting research, even when not specific to TGNC populations, are encouraged to provide a range of options for capturing demographic information about TGNC people so that TGNC people may be included and accurately represented (Conron et al., 2008; Deutsch et al., 2013). One group of experts has recommended that population research, and especially government-sponsored surveillance research, use a two-step method, first asking for sex assigned at birth, and then following with a question about gender identity (GenIUSS, 2013). For research focused on TGNC people, including questions that assess both sex assigned at birth and current gender identity allows the disaggregation of subgroups within the TGNC population and has the potential to increase knowledge of differences within the population. In addition, findings about one subgroup of TGNC people may not apply to other subgroups. For example, results from a study of trans women of color with a history of sex work who live in urban areas (Nemoto, Operario, Keatley, & Villegas, 2004) may not generalize to all TGNC women of color or to the larger TGNC population (Bauer, Travers, Scanlon, & Coleman, 2012; Operario et al., 2008).

In conducting research with TGNC people, psychologists will confront the challenges associated with studying a relatively small, geographically dispersed, diverse, stigmatized, hidden, and hard-to-reach population (IOM, 2011). Because TGNC individuals are often hard to reach (IOM, 2011) and TGNC research is rapidly evolving, it is important to consider the strengths and limitations of the methods that have been or may be used to study the TGNC population, and to interpret and represent findings accordingly. Some researchers have strongly recommended collaborative research models (e.g., participatory action research) in which TGNC community members are integrally involved in these research activities (Clements-Nolle & Bachrach, 2003; Singh, Richmond, & Burnes, 2013). Psychologists who seek to educate the public by communicating research findings in the popular media will also confront challenges, because most journalists have limited knowledge about the scientific method and there is potential for the media to misinterpret, exploit, or sensationalize findings (Garber, 1992; Namaste, 2000).

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

Rationale. The *Ethical Principles of Psychologists and Code of Conduct* (APA, 2010) include gender identity as one factor for which psychologists may need to obtain training, experience, consultation, or supervision in order to ensure their competence (APA, 2010). In addition, when APA-accredited programs are required to demonstrate a commitment to cultural and individual diversity, gender identity is specifically included (APA, 2015). Yet surveys of TGNC people suggest that many mental health care providers lack even basic knowledge and skills required to offer trans-affirmative care (Bradford et al., 2007; O'Hara, Dispenza, Brack, & Blood, 2013; Xavier et al., 2005). The APA Task Force on Gender Identity and Gender Variance (2009) projected that many, if not most, psychologists and graduate psychology students will at some point encounter TGNC people among their clients, colleagues, and trainees. Yet professional education and training in psychology includes little or no preparation for

working with TGNC people (Anton, 2009; APA TFGIGV, 2009), and continuing professional education available to practicing mental health clinicians is also scant (Lurie, 2005). Only 52% percent of psychologists and graduate students who responded to a survey conducted by an APA Task Force reported having had the opportunity to learn about TGNC issues in school; of those respondents, only 27% reported feeling adequately familiar with gender concerns (n = 294; APA TFGIGV, 2009).

Training on gender identity in professional psychology has frequently been subsumed under discussions of sexual orientation or in classes on human sexuality. Some scholars have suggested that psychologists and students may mistakenly believe that they have obtained adequate knowledge and awareness about TGNC people through training focused on LGB populations (Harper & Schneider, 2003). However, Israel and colleagues have found important differences between the therapeutic needs of TGNC people and those of LGB people in the perceptions of both clients and providers (Israel et al., 2008; Israel, Walther, Gorcheva, & Perry, 2011). Nadal and colleagues have suggested that the absence of distinct, accurate information about TGNC populations in psychology training not only perpetuates misunderstanding and marginalization of TGNC people by psychologists but also contributes to continued marginalization of TGNC people in society as a whole (Nadal et al., 2010, 2012).

Application. Psychologists strive to continue their education on issues of gender identity and gender expression with TGNC people as a foundational component of affirmative psychological practice. In addition to these guidelines, which educators may use as a resource in developing curricula and training experiences, ACA (2010) has also adopted a set of competencies that may be a helpful resource for educators. In addition to including TGNC people and their issues in foundational education in health service psychology (e.g., personality development, multiculturalism, research methods), some psychology programs may also provide coursework and training for students interested in developing more advanced expertise on issues of gender identity and gender expression.

Because of the high level of societal ignorance and stigma associated with TGNC people, ensuring that psychological education, training, and supervision is affirmative, and does not sensationalize (Namaste, 2000), exploit, or pathologize TGNC people (Lev, 2004), will require care on the part of educators. Students will benefit from support from their educators in developing a professional, nonjudgmental attitude toward people who may have a different experience of gender identity and gender expression from their own. A number of training resources have been published that may be helpful to psychologists in integrating information about TGNC people into the training they offer (e.g., Catalano, McCarthy, & Shlasko, 2007; Stryker, 2008; Wentling, Schilt, Windsor, & Lucal, 2008). Because most psychologists have had little or no training on TGNC populations and do not perceive themselves as having sufficient understanding of issues related to gender identity and gender expression (APA TFGIGV, 2009), psychologists with relevant expertise are encouraged to develop and distribute continuing education and training to help to address these gaps. Psychologists providing education can incorporate activities that increase awareness of cisgender privilege, antitrans prejudice and discrimination, host a panel of TGNC people to offer personal perspectives, or include narratives of TGNC people in course readings (ACA, 2010). When engaging these approaches, it is important to include a wide variety of TGNC experiences to reflect the inherent diversity within the TGNC community.

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Appendix A
Definitions

Terminology within the health care field and transgender and gender nonconforming (TGNC) communities is constantly evolving (Coleman et al., 2012). The evolution of terminology has been especially rapid in the last decade, as the profession's awareness of gender diversity has increased, as more literature and research in this area has been published, and as voices of the TGNC community have strengthened. Some terms or definitions are not universally accepted, and there is some disagreement among professionals and communities as to the "correct" words or definitions, depending on theoretical orientation, geographic region, generation, or culture, with some terms seen as affirming and others as outdated or demeaning. American Psychological Association (APA) Task Force for *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People* developed the definitions below by reviewing existing definitions put forward by professional organizations (e.g., APA Task Force on Gender Identity and Gender Variance, 2009; the Institute of Medicine, 2011; and the World Professional Association for Transgender Health [Coleman et al., 2012]), health care agencies serving TGNC clients (e.g., Fenway Health Center), TGNC community resources (Gender Equity Resource Center, National Center for Transgender Equality), and professional literature. Psychologists are encouraged to refresh their knowledge and familiarity with evolving terminology on a regular basis as changes emerge in the community and/or the professional literature. The definitions below include terms frequently used within the *Guidelines*, by the TGNC community, and within professional literature.

Ally: a cisgender person who supports and advocates for TGNC people and/or communities.

(*Appendices continue*)

Antitrans prejudice (transprejudice, transnegativity, transphobia): prejudicial attitudes that may result in the devaluing, dislike, and hatred of people whose gender identity and/or gender expression do not conform to their sex assigned at birth. Antitrans prejudice may lead to discriminatory behaviors in such areas as employment and public accommodations, and may lead to harassment and violence. When TGNC people hold these negative attitudes about themselves and their gender identity, it is called *internalized transphobia* (a construct analogous to internalized homophobia). Transmisogyny describes a simultaneous experience of sexism and antitrans prejudice with particularly adverse effects on trans women.

Cisgender: an adjective used to describe a person whose gender identity and gender expression align with sex assigned at birth; a person who is not TGNC.

Cisgenderism: a systemic bias based on the ideology that gender expression and gender identities are determined by sex assigned at birth rather than self-identified gender identity. Cisgenderism may lead to prejudicial attitudes and discriminatory behaviors toward TGNC people or to forms of behavior or gender expression that lie outside of the traditional gender binary.

Coming out: a process by which individuals affirm and actualize a stigmatized identity. Coming out as TGNC can include disclosing a gender identity or gender history that does not align with sex assigned at birth or current gender expression. Coming out is an individual process and is partially influenced by one's age and other generational influences.

Cross dressing: wearing clothing, accessories, and/or make-up, and/or adopting a gender expression not associated with a person's assigned sex at birth according to cultural and environmental standards (Bullough & Bullough, 1993). Cross-dressing is not always reflective of gender identity or sexual orientation. People who cross-dress may or may not identify with the larger TGNC community.

Disorders of sex development (DSD, Intersex): term used to describe a variety of medical conditions associated with atypical development of an individual's physical sex characteristics (Hughes, Houk, Ahmed, & Lee, 2006). These conditions may involve differences of a person's internal and/or external reproductive organs, sex chromosomes, and/or sex-related hormones that may complicate sex assignment at birth. DSD conditions may be considered variations in biological diversity rather than disorders (M. Diamond, 2009); therefore some prefer the terms *intersex*, *intersexuality*, or *differences in sex development* rather than "disorders of sex development" (Coleman et al., 2012).

Drag: the act of adopting a gender expression, often as part of a performance. Drag may be enacted as a political comment on gender, as parody, or as entertainment, and is not necessarily reflective of gender identity.

Female-to-male (FTM): individuals assigned a female sex at birth who have changed, are changing, or wish to change their body and/or gender identity to a more masculine body or gender identity. FTM persons are also often referred to as *transgender men*, *transmen*, or *trans men*.

Gatekeeping: the role of psychologists and other mental health professionals of evaluating a TGNC person's eligibility and readiness for hormone therapy or surgery according to the Standards of Care set forth by the World Professional Association for Transgender Health (Coleman et al., 2012). In the past, this role has been perceived as limiting a TGNC adult's autonomy and contributing to mistrust between psychologists and TGNC clients. Current approaches are sensitive to this history and are more affirming of a TGNC adult's autonomy in making decisions with regard to medical transition (American Counseling Association, 2010; Coleman et al., 2012; Singh & Burnes, 2010).

Gender-affirming surgery (sex reassignment surgery or gender reassignment surgery): surgery to change primary and/or secondary sex characteristics to better align a person's physical appearance with their gender identity. Gender-affirming surgery can be an important part of medically necessary treatment to alleviate gender dysphoria and may include mastectomy, hysterectomy, metoidioplasty, phalloplasty, breast augmentation, orchiectomy, vaginoplasty, facial feminization surgery, and/or other surgical procedures.

Gender binary: the classification of gender into two discrete categories of boy/man and girl/woman.

Gender dysphoria: discomfort or distress related to incongruence between a person's gender identity, sex assigned at birth, gender identity, and/or primary and secondary sex characteristics (Knudson, De Cuypere, & Bockting, 2010). In 2013, the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–5*; American Psychiatric Association, 2013) adopted the term *gender dysphoria* as a diagnosis characterized by "a marked incongruence between" a person's gender assigned at birth and gender identity (American Psychiatric Association, 2013, p. 453). Gender dysphoria replaced the diagnosis of gender identity disorder (GID) in the previous version of the *DSM* (American Psychiatric Association, 2000).

Gender expression: the presentation of an individual, including physical appearance, clothing choice and accessories, and behaviors that express aspects of gender identity or role. Gender expression may or may not conform to a person's gender identity.

(*Appendices continue*)

Gender identity: a person's deeply felt, inherent sense of being a boy, a man, or male; a girl, a woman, or female; or an alternative gender (e.g., genderqueer, gender nonconforming, gender neutral) that may or may not correspond to a person's sex assigned at birth or to a person's primary or secondary sex characteristics. Because gender identity is internal, a person's gender identity is not necessarily visible to others. "Affirmed gender identity" refers to a person's gender identity after coming out as TGNC or undergoing a social and/or medical transition process.

Gender marker: an indicator (M, F) of a person's sex or gender found on identification (e.g., driver's license, passport) and other legal documents (e.g., birth certificate, academic transcripts).

Gender nonconforming (GNC): an adjective used as an umbrella term to describe people whose gender expression or gender identity differs from gender norms associated with their assigned birth sex. Subpopulations of the TGNC community can develop specialized language to represent their experience and culture, such as the term "masculine of center" (MOC; Cole & Han, 2011) that is used in communities of color to describe one's GNC identity.

Gender questioning: an adjective to describe people who may be questioning or exploring their gender identity and whose gender identity may not align with their sex assigned at birth.

Genderqueer: a term to describe a person whose gender identity does not align with a binary understanding of gender (i.e., a person who does not identify fully as either a man or a woman). People who identify as genderqueer may redefine gender or decline to define themselves as gendered altogether. For example, people who identify as genderqueer may think of themselves as both man and woman (bigender, pangender, androgyne); neither man nor woman (genderless, gender neutral, neutrois, agender); moving between genders (genderfluid); or embodying a third gender.

Gender role: refers to a pattern of appearance, personality, and behavior that, in a given culture, is associated with being a boy/man/male or being a girl/woman/female. The appearance, personality, and behavior characteristics may or may not conform to what is expected based on a person's sex assigned at birth according to cultural and environmental standards. Gender role may also refer to the *social* role in which one is living (e.g., as a woman, a man, or another gender), with some role characteristics conforming and others not conforming to what is associated with girls/women or boys/men in a given culture and time.

Hormone therapy (gender-affirming hormone therapy, hormone replacement therapy): the use of hormones to masculinize or feminize a person's body to better align that person's physical characteristics with their gender identity. People wishing to feminize their body receive antiandrogens and/or estrogens; people wishing to masculinize their body receive testosterone. Hormone therapy may be an important part of medically necessary treatment to alleviate gender dysphoria.

Male-to-female (MTF): individuals whose assigned sex at birth was male and who have changed, are changing, or wish to change their body and/or gender role to a more feminized body or gender role. MTF persons are also often referred to as *transgender women*, *transwomen*, or *trans women*.

Passing: the ability to blend in with cisgender people without being recognized as transgender based on appearance or gender role and expression; being perceived as cisgender. Passing may or may not be a goal for all TGNC people.

Puberty suppression (puberty blocking, puberty delaying therapy): a treatment that can be used to temporarily suppress the development of secondary sex characteristics that occur during puberty in youth, typically using gonadotropin-releasing hormone (GnRH) analogues. Puberty suppression may be an important part of medically necessary treatment to alleviate gender dysphoria. Puberty suppression can provide adolescents time to determine whether they desire less reversible medical intervention and can serve as a diagnostic tool to determine if further medical intervention is warranted.

Sex (sex assigned at birth): sex is typically assigned at birth (or before during ultrasound) based on the appearance of external genitalia. When the external genitalia are ambiguous, other indicators (e.g., internal genitalia, chromosomal and hormonal sex) are considered to assign a sex, with the aim of assigning a sex that is most likely to be congruent with the child's gender identity (MacLaughlin & Donahoe, 2004). For most people, gender identity is congruent with sex assigned at birth (see *cisgender*); for TGNC individuals, gender identity differs in varying degrees from sex assigned at birth.

Sexual orientation: a component of identity that includes a person's sexual and emotional attraction to another person and the behavior and/or social affiliation that may result from this attraction. A person may be attracted to men, women, both, neither, or to people who are genderqueer, androgynous, or have other gender identities. Individuals may identify as lesbian, gay, heterosexual, bisexual, queer, pansexual, or asexual, among others.

Stealth (going stealth): a phrase used by some TGNC people across the life span (e.g., children, adolescents) who choose to make a transition in a new environment (e.g., school) in their affirmed gender without openly sharing their identity as a TGNC person.

(*Appendices continue*)

TGNC: an abbreviation used to refer to people who are transgender or gender nonconforming.

Trans: common short-hand for the terms transgender, transsexual, and/or gender nonconforming. Although the term "trans" is commonly accepted, not all transsexual or gender nonconforming people identify as trans.

Trans-affirmative: being respectful, aware and supportive of the needs of TGNC people.

Transgender: an adjective that is an umbrella term used to describe the full range of people whose gender identity and/or gender role do not conform to what is typically associated with their sex assigned at birth. Although the term "transgender" is commonly accepted, not all TGNC people self-identify as transgender.

Transgender man, trans man, or transman: a person whose sex assigned at birth was female, but who identifies as a man (see FTM).

Transgender woman, trans woman, or transwoman: a person whose sex assigned at birth was male, but who identifies as a woman (see MTF).

Transition: a process some TGNC people progress through when they shift toward a gender role that differs from the one associated with their sex assigned at birth. The length, scope, and process of transition are unique to each person's life situation. For many people, this involves developing a gender role and expression that is more aligned with their gender identity. A transition typically occurs over a period of time; TGNC people may proceed through a social transition (e.g., changes in gender expression, gender role, name, pronoun, and gender marker) and/or a medical transition (e.g., hormone therapy, surgery, and/or other interventions).

Transsexual: term to describe TGNC people who have changed or are changing their bodies through medical interventions (e.g., hormones, surgery) to better align their bodies with a gender identity that is different than their sex assigned at birth. Not all people who identify as transsexual consider themselves to be TGNC. For example, some transsexual individuals identify as female or male, without identifying as TGNC. Transsexualism is used as a medical diagnosis in the World Health Organization's (2015) International Classification of Diseases version 10.

Two-spirit: term used by some Native American cultures to describe people who identify with both male and female gender roles; this can include both gender identity and sexual orientation. Two-spirit people are often respected and carry unique spiritual roles for their community.

Appendix B
Guidelines for Psychological Practice With Transgender and Gender Nonconforming People

Foundational Knowledge and Awareness

Guideline 1. Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth.

Guideline 2. Psychologists understand that gender identity and sexual orientation are distinct but interrelated constructs.

Guideline 3. Psychologists seek to understand how gender identity intersects with the other cultural identities of TGNC people.

Guideline 4. Psychologists are aware of how their attitudes about and knowledge of gender identity and gender expression may affect the quality of care they provide to TGNC people and their families.

Stigma, Discrimination, and Barriers to Care

Guideline 5. Psychologists recognize how stigma, prejudice, discrimination, and violence affect the health and well-being of TGNC people.

Guideline 6. Psychologists strive to recognize the influence of institutional barriers on the lives of TGNC people and to assist in developing TGNC-affirmative environments.

Guideline 7. Psychologists understand the need to promote social change that reduces the negative effects of stigma on the health and well-being of TGNC people.

(*Appendices continue*)

Life Span Development

Guideline 8. Psychologists working with gender-questioning and TGNC youth understand the different developmental needs of children and adolescents and that not all youth will persist in a TGNC identity into adulthood.

Guideline 9. Psychologists strive to understand both the particular challenges that TGNC elders experience and the resilience they can develop.

Assessment, Therapy, and Intervention

Guideline 10. Psychologists strive to understand how mental health concerns may or may not be related to a TGNC person's gender identity and the psychological effects of minority stress.

Guideline 11. Psychologists recognize that TGNC people are more likely to experience positive life outcomes when they receive social support or trans-affirmative care.

Guideline 12. Psychologists strive to understand the effects that changes in gender identity and gender expression have on the romantic and sexual relationships of TGNC people.

Guideline 13. Psychologists seek to understand how parenting and family formation among TGNC people take a variety of forms.

Guideline 14. Psychologists recognize the potential benefits of an interdisciplinary approach when providing care to TGNC people and strive to work collaboratively with other providers.

Research, Education, and Training

Guideline 15. Psychologists respect the welfare and rights of TGNC participants in research and strive to represent results accurately and avoid misuse or misrepresentation of findings.

Guideline 16. Psychologists Seek to Prepare Trainees in Psychology to Work Competently With TGNC People.

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TAB 176-6

Pl. Trial Ex. 046

AMERICAN PSYCHOLOGICAL ASSOCIATION

APA RESOLUTION on Gender Identity Change Efforts

FEBRUARY 2021

The foundational professional guideline for working with gender diverse persons acknowledges that, "Psychologists understand that gender is a nonbinary construct that allows for a range of gender identities and that a person's gender identity may not align with sex assigned at birth." (APA, 2015, p. 834). Gender identity refers to "a person's deep felt, inherent sense of being a girl, woman, or female; a boy, a man, or male; a blend of male or female; [or another] gender" (APA, 2015, p. 862). While gender refers to the trait characteristics and behaviors culturally associated with one's sex assigned at birth, in some cases, gender may be distinct from the physical markers of biological sex (e.g., genitals, chromosomes). Gender identity is also distinct from gender expression, which refers to "the presentation of an individual including physical appearance, clothing choice and accessories, and behaviors that express aspects of gender identity" (APA, 2015, p. 861). Cisgender refers to "a person whose gender identity aligns with sex assigned at birth" (e.g., an individual assigned female at birth who identifies as a woman/girl; APA, 2015, p. 861). Transgender is "an umbrella term used to describe the full range of people whose gender identity and/or gender role do not conform to what is typically associated with their sex assigned at birth" (APA, 2015, p. 863). For the purpose of this resolution, we are using a broad definition of transgender to include transgender women/girls, transgender men/boys, nonbinary individuals (i.e., people who may identify as a gender other than a woman/girl or a man/boy), and any individual who articulates a gender identity different from societal expectations based on their sex assigned at birth.

Some transgender and gender nonbinary individuals seek gender-affirming medical care (e.g., hormone therapy, surgery) while others do not. Similarly, some transgender and gender nonbinary individuals seek to change their gender marker and/or their name on legal documents, while others do not. In this resolution, we strive to be inclusive of all gender diversity regardless of a person's pursuance of social, medical, or legal transition.

The fields of psychiatry and psychology have a long history of pathologizing individuals and those who question their gender identity (Barkai, 2017; Benson, 2013; Bouman et al, 2014; Burke, 2011; Drescher, 2010; Nadal et al., 2010; Riggs et al. 2019). This history is informed by, and parallels, the larger Western and United States-based, medical-model, narratives that 1) define gender as binary and conflate it with physical markers, 2) define masculinity, and characteristics historically attributed to men/boys, as superior to femininity and characteristics historically attributed to women/girls, 3) create systems that confer privilege to cisgender people and label cisgender identities and expressions as normative, 4) discriminate against transgender and gender nonbinary individuals (Stryker, 2017).

Gender identity change efforts (GICE) refer to a range of techniques used by mental health professionals and non-professionals with the goal of changing gender identity, gender expression, or associated components of these to be in alignment with gender role behaviors that are stereotypically associated with sex assigned at birth, (Hill et al., 2010; SAMHSA, 2015). In addition to explicit attempts to change individuals' gender according to cisnormative pressures, GICE has also been a component of sexual orientation change efforts (SOCE). As intense focus on cisnormative conformity is a frequent characteristic of SOCE it is possible that authors in the literature describing sexual orientation change efforts misgendered their participants (Hipp et al., 2019). Moreover, "ex-gay" literature and discourse conceptualize gender diversity as a sin, a mental illness, and harmful, perpetuating cisgenderism and transmisogyny (Robinson & Spivey, 2019). Finally, Hipp et al. (2019) identified forms of GICE that are often not discussed in the psychological literature but that appear to disproportionately affect Black transgender and gender nonbinary individuals including violence, "church hurt" (i.e., religious or faith-based trauma), and gatekeeping from gender affirming care. These efforts may be referred to as "conversion therapies", "corrective" treatments, or "normalizing" therapies (Hill et al., 2010). However, to consider these techniques as therapies or treatments is inaccurate and inappropriate because, the incongruence between sex and gender in and of itself is not a mental disorder (World Health Organization, n.d.) so, any behavioral health or GICE technique or treatment that seeks to change an individual's gender identity or expression is not indicated; thus, any behavioral health or GICE effort that attempt to change an individual's gender identity or expression is inappropriate (Hill et al. 2010; SAMHSA, 2015).

With roots in this history, GICE are founded on the notion that any gender identity that is not concordant with sex assigned at birth is disordered, and that a cisgender identity is healthier, preferable, and superior to a transgender or gender nonbinary identity (Ansara & Hegarty, 2011; Hill et al., 2010; Robinson & Spivey, 2019).

GICE cause harm by reinforcing anti-transgender and anti-gender nonbinary stigma and discrimination (Turban et al., 2020); and by creating social pressure on an individual to conform to an

identity and/or presentation that may not be consistent with their sense of self (e.g., Bockting et al., 2013; Egan & Perry, 2001; Meyer, 2003; Nadal et al., 2012; Russell et al., 2012; Toomey et al., 2010; Sandfort et al., 2007). Furthermore, GICE are not supported by empirical evidence as effective practices for changing gender identity and are associated with psychological and social harm (Brinkman et al., 2014; Carr, 1998; Gagné & Tewksbury, 1998; Horn, 2007; Price et al., 2019; Smith & Leaper, 2006). The American Psychological Association (APA), as well as other healthcare organizations, (e.g., American Counseling Association, World Professional Association for Transgender Health) have established empirically-supported practice guidelines that encourage clinicians to use gender-affirming practices when addressing gender identity issues (ACA, 2010; APA, 2015; Coleman et al., 2012). Additionally, a number of national and international professional healthcare organizations have publicly warned against the harmful effects of GICE and SOCE (Sexual Orientation Change Efforts) by endorsing the United States Joint Statement Against Conversion Efforts (USJS, n.d.), including the American Academy of Family Physicians, American Academy of Nursing, American Association of Sexual Educators, Counselors and Therapists, American Counseling Association, American Medical Association, American Medical Student Association, American Psychoanalytic Association, The Association of LGBTQ Psychiatrists, Society for Affectional, Intersex, and Gender Expansive Identities, Clinical Social Work Association, GLMA: Health Professionals Advancing LGBTQ Equality, The Association of Lesbian, Gay, Bisexual, Transgender Addiction Professionals and their Allies, and the World Professional Association for Transgender Health. A growing number of states and municipalities have enacted laws that prohibit licensed mental health professionals from engaging in sexual orientation and gender identity change efforts with minors (Movement Advancement Project, n.d.)

GENDER DIVERSITY, STIGMA, AND DISCRIMINATION

WHEREAS diversity in gender identity and expression is part of the human experience and transgender and gender nonbinary identities and expressions are healthy, incongruence between one's sex and gender is neither pathological nor a mental health disorder (APA, 2009, 2015; SAMHSA, 2015);

WHEREAS gender diverse individuals experience cissexist discrimination and prejudice throughout the lifespan and life domains (APA, 2009) including significant discrimination in healthcare settings (Burnes et al., 2016; Fredriksen-Goldsen et al., 2014; Grant et al., 2011; James et al., 2016; Johns et al, 2019; Lambda Legal, 2010; Macapagal et al., 2016; Reisner et al., 2015; White Hughto et al., 2015);

WHEREAS the practice of GICE reinforces stigma and discrimination against transgender and gender diverse people (Turban et al., 2020);

WHEREAS gender-related bias, victimization, discrimination, criminalization, and forced-gender conformity experienced by transgender and gender nonbinary people are associated with poor psychosocial outcomes, such as heightened psychological distress, compromised overall wellbeing, and disparities across various contexts (e.g., healthcare, schools/education, workplace, law) (Bockting et al., 2013; dickey et al., 2016; Egan & Perry, 2001; Meyer, 2003; Nadal et al., 2012; Russell et al., 2012; Hendricks & Testa, 2012; Toomey et al., 2010; Sandfort et al., 2007);

WHEREAS invalidation and rejection of transgender and gender nonbinary identities and diverse gender expressions by others (e.g., families, therapists, school personnel) are forms of discrimination, stigma, and victimization, which result in psychological distress (Bockting et al., 2013; D'Augelli et al., 2006; Egan & Perry, 2001; Hendricks & Testa, 2012; Hidalgo et al., 2015; Landolt et al., 2004; Meyer, 2003; Nadal et al., 2012; Price, et al., 2019; Roberts et al., 2012; Sandfort et al., 2007; Stotzer, 2012; Russell et al., 2012; Toomey et al., 2010; Truong et al., 2020a, 2020b; Zongrone et al., 2020);

GICE AND RISKS OF HARM

WHEREAS individuals who have experienced pressure or coercion to conform to their sex assigned at birth or therapy that was biased toward conformity to one's assigned sex at birth have reported harm resulting from these experience such as emotional distress, loss of relationships, and low self-worth (Brinkman et al., 2014; Carr, 1998; Gagné & Tewksbury, 1998; Horn, 2007; Price et al., 2019; Smith & Leaper, 2006);

WHEREAS in one study of a large online sample of LGBTQ young people, those who reported experiencing change efforts were more than twice as likely to report having attempted suicide and having multiple suicide attempts as those who did not experience change efforts, (Green et al., 2020);

WHEREAS GICE have not been shown to alleviate or resolve gender dysphoria (Bradley & Zucker, 1997; Cohen-Kettenis & Kuiper, 1984; Gelder & Marks, 1969; Greenson, 1964; Pauly, 1965, SAMHSA, 2015);

WHEREAS GICE can cause undue stress and suffering and interfere with healthy sexual and gender identity development (Hiestand & Levitt, 2005; SAMHSA, 2015);

WHEREAS GICE can reduce one's willingness to pursue future mental health treatment (Craig et al., 2017);

WHEREAS GICE often involves the promotion of stereotyped gender behaviors consistent with cultural expectations (Coleman et al., 2012; Hill et al., 2010);

WHEREAS GICE are associated with harmful social and emotional effects for many individuals, including but not limited to, the onset or increase of depression, anxiety, suicidality, loss of sexual feeling, impotence, deteriorated family relationships, a range of post-traumatic responses, and substance abuse (c.f. Burnes et al., 2016; Green et al., 2020; SAMHSA 2015 for a review; Turban et al., 2019);

WHEREAS diverse gender expressions and transgender and gender nonbinary identities are not mental disorders (American Psychiatric Association, 2013) and many transgender and gender nonbinary individuals lead satisfying lives and have healthy relationships (APA, 2015; SAMHSA, 2015);

GENDER AFFIRMING PRACTICES

WHEREAS transgender and gender nonbinary people whose gender has been affirmed report increased quality of life (Ainsworth & Spiegel, 2010; APA, 2015; Gerhardstein & Anderson, 2010; Kraemer et al., 2008; Newfield et al., 2006);

WHEREAS self-determination in defining one's gender identity is a source of resilience for transgender and gender nonbinary people and associated with improvements in wellbeing and reductions in psychological distress (Menvielle & Tuerk, 2002; Pickstone-Taylor, 2003; Rosenburg, 2002; Singh et al., 2011; Singh et al., 2014);

WHEREAS individuals who have experienced gender-affirming psychological and medical practices report improved psychological functioning, quality of life, treatment retention and engagement, and reductions in psychological distress, gender dysphoria, and maladaptive coping mechanisms (Austin & Craig, 2015; de Vries et al., 2014; Haas et al., 2011; Sevelius, 2013; White Hughto & Reisner, 2016);

WHEREAS professional consensus recommends affirming therapeutic interventions for transgender and gender nonbinary adults who request that a therapist engage in GICE, and for trans youth whose parents/guardians or other custodians (e.g., state, foster care) request that a therapist engage in GICE (American Counseling Association, 2009; APA, 2012; 2015; American Psychiatric Association, 2018; Byne et al., 2012; Edwards-Leeper et al., 2016);

WHEREAS affirming therapeutic practices and guidelines recommend that the therapist should remain objective and nonjudgmental to the outcome, focusing on empowering the client to be active in exploring, discovering, and understanding their own identity (American Counseling Association, 2009; APA, 2012; 2015; American Psychiatric Association, 2018; Byne et al., 2012; Edwards-Leeper et al., 2016);

APA POLICY

WHEREAS APA opposes discrimination on the basis of gender identity, gender expression, and transgender and gender nonbinary identities, and actively opposes the adoption of discriminatory legislation (APA, 2008);

WHEREAS APA supports the passage of laws and policies protecting the legal rights and freedoms of transgender and gender nonbinary people, regardless of gender identity or expression (APA, 2008);

WHEREAS Psychologists' work is based upon established scientific and professional knowledge of the discipline. (APA, 2017b, p. 5);

WHEREAS APA recognizes that psychologists work is based upon Respect for People's Rights and Dignity (Principle E), Avoiding Harm (3.04), and Unfair Discrimination (3.01; APA, 2017b);

WHEREAS gender affirming psychotherapy is founded in clinical practice guidelines, and harm has not been identified for any of these gender-affirming treatment practices (APA, 2015, 2017b; Byne et al., 2012);

WHEREAS the APA policy and practice guidelines (e.g., Multicultural Guidelines: An Ecological Approach to Context, Identity, and Intersectionality; Guidelines for Psychological Practice with Transgender and Gender Nonconforming People) affirm that psychologists do not engage in discriminatory or biased practices and urge psychologists to take a leadership role in preventing discrimination towards transgender and gender diverse people (APA, 2009, 2015, 2017a);

WHEREAS APA's 2005 Policy Statement on Evidence-Based Practice in Psychology defines evidence-based practice as the integration of the best available research with clinical expertise in the context of patient characteristics, culture, and preferences (APA, 2005);

BE IT THEREFORE RESOLVED that consistent with the APA definition of evidence-based practice (APA, 2005), the APA affirms that scientific evidence and clinical experience indicate that GICE put individuals at significant risk of harm;

BE IT FURTHER RESOLVED that the APA opposes GICE because such efforts put individuals at significant risk of harm and encourages individuals, families, health professionals, and organizations to avoid GICE;

BE IT FURTHER RESOLVED that APA opposes the idea that incongruence between sex and gender is a mental disorder (Hill et al., 2010; SAMHSA, 2015; WHO).

BE IT FURTHER RESOLVED that after reviewing scientific evidence on GICE harm, affirmative treatments, and professional practice guidelines, the APA affirms GICE are associated with reported harm.

BE IT FURTHER RESOLVED that the APA opposes GICE because of their association with harm.

BE IT FURTHER RESOLVED that Transgender and gender nonbinary identities, as well as other gender identities that transcend culturally prescriptive binary notions of gender, represent normal variations in human expression of gender.

BE IT FURTHER RESOLVEDthat neither transgender or gender nonbinary identities nor the pursuit of gender-affirming medical care constitutes evidence of a mental disorder.

BE IT FURTHER RESOLVED that APA opposes portrayals of transgender and gender nonbinary people as mentally ill because of their gender identities and expressions.

BE IT FURTHER RESOLVED that evidence supports psychologists in their professional roles to use affirming and culturally relevant approaches with individuals of diverse gender expressions and identities.

BE IT FURTHER RESOLVED that APA is committed to promoting accurate scientific data regarding gender identity and expression in its own policy, public advocacy, judicial proceedings, media, and public opinion;

BE IT FURTHER RESOLVED that APA encourages collaboration between and among individuals and organizations to promote the wellbeing of transgender and gender nonbinary people;

BE IT FURTHER RESOLVED that the APA encourages psychologists to be aware of multiple and intersecting factors in identity, such as sex assigned at birth, gender expression, gender identity, age, race, ethnicity, religion, spirituality, socioeconomic status, disability, national origin, and sexual orientation in conceptualization, treatment, research, and teaching about transgender and gender nonbinary people;

BE IT FURTHER RESOLVED that the APA opposes the dissemination of inaccurate information about gender identity, gender expression, and the efficacy of GICE, including the claim that gender identity can be changed through treatment, the characterization of transgender or gender nonbinary identity as a mental disorder and the promotion of treatments that prescribe gender identity or expression consistent with one's birth-assigned sex as effective for clients with gender dysphoria;

BE IT FURTHER RESOLVED that APA encourages the development and dissemination of evidence-based, multiculturally-informed, and gender affirmative educational resources that inform psychologists, the community and education and mental health institutions about the harms of GICE;

BE IT FURTHER RESOLVED that APA re-affirms that APA (2015) encourages psychologists to:

- Acknowledge the diversity and complexity of identities and experiences and recognize transgender and gender nonbinary identities as healthy expressions of gender
- Recognize that descriptions of any gender identity or expression as unnatural, abhorrent, or unhealthy perpetuate stigma for sexual and gender minorities, and have negative mental health and social consequences
- Assist clients in a developmentally appropriate manner to explore and understand the cultural and familial influence on gender roles and expression. Psychologists are urged to help clients in a developmentally appropriate manner understand the societal contexts of sexism, heterosexism, transphobia, racism and other forms of social oppression, and to use a developmental multicultural- and gender-affirmative framework in research, teaching, training, and supervision;

BE IT FURTHER RESOLVED that the American Psychological Association opposes GICE because there is evidence of former participants reporting harm resulting from their experiences of GICE and the contribution that such efforts make to social stigma, injustice, and prejudice directed at gender diverse individuals, consistent with other major professional mental health associations, including the American Psychiatric Association (2018); American Counseling Association (2017), SAMHSA (2015), American Academy of Child & Adolescent Psychiatry (2018), World Health Organization (n.d.) and World Psychiatric Association (2016);

BE IT FURTHER RESOLVED that the APA, because of evidence of harm and lack of evidence of efficacy, supports public policies and legislation that prohibit, or aim to reduce GICE, cissexism, and anti-transgender and anti-gender nonbinary bias and that increase support for gender diversity;

BE IT FURTHER RESOLVED that the APA supports collaboration and partnerships with global, national and state and local partners to achieve the aims of this resolution;

BE IT FURTHER RESOLVED that the APA promotes professional training in gender-affirming practices and opposes professional training in GICE in any stage of the education of psychologists, including graduate training, continuing education, and professional development.

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TAB 176-7

APA Official Actions

Position Statement on Treatment of Transgender (Trans) and Gender Diverse Youth

Approved by the Board of Trustees, July 2020
Approved by the Assembly, April 2020

"Policy documents are approved by the APA Assembly and Board of Trustees. . . These are . . . position statements that define APA official policy on specific subjects. . ." – *APA Operations Manual*

Issue:

Transgender and gender non-conforming youth often experience an intensification of emotional distress when the physical changes of puberty occur in opposition to the adolescent's gender identity and sense of self. The onset of menses, for example, is unwanted and psychologically devastating for an adolescent transman (assigned female at birth). Worsening dysphoria may manifest as depression, anxiety, poor relationships with family and peers, self-harm and suicide. Racism, misogyny, economic disadvantage and neurodiversity can compound the risk of negative outcomes. Due to the dynamic nature of puberty development, lack of gender-affirming interventions (i.e. social, psychological, and medical) is not a neutral decision; youth often experience worsening dysphoria and negative impact on mental health as the incongruent and unwanted puberty progresses. Trans-affirming treatment, such as the use of puberty suppression, is associated with the relief of emotional distress, and notable gains in psychosocial and emotional development, in trans and gender diverse youth.

Gender-affirming treatment of trans and gender diverse youth who experience gender dysphoria due to the physical changes of puberty, may include suppression of puberty development with GnRH (gonadotropin releasing hormone) agonists, commonly referred to as "puberty blockers." Use of GnRH agonists, despite potential side effects (e.g., hot flashes, depression) can allow the adolescent a period of time, often several years, in which to further explore their gender identity and benefit from additional cognitive and emotional development. During this time, the youth and family can receive mental health and social support services, if needed, to navigate the gender affirmation process including the consideration of whether gender affirming hormone therapy is an appropriate next step. If during this discernment period further adolescent development leads to increased comfort with the birth-assigned gender, the GnRH agonist can be discontinued, and puberty allowed to resume. If the developmental trajectory affirms the trans identity, treatment with estrogen or testosterone can be instituted to facilitate development of affirmed secondary sex characteristics, if desired. Gender-affirming surgeries may follow in later adolescence or young adulthood. However, affirmation of gender identity is a highly individualized process. For gender diverse youth and their families, decisions to which gender-affirming medical, surgical, social, and/or legal procedures to pursue are best managed via an informed consent approach.

APA Position:

The American Psychiatric Association:

Pl. Trial Ex. 047

1. **Supports access to affirming and supportive treatment for trans and gender diverse youth and their families, including appropriate mental health services, and when indicated puberty suppression and medical transition support.**
2. **Opposes all legislative and other governmental attempts to limit access to these services for trans and gender diverse youth, or to sanction or criminalize the actions of physicians and other clinicians who provide them.**

TAB 176-8

APA Official Actions

Position Statement on Access to Care for Transgender and Gender Diverse Individuals

Approved by the Board of Trustees, July 2018
Approved by the Assembly, May 2018

"Policy documents are approved by the APA Assembly and Board of Trustees. . . . These are . . . position statements that define APA official policy on specific subjects. . ." – *APA Operations Manual*

Issue:
Significant and long-standing medical and psychiatric literature exists that demonstrates clear benefits of medical and surgical interventions to assist gender diverse individuals seeking transition. However, private and public insurers often do not offer, or may specifically exclude, coverage for medically necessary treatments for gender transition. Access to medical care (both medical and surgical) positively impacts the mental health of transgender and gender diverse individuals.

The APA's vision statement includes the phrase: "Its vision is a society that has available, accessible, quality psychiatric diagnosis and treatment," yet currently, transgender and gender diverse individuals frequently lack available and accessible gender-affirming treatment. In addition, APA's values include the following points:

- best standards of clinical practice
- patient-focused treatment decisions
- scientifically-established principles of treatment
- advocacy for patients

Transgender and gender diverse individuals currently lack access to the best standards of clinical practice, do not have the opportunity to pursue patient-focused gender-affirming treatment decisions, and do not receive scientifically-established treatment. They could benefit significantly from APA's advocacy.

Position:

Therefore, the American Psychiatric Association:

1. **Recognizes that appropriately evaluated transgender and gender diverse individuals can benefit greatly from medical and surgical gender-affirming treatments.**
2. **Advocates for removal of barriers to care and supports both public and private health insurance coverage for gender transition treatment.**
3. **Opposes categorical exclusions of coverage for such medically necessary treatment when prescribed by a physician.**
4. **Supports evidence-based coverage of all gender-affirming procedures which would help the**

Pl. Trial Ex. 048

mental well-being of gender diverse individuals

Authors:
Authors: Jack Drescher, M.D., Ellen Haller, M.D., APA Caucus of Lesbian, Gay and Bisexual Psychiatrists. Revised 2017 Eric Yarbrough, M.D., APA Caucus of LGBTQ Psychiatrists and the Council on Minority Mental Health and Health Disparities

TAB 176-9

ENDOCRINE SOCIETY
Hormone Science to Health

PES PEDIATRIC ENDOCRINE SOCIETY

TRANSGENDER HEALTH POSITION STATEMENT

INTRODUCTION

Over the last few decades, there has been a rapid expansion in the understanding of gender identity along with the implications for the care of transgender and gender diverse individuals. In parallel with the greater societal awareness of transgender individuals, evidence-based practices in caring for pediatric and adult transgender patients have been developed in response to scientific research. While there continue to be gaps in knowledge about the optimal care for transgender individuals, the framework for providing care is increasingly well-established as is the recognition of needed policy changes.

BACKGROUND

The medical consensus in the late 20th century was that transgender and gender incongruent individuals suffered a mental health disorder termed "gender identity disorder." Gender identity was considered malleable and subject to external influences. Today, however, this attitude is no longer considered valid. Considerable scientific evidence has emerged demonstrating a durable biological element underlying gender identity.[1,2] Individuals may make choices due to other factors in their lives, but there do not seem to be external forces that genuinely cause individuals to change gender identity.

Although the specific mechanisms guiding the biological underpinnings of gender identity are not entirely understood, there is evolving consensus that being transgender is not a mental health disorder. Such evidence stems from scientific studies suggesting that: 1) attempts to change gender identity in intersex patients to match external genitalia or chromosomes are typically unsuccessful[1,2]; 2) identical twins (who share the exact same genetic background) are more likely to both experience transgender identity as compared to fraternal (non-identical) twins[3]; 3) among individuals with female chromosomes (XX), rates of male gender identity are higher for those exposed to higher levels of androgens *in utero* relative to those without such exposure, and male (XY)-chromosome individuals with complete androgen insensitivity syndrome typically have female gender identity[4]; and 4) there are associations of certain brain scan or staining patterns with gender identity rather than external genitalia or chromosomes.[1,2]

CONSIDERATIONS

Transgender individuals are often denied insurance coverage for appropriate medical and psychological treatment. Those gender diverse youth who have barriers to accessing adequate healthcare have poorer overall physical and mental health compared to their cisgender peers.[5] Over the last decade, there has been considerable research on and development of evidence-based standards of care that have proven to be both safe and efficacious for the treatment of gender dysphoria/gender incongruence in youth and adults. There is also a growing understanding of the positive impact that increased access to such treatments can have on the mental health of these individuals.

The Endocrine Society's Clinical Practice Guideline on gender dysphoria/gender incongruence[6] provides the standard of care for supporting transgender individuals. The guideline establishes a methodical, conservative framework for gender-affirming care, including pubertal suppression, hormones and surgery and standardizes terminology to be used by healthcare professionals. These recommendations include evidence that treatment of gender dysphoria/incongruence is medically necessary and should be covered by insurance.

Despite increased awareness, many barriers to improving the health and well-being of transgender youth and adults remain. Oftentimes, medical treatment for gender dysphoria/gender incongruence is considered elective by insurance companies, which fail to provide coverage for physician-prescribed treatment. Access to appropriately trained healthcare professionals can also be challenging as there

[1]Saraswat A, Weinand JD, Safer JD. Evidence supporting the biologic nature of gender identity. *Endocr Pract.* Feb 2015;21(2):199-204. doi:10.4158/ep14351.ra

[2]Rosenthal SM. Approach to the patient: transgender youth: endocrine considerations. *J Clin Endocrinol Metab.* Dec 2014;99(12):4379-89. doi:10.1210/jc.2014-1919

[3]Heylens G, De Cuypere G, Zucker KJ, et al. Gender identity disorder in twins: a review of the case report literature. *J Sex Med.* Mar 2012;9(3):751-7. doi:10.1111/j.1743-6109.2011.02567.x

[4]Dessens AB, Slijper FM, Drop SL. Gender dysphoria and gender change in chromosomal females with congenital adrenal hyperplasia. *Arch Sex Behav.* Aug 2005;34(4):389-97. doi:10.1007/s10508-005-4338-5

[5]Rider GN, McMorris BJ, Gower AL, Coleman E, Eisenberg ME. Health and Care Utilization of Transgender and Gender Nonconforming Youth: A Population-Based Study. *Pediatrics.* 2018;141(3):e20171683. doi:10.1542/peds.2017-1683

[6]Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* Nov 1 2017;102(11):3869-3903. doi:10.1210/jc.2017-01658

is a lack of formal education on gender dysphoria/gender incongruence among clinicians trained in the United States. A 2016 survey of endocrinologists, the physicians most likely to care for these patients, found that over 80% have never received training on care of transgender patients.[7]

This can have an adverse impact on patient outcomes, particularly in rural and underserved areas. In fact, studies have indicated that 70% of transgender individuals have experienced maltreatment by medical providers, including harassment and violence.[7] Many transgender individuals have been subjected to conversion therapy, or efforts to change a transgender person's gender identity using psychological interventions; this is known to be associated with adverse mental health outcomes, including suicidality, and is banned in 20 states and the District of Columbia.[8]

Transgender individuals who have been denied care show an increased likelihood of dying by suicide and engaging in self-harm.[7] Transgender/gender incongruent youth who had access to pubertal suppression, a treatment which is fully reversible and prevents development of secondary sex characteristics not in alignment with their gender identity, have lower lifetime odds of suicidal ideation compared to those youth who desired pubertal suppression but did not have access to such treatment.[9] Youth who are able to access gender-affirming care, including pubertal suppression, hormones and surgery based on conservative medical guidelines and consultation from medical and mental health experts, experience significantly improved mental health outcomes over time, similar to their cis-gender peers.[10-12] Pre-pubertal youth who are supported and affirmed in their social transitions long before medical interventions are indicated, experience no elevation in depression compared to their cis-gender peers.[12] It is critical that transgender individuals have access to the appropriate treatment and care to ensure their health and well-being.

FUTURE CONSIDERATIONS

While the data are strong for both a biological underpinning to gender identity and the relative safety of hormone treatment (when appropriately monitored medically), there are gaps in knowledge that are necessary to address in order to optimize care. Comparative effectiveness research in hormone regimens is needed to determine: the best endocrine and surgical protocols[13], as it is not yet known if certain regimens are safer or more effective than others; the degree of improvement as a result of the intervention (e.g. decrease in mental health diagnoses); the need for training of health care providers and the most effective training methods; and to build the body of evidence pertaining to cardiovascular, malignancy, or other long-term risks from hormone interventions, particularly as the transgender individual ages. Additional studies are needed to elucidate the biological processes underlying gender identity; such studies may lead to destigmatization and may also decrease health disparities for gender minorities. In addition, further studies are needed to determine strategies for fertility preservation and to investigate long-term outcomes of early medical intervention, including pubertal suppression, gender-affirming hormones and gender-affirming surgeries for transgender/gender incongruent youth. To successfully establish and enact these protocols requires long-term, large-scale studies across countries that employ similar care protocols.

POSITIONS

- There is a durable biological underpinning to gender identity that should be considered in policy determinations.
- Medical intervention for transgender youth and adults (including puberty suppression, hormone therapy and medically indicated surgery) is effective, relatively safe (when appropriately monitored), and has been established as the standard of care.[6] Federal and private insurers should cover such interventions as prescribed by a physician as well as the appropriate medical screenings that are recommended for all body tissues that a person may have.
- Increased funding for national pediatric and adult transgender health research programs is needed to close the gaps in knowledge regarding transgender medical care and should be made a priority.

[7]Davidge-Pitts C, Nippoldt TB, Danoff A, Radziejewski L, Natt N. Transgender Health in Endocrinology: Current Status of Endocrinology Fellowship Programs and Practicing Clinicians. *J Clin Endocrinol Metab*. Apr 1 2017;102(4):1286-1290. doi:10.1210/jc.2016-3007

[8]Turban JL, Beckwith N, Reisner SL, Keuroghlian AS. Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults. *JAMA Psychiatry*. Sep 11 2019;77(1):1-9. doi:10.1001/jamapsychiatry.2019.2285

[9]Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. Feb 2020;145(2)doi:10.1542/peds.2019-1725

[10]de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. Oct 2014;134(4):696-704. doi:10.1542/peds.2013-2958

[11]Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. *Pediatrics*. Apr 2020;145(4)doi:10.1542/peds.2019-3006

[12]Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol*. 2020;2020:8. doi:10.1186/s13633-020-00078-2

[13]Safer JD, Tangpricha V. Care of the Transgender Patient. *Ann Intern Med*. Jul 2 2019;171(1):Itc1-Itc16. doi:10.7326/aitc201907020

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

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TAB 176-22

EPSDT - A Guide for States:
Coverage in the Medicaid Benefit for Children and Adolescents

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Early and Periodic Screening, Diagnostic and Treatment (EPSDT)

JUNE 2014

Available at http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Early-and-Periodic-Screening-Diagnostic-and-Treatment.html

Pl. Trial Ex. 062

PLAINTIFFS001533

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www.NORC.org

I. INTRODUCTION

The Medicaid program's benefit for children and adolescents is known as Early and Periodic Screening, Diagnostic and Treatment services, or EPSDT. EPSDT provides a comprehensive array of prevention, diagnostic, and treatment services for low-income infants, children and adolescents under age 21, as specified in Section 1905(r) of the Social Security Act (the Act). The EPSDT benefit is more robust than the Medicaid benefit for adults and is designed to assure that children receive early detection and care, so that health problems are averted or diagnosed and treated as early as possible. The goal of EPSDT is to assure that individual children get the health care they need when they need it – the right care to the right child at the right time in the right setting.

EPSDT's goal is to assure that individual children get the health care they need when they need it – the right care to the right child at the right time in the right setting.

States share responsibility for implementing the benefit, along with the Centers for Medicare & Medicaid Services (CMS). States have an affirmative obligation to make sure that Medicaid-eligible children and their families are aware of EPSDT and have access to required screenings and necessary treatment services.[1] States also have broad flexibility to determine how to best ensure such services are provided. In general, they either administer the benefit outright (through fee for service arrangements) or provide oversight to private entities with whom they have contracted to administer the benefit (e.g., managed care entities). States must arrange (directly or through delegations or contracts) for children to receive the physical, mental, vision, hearing, and dental services they need to treat health problems and conditions. Through the EPSDT benefit, children's health problems should be addressed before they become advanced and treatment is more difficult and costly.

[1] CMS, State Medicaid Manual §§ 5010, 5121, 5310 (requiring states to "[a]ssure that health problems found are diagnosed and treated early, before they become more complex and their treatment more costly,. . . that informing methods are effective, . . . [and] that services covered under Medicaid are available.")

EPSDT entitles enrolled infants, children and adolescents to any treatment or procedure that fits within any of the categories of Medicaid-covered services listed in Section 1905(a) of the Act if that treatment or service is necessary to "correct or ameliorate" defects and physical and mental illnesses or conditions.[2] This includes physician, nurse practitioner and hospital services; physical, speech/language, and occupational therapies; home health services, including medical equipment, supplies, and appliances; treatment for mental health and substance use disorders; treatment for vision, hearing and dental diseases and disorders, and much more. This broad coverage requirement results in a comprehensive, high-quality health benefit for children under age 21 enrolled in Medicaid.

Children's health problems should be addressed before they become advanced and treatment is more difficult and costly.

States report annually to CMS certain data about their delivery of services under the EPSDT benefit.[3] The reporting is made on the CMS Form 416. CMS and states use this data to monitor EPSDT performance.

This guide is intended to help states, health care providers and others to understand the scope of services that are covered under EPSDT so that they may realize EPSDT's goals and provide the best possible child and adolescent health benefit through their Medicaid programs. While it does not establish new EPSDT policy, this guide serves the important purpose of compiling into a single document various EPSDT policy guidances that CMS has issued over the years.

This guide outlines:

- ✓ EPSDT's screening requirements, including when interperiodic screening should be provided;
- ✓ Scope of services covered under EPSDT;
- ✓ EPSDT's requirements governing dental, vision, and hearing services;
- ✓ Permissible limitations on service coverage under EPSDT;

[2] Section 1905(r)(5) of the Social Security Act.
[3] Sections 1902(a)(43)(D) and 2108(e) of the Social Security Act; CMS, State Medicaid Manual § 2700.4.

- ✓ States' responsibilities to assure access to EPSDT services and providers;
- ✓ Assistance to states as they work with managed care plans to provide the best child health benefit possible; and
- ✓ Notice and appeal procedures required when services are denied, reduced or terminated.

II. PERIODIC AND INTERPERIODIC SCREENINGS

EPSDT covers regular screening services (check-ups) for infants, children and adolescents. These screenings are designed to identify health and developmental issues as early as possible. States have the responsibility to ensure that all eligible children (and their families) are informed of both the availability of screening services, and that a formal request for an EPSDT screening service is not required. States must provide or arrange for screening services both at established times and on an as-needed basis. Covered screening services are medical, mental health, vision, hearing and dental. Medical screenings has five components:

- ✓ Comprehensive health and developmental history that assesses for both physical and mental health, as well as for substance use disorders;4
- ✓ Comprehensive, unclothed physical examination;
- ✓ Appropriate immunizations, in accordance with the schedule for pediatric vaccines established by the Advisory Committee on Immunization Practices;
- ✓ Laboratory testing (including blood lead screening appropriate for age and risk factors);5 and
- ✓ Health education and anticipatory guidance for both the child and caregiver.6

Under the Act, states must establish a periodicity schedule for each type of screening service: medical, vision, hearing, and dental. The periodicity schedules set the frequency by which certain services should be provided and will be covered.[7] The schedules are not prescribed by federal law, but should be based on current standards of pediatric medical and dental practice, and states are required to consult with recognized medical and dental organizations involved in child health care to assist in developing their periodicity schedules. One commonly used source is Bright Futures (developed by the American Academy of Pediatrics), which, for example, suggests that developmental screenings be conducted when children are ages 9 months, 18 months, and 30 months. The American Academy of Pediatric Dentistry (AAPD) has published a recommended periodicity schedule for dental services for children and adolescents. States should review their EPSDT periodicity schedules regularly to keep them up to date.

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[4] CMS issued an Informational Bulletin on March 27, 2013, discussing Prevention and Early Identification of Mental Health and Substance Use Conditions in Children and informing states about resources available to help them meet the needs of children under EPSDT.
[5] CMS issued guidance on June 22, 2012 to align blood lead screening for Medicaid children with recommendations of the Centers for Disease Control and Prevention (CDC). After providing data that demonstrates that universal screening is not the most effective approach to identifying childhood exposure to lead, a state may request to implement a targeted lead screening plan rather than continue universal screening of all Medicaid-eligible children ages 1 and 2.
[6] Section 1905(r)(1)(B) of the Social Security Act.
[7] 42 C.F.R. § 441.58; CMS, State Medicaid Manual §§ 5110, 5140.

States should review their EPSDT periodicity schedules regularly to keep them up to date.

EPSDT also requires coverage of medically necessary "interperiodic" screening outside of the state's periodicity schedule. Coverage for such screenings is required based on an indication of a medical need to diagnose an illness or condition that was not present at the regularly scheduled screening or to determine if there has been a change in a previously diagnosed illness or condition that requires additional services. The determination of whether a screening service outside of the periodicity schedule is necessary may be made by the child's physician or dentist, or by a health, developmental, or educational professional who comes into contact with a child outside of the formal health care system. This includes, for example, personnel working for state early intervention or special education programs, Head Start, and the Special Supplemental Nutrition Program for Women, Infants, and Children. A state may not limit the number of medically necessary screenings a child receives and may not require prior authorization for either periodic or "interperiodic" screenings.

Example of Screenings Beyond Those Required by the Periodicity Schedule
A child receives a regularly scheduled periodic vision screening at age 5 at which no problem is detected. According to the state's periodicity schedule, his next vision screening is due at age 7. At age 6, the school nurse recommends to the child's parent that the child see an optometrist because a teacher suspects a vision problem. Even though the next scheduled vision screening is not due until the age of 7, the child would be entitled to receive a timely "interperiodic" screening to determine if there is a vision problem for which treatment is needed. The screening should not be delayed if there is a concern the child may have a vision problem. Source: NPRM, 58 Fed. Reg. 51288, 51290, 51291 (Oct. 1, 1993)

Screening services provide the crucial link to necessary covered treatment, as EPSDT requires states to "arrang[e] for . . . corrective treatment," either directly or through referral to appropriate providers or licensed practitioners, for any illness or condition detected by a screening.[8] The affirmative obligation to connect children with necessary treatment makes EPSDT different from Medicaid for adults.[9] It is a crucial component of a quality child health benefit.

[8] Section 1902(a)(43)(C) of the Social Security Act.
[9] CMS, State Medicaid Manual § 5124.B.

The affirmative obligation to connect children with necessary treatment makes EPSDT different from Medicaid for adults.

Any qualified provider operating within the scope of his or her practice, as defined by state law, can provide a screening service. The screening *need not be* conducted by a Medicaid provider in order to trigger EPSDT coverage for follow up diagnostic services and medically necessary treatment by a qualified Medicaid provider. A screening service provided before a child enrolls in Medicaid is sufficient to trigger EPSDT coverage, after enrollment, for follow-up diagnostic services and necessary treatment. The family or beneficiary need not formally request an EPSDT screening in order to receive the benefits of EPSDT. Rather, any visit or contact with a qualified medical professional is sufficient to satisfy EPSDT's screening requirement, and states should consider a beneficiary who is receiving services to be participating in EPSDT, whether the beneficiary requested screening services directly from the state or the health care provider.[10]

Any qualified provider operating within the scope of his or her practice, as defined by state law, can provide a screening service.

States establish their own fee schedules for screening services and should be using Health Insurance Portability and Accountability Act (HIPAA) compliant billing codes. States may develop a bundled payment rate to pay for the physical health screening components under one billing code. States may also recognize each component of the EPSDT screening separately. For example, one state pays for the visit itself with one code and pays separately for each individual screening service delivered during the visit. This payment methodology not only encourages providers to perform every component of an EPSDT well-child visit, it also provides the state, through claims, information as to whether the physician actually met the elements of the EPSDT guidelines set out in the periodicity

[10] CMS, State Medicaid Manual § 5310; HCFA, Title XIX State Agency Letter No. 91-33 (April 3, 1991).

schedules. States may encourage providers to perform all five components of the EPSDT screening but may not exclude providers who perform only partial screenings from being reimbursed for the parts they do provide.

Professional guidelines (e.g., Bright Futures) recommend that physicians include an oral health screening as part of the well-child visit at specified ages. In addition, states are permitted to include dental or oral health screening as a separately covered EPSDT service. These screening services, which may be performed by dental professionals or by medical professionals according to state scope of practice rules, can take place in community or group settings as well as in clinics or medical and dental offices. Such screenings can be helpful in identifying children with unmet dental care needs so they can be referred to a dental professional for treatment. Two new procedure codes were added to the Code on Dental Procedures and Nomenclature (CDT) in 2012 to facilitate payment for oral health screenings and assessments: CDT 0190 and CDT 0191.

In 2012, two new procedure codes were added to facilitate payment for oral health screenings and assessments: CDT 0190 and 0191.

Vision and hearing screening services must also be provided. States should consult with ophthalmologists and optometrists to determine what procedures should be used during a vision screening and to establish the criteria for referral for a diagnostic examination. For hearing screenings, appropriate procedures for screening and methods of administering them can be obtained from audiologists or from state health or education departments.[11]

[11] CMS, State Medicaid Manual § 5123.2.F.

III. DIAGNOSTIC SERVICES

EPSDT covers medically necessary diagnostic services. When a screening examination indicates the need for further evaluation of a child's health, the child should be appropriately referred for diagnosis without delay.

A child's diagnosis may be performed by a physician, dentist or other practitioner qualified to evaluate and diagnose health problems at locations, including practitioners' offices, maternal and child health (MCH) facilities, community health centers, rehabilitation centers, and hospital outpatient departments. Diagnosis can generally be made on an outpatient basis. However, inpatient services are covered when necessary to complete a diagnosis.

When a screening examination indicates the need for further evaluation of a child's health, the child should be referred for diagnosis without delay.

IV. THE SCOPE OF EPSDT TREATMENT SERVICES

A. Scope of Services

The Act provides for coverage of all medically necessary services that are included within the categories of mandatory and optional services listed in section 1905(a), regardless of whether such services are covered under the State Plan. These include physician and hospital services, private duty nursing, personal care services, home health and medical equipment and supplies, rehabilitative services, and vision, hearing, and dental services. Covered EPSDT services also include "any other medical care, and any other type of remedial care recognized under State law, specified by the Secretary."[12] The role of states is to make sure the full range of EPSDT services is available as well as to assure that families of enrolled children are aware of and have access to those services so as to meet the individual child's needs. The broad scope of services enables states to design a child health benefit to meet the individual needs of the children served by its Medicaid program—a benefit design that has the potential to result in better care and healthier children at a lower overall cost. As discussed in the next section: while children enrolled in Medicaid are entitled to a broad scope of treatment services, no such service is covered under Medicaid unless medically necessary for that particular child.

The Act provides for coverage of all medically necessary services that are included within the categories of mandatory and optional services listed in section 1905(a), regardless of whether such services are covered under the State Plan.

[12] Section 1905(a)(29) of the Social Security Act.

If a service, supply or equipment that has been determined to be medically necessary for a child is not listed as covered (for adults) in a State Medicaid Plan, the state will nonetheless need to provide it to the child as long as the service or supply could be covered under the State Plan, that is, as long as it is included within the categories of mandatory and optional services listed in section 1905(a). In such circumstances, the state would need to develop a payment methodology for the service, supply or equipment, including the possibility that payment may need to be made using a single-service agreement with an in-state provider or an out-of-state provider who will accept Medicaid payment.

A service need not cure a condition in order to be covered under EPSDT. Services that maintain or improve the child's current health condition are also covered in EPSDT because they "ameliorate" a condition. Maintenance services are defined as services that sustain or support rather than those that cure or improve health problems. Services are covered when they prevent a condition from worsening or prevent development of additional health problems. The common definition of "ameliorate" is to "make more tolerable." Thus, services such as physical and occupational therapy are covered when they have an ameliorative, maintenance purpose. This is particularly important for children with disabilities, because such services can prevent conditions from worsening, reduce pain, and avert the development of more costly illnesses and conditions. Other, less common examples include items of durable medical equipment, such as decubitus cushions, bed rails and augmentative communication devices. Such services are a crucial component of a good, comprehensive child-focused health benefit.

B. Covering a Range of Treatment Services to Meet a Child's Needs

As noted above, EPSDT covers physical and mental health and substance use disorder services, regardless of whether these services are provided under the State Plan and regardless of any restrictions that states may impose on coverage for adult services, as long as those services *could* be covered under the State Plan. This section provides some examples of EPSDT's broad scope of services, focusing on mental health and substance use services, personal care services, oral health and dental services, and vision and hearing services.

a. Mental Health and Substance Use Services

Treatment for mental health and substance use issues and conditions is available under a number of Medicaid service categories, including hospital and clinic services, physician services, and services provided by a licensed professional such as a psychologist. States should also make use of rehabilitative services. While rehabilitative services can meet a range of children's treatment needs, they

can be particularly critical for children with mental health and substance use issues. Rehabilitative services are defined to include:

> *any medical or remedial services (provided in a facility, a home, or other setting) recommended by a physician or other licensed practitioner of the healing arts within the scope of their practice under State law, for the maximum reduction of physical or mental disability and restoration of an individual to the best possible functional level.*[13]

Like other services covered under EPSDT, rehabilitative services need not actually cure a disability or completely restore an individual to a previous functional level. Rather, such services are covered when they ameliorate a physical or mental disability, as discussed above. Moreover, determinations of whether a service is rehabilitative must take into consideration that a child may not have attained the ability to perform certain functions. That is, a child's rehabilitative services plan of care should reflect goals appropriate for the child's developmental stage.

Rehabilitative services are particularly critical for children with mental health and substance use issues.

Depending on the interventions that the individual child needs, services that can be covered as rehabilitative services include:

- ✓ Community-based crisis services, such as mobile crisis teams, and intensive outpatient services;
- ✓ Individualized mental health and substance use treatment services, including in non-traditional settings such as a school, a workplace or at home;
- ✓ Medication management;
- ✓ Counseling and therapy, including to eliminate psychological barriers that would impede development of community living skills; and
- ✓ Rehabilitative equipment, for instance daily living aids.

With respect to the provision of rehabilitative services, including those noted above, CMS requires more specificity of providers and services due to the wide spectrum of rehabilitative services coverable under the broad definition. CMS

[13] Section 1905(a)(13) of the Social Security Act; 42 C.F.R. § 440.130(d).

would expect a state to include in their State Plan the services, and providers with their qualifications, as well as a reimbursement methodology for each service it provides. CMS is available to provide technical assistance to states that are covering a service for children that has not otherwise been identified in their State Plan.

A number of home and community-based services, including those that can be provided through EPSDT, have proven to significantly enhance positive outcomes for children and youth. These include intensive care coordination ("wraparound"), intensive in-home services, and mobile crisis response and stabilization.

CMS has issued detailed guidance encouraging states to include screening, assessments, and treatments focusing on children who have been victims of complex trauma. EPSDT can be a crucial tool in addressing the profound needs of this population, including children who are involved in the child welfare system.

b. Personal Care Services

EPSDT requires coverage of medically necessary personal care services, which:

> *are furnished to an individual who is not an inpatient or resident of a hospital, nursing facility, intermediate care facility . . . or institution for mental disease, that are (A) authorized for the individual by a physician in accordance with a plan of treatment or (at the option of the State), otherwise authorized for the individual in accordance with a service plan approved by the State; (B) provided by an individual who is qualified to provide such services and is not a member of the individual's family; and (C) furnished in a home or . . . in other location.*[14]

Personal care services provide a range of assistance with performing activities of daily living, such as dressing, eating, bathing, transferring, and toileting; and instrumental activities of daily living, such as preparing meals and managing medications.[15] While it is optional for states to provide personal care services for adults in locations other than the home, this is not the case for a child. Under EPSDT, personal care services are to be provided, for example, in a school or group home if necessary to "correct or ameliorate" a condition.

The determination of whether a child needs personal care services must be based upon the child's individual needs and provided in accordance with a plan of treatment or service plan. Under regular State Plan Medicaid, no Medicaid payments are available for personal care services provided by the child's legally

[14] Section 1905(a)(24) of the Social Security Act; 42 C.F.R. § 440.167.
[15] CMS, State Medicaid Manual § 4480.

responsible relatives.[16] In addition, the determination of whether a child needs personal care services must be based upon the child's individual needs and a consideration of family resources that are actually—not hypothetically—available.

c. Oral Health and Dental Services

Dental services required in the EPSDT benefit include:[17]

- ✓ Dental care needed for relief of pain, infection, restoration of teeth, and maintenance of dental health (provided at as early an age as necessary); and
- ✓ Emergency, preventive, and therapeutic services for dental disease that, if left untreated, may become acute dental problems or cause irreversible damage to the teeth or supporting structures.18

In addition, medically necessary oral health and dental services,[19] including those identified during an oral screening or a dental exam, are covered for children. States must provide orthodontic services to EPSDT-eligible children to the extent necessary to prevent disease and promote oral health, and restore oral structures to health and function.[20] Orthodontic services for cosmetic purposes are not covered.

Once a child reaches the age specified by the state in its pediatric dental periodicity schedule, typically age one, a direct dental referral is required.[21] The referral must be for an encounter with a dentist or with another dental professional, such as a dental hygienist, working under the supervision of a dentist.[22] Dental supervision includes the entire range, for example, direct, indirect, general, public health and collaborative practice arrangements.

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[16] 42 C.F.R. § 440.167.

[17] Information on CMS efforts working with states to improve access to oral health services for children enrolled in Medicaid and CHIP can be found in CMS, *Improving Access to and Utilization of Oral Health Services for Children in Medicaid and CHIP Programs: CMS Oral Health Strategy* (April 11, 2011). Approaches states can use to improve the delivery of dental and oral health services to children in Medicaid and CHIP can be found in *Keep Kids Smiling: Promoting Oral Health Through the Medicaid Benefit for Children and Adolescents* and in *Improving Oral Health Care Delivery in Medicaid and CHIP: A Toolkit for States*. All of these documents are available at http://www.medicaid.gov/Medicaid-CHIP-Program-Information/By-Topics/Benefits/Dental-Care.html.

[18] CMS, State Medicaid Manual § 5124.B.2.b.

[19] CMS, State Medicaid Manual § 2700.4 (Form 416 Instructions, Note for Line 12 Data). Dental services are those performed by or under the supervision of a dentist. Oral health services are those performed by other licensed providers not working under the supervision of a dentist, for example, a physician or nurse, or by a dental professional operating without a supervisory relationship to a dentist (e.g., an independent practice dental hygienist).

[20] CMS, State Medicaid Manual § 5124.B.2.b

[21] 42 C.F.R. § 441.56(b)(vi).

[22] CMS, State Medicaid Manual § 5123.2.G.

Current clinical guidelines recommend that a child have a first dental visit when the first tooth erupts or by age one.

Dental care must be provided at intervals indicated in the pediatric dental periodicity schedule adopted by the state after consultation with a recognized dental organization involved in child health care.[23] Current clinical guidelines recommend that a child have a first dental visit when the first tooth erupts or by age one, whichever occurs first. Dental care that is deemed medically necessary for an individual child is covered even when the frequency is greater than specified in the periodicity schedule.[24] For example, a child determined by a qualified provider to be at moderate or high risk for developing early childhood caries could be covered to receive dental exams and preventive treatments more frequently than the twice-yearly periodicity schedule recommended by the AAPD.

As determined by dental practice acts in individual states, there is a wide range of dental professionals who can work under the supervision of a dentist, for example, dental hygienists, dental therapists, dental health aide therapists, dental hygienists in advanced practice, advanced practice dental therapists, dental assistants, and community dental health coordinators. Some state practice acts permit specified dental professionals to work without dentist supervision in certain circumstances. Such provisions can help ensure access to dental care as well as promote an integrated health care delivery system. As with medical care, any qualified provider operating within the scope of his or her practice, as defined by state law, can provide a dental or oral health service to a Medicaid enrollee. To qualify for federal matching funds, State Plans must list all provider types that will be permitted to bill for dental or oral health services. However, rendering providers (providers who actually serve the patient) need not be separately enumerated in the State Plan.

Better integration of primary medical care with dental care can help identify children at risk for tooth decay at the youngest age possible, offer evidence-based preventive care, such as fluoride varnish and oral health education, and refer children to a dental professional for a complete check-up and any needed treatment. Three oral health risk assessment CDT billing codes can support this

[23] Section 1905(r)(3) of the Social Security Act; CMS, State Medicaid Manual § 5110.
[24] CMS, State Medicaid Manual § 5110.

approach, potentially preventing the need for costly treatment, such as that provided in an operating room.

State Medicaid and CHIP programs can use risk assessment codes to help children access services based on their individual levels of risk, instead of assuming that all children need the same level of intervention. AAPD guidelines encourage providers to customize care plans based on an assessment of each child's individual risk for developing dental disease. Risk assessment resources are available for providers, including an assessment tool from AAPD that includes a caries-risk assessment form, clinical guidelines and treatment protocols.

In addition to dental providers, states may reimburse primary care medical providers for conducting oral health risk assessments, providing oral health education to parents and children, applying preventive measures such as fluoride varnish, and making referrals to dental professionals. The CMCS oral health strategy guide, *Keep Kids Smiling: Promoting Oral Health Through the Medicaid Benefit for Children & Adolescents*, provides additional information on oral health and EPSDT.

d. Vision and Hearing Services

Vision and hearing services are an essential component of the EPSDT benefit. Hearing impairments can lead to other problems, including interference with normal language development in young children. They can also delay a child's social, emotional, and academic development. Vision problems can be evidence of serious, degenerative conditions, and can also lead to delays in learning and social development.

EPSDT requires that vision and hearing services be provided at intervals that meet reasonable standards as determined in consultation with medical experts, and at other intervals, as medically necessary, to determine the existence of a suspected illness or condition. At a minimum, vision services must include diagnosis and treatment for defects in vision, including eyeglasses. Glasses to replace those that are lost, broken, or stolen also must be covered. Hearing services must include, at a minimum, diagnosis and treatment for defects in hearing, including hearing aids.[25]

In addition, if hearing and vision problems are detected through screening, medically necessary services that are coverable under section 1905(a) must be covered. This includes not only physician and clinic services, but services from licensed professionals such as ophthalmologists, and equipment such as augmentative communication devices and cochlear implants.

[25] Sections 1905(r)(2) and (4) of the Social Security Act.

e. *Other Services*

Examples of other services covered for children under Medicaid when medically necessary (and for which a federal match is available) include, but are not limited to, case management services (including targeted case management);[26] incontinence supplies; organ transplants and any related services; a specially adapted car seat that is needed by a child because of a medical problem or condition; and nutritional supplements.

Physicians and other providers use medical terminology, not Medicaid terms or legal terms, when recommending or prescribing medical services and treatments. If a requested service or treatment is not listed by name in Medicaid's list of services, it should nonetheless be provided if the service or item is determined to be medically necessary and coverable under the list of services at section 1905(a). In general, states are encouraged to include in their State Plans a range of provider types and settings likely to be sufficient to meet the needs of enrollees. Nonetheless, there may be cases in which the type of provider that is needed is not already participating in Medicaid. In such an instance, the state could meet the EPSDT requirement by, for example, entering into a single-service agreement with the needed provider.

When providers use medical terminology instead of Medicaid or legal terms to recommend medically necessary services, the recommended services should be covered if coverable under section 1905(a).

C. Enabling Services

a. *Transportation Services*

In order to promote access to needed preventive, diagnostic and treatment services, states must offer appointment scheduling assistance and are required to assure necessary transportation, to and from medical appointments, for children

[26] Section 1905(a)(19) of the Social Security Act; 42 C.F.R. §§ 440.169, 441.18.

enrolled in Medicaid.[27] This includes covering the costs of an ambulance, taxi, bus, or other carrier. It can also include reimbursing for mileage. As with other services covered through EPSDT, states may cover the least expensive means of transportation if it is actually available, accessible, and appropriate. For example, public transportation can be covered instead of a taxi if the public transportation is physically accessible for a particular beneficiary and takes a reasonable amount of time. In addition, "related travel expenses" are covered if medically necessary, including meals and lodging for a child and necessary attendant.[28]

Some states have addressed the transportation requirement by offering non-emergency transportation through brokers who coordinate transportation services, or through administrative managers who act as gatekeepers for transportation services. Transportation may also be included in managed care contracts. If a state chooses not to include transportation services in their managed care contracts, or otherwise to contract out administration of the service, the state must administer the service itself. No matter the type of arrangement, it is important to remember that the state has ultimate responsibility for ensuring the provision of transportation services.

b. Language Access and Culturally Appropriate Services

Many Medicaid-enrolled children live in families where English is not spoken at home. State Medicaid agencies and their contractors should inform eligible individuals about the EPSDT benefit with a combination of written and oral methods "using clear and nontechnical language" and "effectively informing those individuals who . . . cannot read or understand the English language."[29] State Medicaid agencies and Medicaid managed care plans, as recipients of federal funds, also have responsibilities to assure that covered services are delivered to children without a language barrier. They are required take "reasonable steps" to assure that individuals who are limited English proficient have meaningful access to Medicaid services.[30] This may include providing interpreter services, including at medical appointments, depending on factors such as the number of limited English proficient individuals served by the program.[31]

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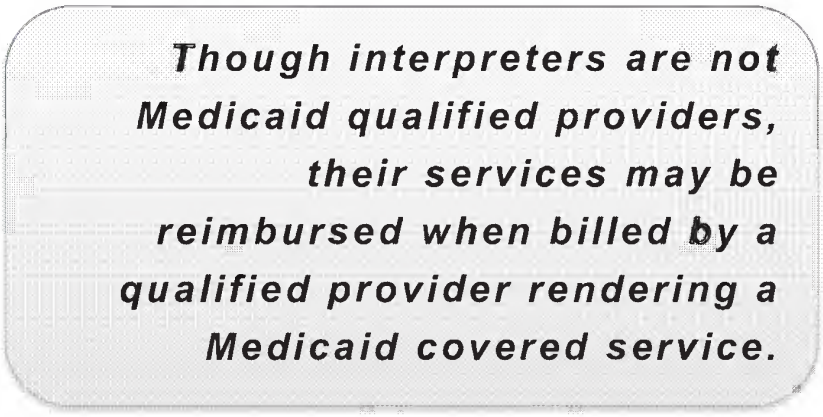
[27] Section 1905(a)(29) of the Social Security Act; 42 C.F.R. §§ 440.170, 441.62.
[28] 42 C.F.R. § 440.170(a).
[29] 42 C.F.R. § 441.56(a); CMS, State Medicaid Manual §§ 5121.A, 5121.C.
[30] 42 U.S.C. § 2000d (Title VI of the Civil Rights Act); Affordable Care Act § 1557; CMS Dear State Medicaid Director (Aug. 31, 2000).
[31] Department of Health & Human Services, Guidance to Federal Financial Assistance Recipients Regarding Title VI Prohibition Against National Origin Discrimination Affecting Limited English Proficient Persons, 68 Fed. Reg. 47311 (August 8, 2003).

Though interpreter services are not classified as mandatory 1905(a) services, all providers who receive federal funds from HHS for the provision of Medicaid services are obligated, under Title VI of the Civil Rights Act, to make language services available to those with limited English proficiency.



States are not required to (but may) reimburse providers for the cost of language services. States may consider the cost of language services to be included in the regular rate of reimbursement for the underlying direct service. In those cases, Medicaid providers are obligated to provide language services to those with limited English proficiency and to bear the costs for doing so. Alternatively, states may allow providers to bill specifically for interpreter services. States have the option to claim for the cost of interpretation services, either as medical-assistance related expenditures or as administration.[32]

Claiming Federal Matching Funds for Interpreter Services. Interpreters are not Medicaid qualified providers. However, their services may be reimbursed when billed by a qualified provider rendering a Medicaid covered service. Interpreters may not be paid separately. As of February 2009, oral interpreter services can be claimed using billing code T-1013 along with the CPT code used for the medical encounter. States can also raise reimbursement rates to recognize additional service costs, including interpreter costs, but must do so for services rendered by all providers in the class. With the enactment of the Children's Health Insurance Program Reauthorization Act in 2009, states were given the option to claim a higher federal matching rate (75% under Medicaid) for translation and interpretation services that are claimed as administration and are related to the enrollment, retention and use of services under Medicaid and CHIP by children of families for whom English is not their primary language.[33] Otherwise, longstanding CMS policy permits reimbursement at the standard 50% federal

[32] CMS, Dear State Medicaid Director (July 1, 2010); CMS, CMCS Informational Bulletin: *Recent Developments in Medicaid* (April 26, 2011).
[33] Section 1903(a)(2)(E) of the Social Security Act.

matching rate for translation and interpretation activities that are claimed as an administrative expense, so long as they are not included and paid for as part of the reimbursement rate for direct services.[34]

The HHS Office for Civil Rights and the Department of Justice have provided guidance for recipients of federal funds on expectations of how to provide language services.[35]

State Medicaid programs, managed care entities, and Medicaid-participating health care providers should all be culturally competent. This means they need to recognize and understand the cultural beliefs and health practices of the families and children they serve, and use that knowledge to implement policies and inform practices that support quality interventions and good health outcomes for children. Given changing demographics, this process is ongoing. The DHHS Office of Minority Health offers numerous resources, including:

- ✓ Center for Linguistic and Cultural Competence in Health Care;
- ✓ Think Cultural Health;
- ✓ A Physician's Practical Guide to Culturally Competent Care;
- ✓ The National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (the National CLAS Standards); and
- ✓ The National CLAS Standards' implementation guide, A Blueprint for Advancing and Sustaining CLAS Policy and Practice.

D. Settings and Locations for Services

a. Services Provided Out of State

States may need to rely upon out-of-state services if necessary covered services are not available locally, or if a Medicaid beneficiary is out of state at the time a need for medical services arises. States are required to pay for services provided

[34] CMS, Dear State Medicaid Director (August 31, 2000).
[35] *Id*; U.S. Department of Justice, Executive Order 13166.

in another state to the same extent services furnished in-state would be paid for if:

- ✓ The out-of-state services are required because of an emergency;
- ✓ The child's health would be endangered if she or he were required to travel to their home state;
- ✓ The state determines that the needed services are more readily available in the other state; or
- ✓ It is a general practice of the locality to use the services of an out-of-state provider, for example, in areas that border another state.[36]

Including out-of-state providers gives states the opportunity to expand the range and accessibility of Medicaid services that are available to their enrollees.[37]

b. Services Provided in Schools

Services provided in schools can play an important role in the health care of adolescents and children. Whether implemented for children with special needs under the Individuals with Disabilities Education Act (IDEA) or through school-based or linked health clinics, school-centered programs may be able to provide medical and dental care efficiently and effectively while avoiding extended absences from school.

In order for Medicaid to reimburse for health services provided in the schools, the services must be included among those listed in section 1905(a) of the Act and included in the State Plan, or be available under the EPSDT benefit. There is no benefit category in the Medicaid statute titled "school health services" or "early intervention services." Therefore a state must describe its school health services in terms of the specific section 1905(a) services which will be provided. In addition, there must be a provider agreement in place between the state Medicaid agency and the provider billing for the service; and the school must agree to comply with Medicaid-specific requirements regarding service documentation and claims submission.[38] States are encouraged to promote relationships between school-based providers and managed care plans.

Services provided in schools can play an important role in the health care of adolescents and children.

[36] Section 1902(a)(16) of the Social Security Act; 42 C.F.R. § 431.52.
[37] HCFA, Dear State Medicaid Director (July 25, 2000).
[38] 42 C.F.R. § 431.107.

Schools are particularly appropriate places to provide medical, vision, and hearing screenings; vaccinations; some dental care; and behavioral health services. The Individuals with Disabilities Education Act (IDEA) requires that every child with a disability have available a free appropriate public education that includes special education and related services. Part B of IDEA requires the development and implementation of an individualized education program (IEP) that addresses the unique needs of each child with a disability ages 3 through 21.[39] A child's IEP identifies the special education and related services needed by that child. Medicaid covered services included in the IEP may be provided in, and reimbursed to, schools. Part C of IDEA covers early intervention services, which are developmental services designed to meet a child's developmental needs in physical, cognitive, communication, adaptive, and social and emotional development, for children from birth to age 3. These services are provided pursuant to an Individualized Family Service Plan (IFSP).

Examples of IDEA services that can be covered by Medicaid for a Medicaid eligible child include physical therapy, occupational therapy, personal care, and services for children with speech, hearing and language disorders.[40]

c. Most Integrated Setting Appropriate

Title II of the Americans with Disabilities Act (ADA) prohibits discrimination on the basis of disability in public programs, including Medicaid. In *Olmstead v. L.C.,* the Supreme Court held that unjustified institutionalization of Medicaid beneficiaries violates the ADA. Accordingly, states must cover services in the community, rather than in an institution, when the need for community services can be reasonably accommodated and providing services in the community will not fundamentally alter the state's Medicaid program.

Community-based care is a best practice for supporting children with disabilities and chronic conditions.

CMS has long encouraged states to provide services in home and community settings, particularly for children, not only because of *Olmstead,* but because community-based care is considered a best practice for supporting children with

[39] While EPSDT covers children only through age 20 (up to the 21st birthday), the IDEA covers children through age 21 (up to the 22nd birthday).
[40] Additional information about Medicaid-covered services provided in schools can be found in the CMS, *Medicaid School Based Administrative Claiming Guide* (2003).

disabilities and chronic conditions. In addition, it is generally more cost-effective.[41]

EPSDT provides states with many options for covering physical and mental health services in the community. The EPSDT benefit requires coverage of medically necessary personal care, private duty nursing, physical, occupational and speech-language therapy. And, as discussed below, optional services provided through home and community based services waivers can further advance the state's efforts to provide services in the community.

[41] HCFA, Dear State Medicaid Director, Olmstead Update Nos. 2 and 3 (July 25, 2000), No. 5 (January 10, 2001); CMS, Dear State Medicaid Director (May 20, 2010); CMS, Joint CMCS and SAMHSA Informational Bulletin: *Coverage of Behavioral Health Services for Children, Youth, and Young Adults with Significant Mental Health Conditions* (May 7, 2013).

V. PERMISSIBLE LIMITATIONS ON COVERAGE OF EPSDT SERVICES

A. Individual Medical Necessity

Services that fit within the scope of coverage under EPSDT must be provided to a child only if necessary to correct or ameliorate the individual child's physical or mental condition, i.e., only if "medically necessary." The determination of whether a service is medically necessary for an individual child must be made on a case-by-case basis, taking into account the particular needs of the child. The state (or the managed care entity as delegated by the state) should consider the child's long-term needs, not just what is required to address the immediate situation. The state should also consider all aspects of a child's needs, including nutritional, social development, and mental health and substance use disorders. States are permitted (but not required) to set parameters that apply to the determination of medical necessity in individual cases, but those parameters may not contradict or be more restrictive than the federal statutory requirement. As discussed above, services such as physical and occupational therapy are covered when they have an ameliorative, maintenance purpose.

Determination of whether a service is medically necessary must be made on a case-by-case basis, taking into account a particular child's needs.

Because medical necessity decisions are individualized, flat limits or hard limits based on a monetary cap or budgetary constraints are not consistent with EPSDT requirements.[42] States may adopt a definition of medical necessity that places tentative limits on services pending an individualized determination by the state, or that limits a treating provider's discretion, as a utilization control, but additional services must be provided if determined to be medically necessary for

[42] HCFA, *Regional Transmittal Notice* (Region IV) (Sept. 18, 1990); Memorandum from Rozann Abato, Acting Director, HCFA, to Associate Regional Administrator, Atlanta (Sept. 5, 1990); Memorandum from Christine Nye, HCFA Medicaid Director, to Regional Administrator Region VIII (FME-42) (1991).

an individual child.[43] For example, while a state may place in its State Plan a limit of a certain number of physical therapy visits per year for individuals age 21 and older, such a "hard" limit could not be applied to children. A state could impose a "soft" limit of a certain number of physical therapy visits annually for children, but if it were to be determined in an individual child's case, upon review, that additional physical therapy services were medically necessary to correct or ameliorate a diagnosed condition, those services would have to be covered.

While the treating health care provider has a responsibility for determining or recommending that a particular covered service is needed to correct or ameliorate the child's condition,[44] both the state and a child's treating provider play a role in determining whether a service is medically necessary. If there is a disagreement between the treating provider and the state's expert as to whether a service is medically necessary for a particular child, the state is responsible for making a decision, for the individual child, based on the evidence. That decision may be appealed by the child (or the child's family) under the state's Medicaid fair hearing procedures, as described in Section VIII below.

B. Prior Authorization

States may impose utilization controls to safeguard against unnecessary use of care and services. For example, a state may establish tentative limits on the amount of a treatment service a child can receive and require prior authorization for coverage of medically necessary services above those limits.[45] Prior authorization must be conducted on a case-by-case basis, evaluating each child's needs individually. Importantly, prior authorization procedures may not delay delivery of needed treatment services and must be consistent with the "preventive thrust" of EPSDT.[46] As such, prior authorization may not be required for any EPSDT screening services. In addition, medical management techniques used for mental health and substance use disorders should comply with the Mental Health Parity and Addiction Equity Act.

C. Experimental Treatments

EPSDT does not require coverage of treatments, services, or items that are experimental or investigational. Such services and items may, however, be covered at the state's discretion if it is determined that the treatment or item would be effective to address the child's condition.[47] Neither the Federal Medicaid statute nor the regulations define what constitutes an experimental

[43] 42 C.F.R. §§ 440.230(c), (d); HCFA Dear State Medicaid Director (May 26, 1993).
[44] Sections 1905(a) and (r) of the Social Security Act.
[45] *Id.*
[46] H.R. Rep. No. 101-247 at 399, *reprinted in* U.S.C.C.A.N. 1906, 2125.
[47] CMS, State Medicaid Manual §§ 4385.C.1, 5122.F.

treatment. The state's determination of whether a service is experimental must be reasonable and should be based on the latest scientific information available.[48]

Medicare guidance on whether a service is experimental or investigational is not determinative of the issue and may not be relevant to the pediatric population.[49]

D. Cost-Effective Alternatives

A state may not deny medically necessary treatment to a child based on cost alone, but may consider the relative cost effectiveness of alternatives as part of the prior authorization process. Also, a state need not make services available in every possible setting as long as the services are reasonably available through the settings where the service is actually offered. States may cover services in the most cost effective mode as long as the less expensive service is equally effective and actually available.[50] The child's quality of life must also be considered.[51] In addition, the ADA and the *Olmstead* decision require states to provide services in the most integrated setting appropriate to a child's needs, as long as doing so does not fundamentally alter the state's program. See above, Section IV.D. Thus, if an institutional setting is less costly than providing services in a home or community, the ADA's integration mandate may nevertheless require that the services be provided in the community.[52]

A state may not deny medically necessary treatment based on cost alone, but may consider the relative cost effectiveness of alternatives as part of the prior authorization process.

[48] Memorandum from S. Richardson to State Medicaid Directors (April 17, 1995).
[49] Memorandum from S. Richardson to State Medicaid Directors (April 17, 1995).
[50] CMS, Dear State Medicaid Director, Olmstead Update No. 4 (January 10, 2001); Letter from Rozann Abato, Acting Director, Medicaid Bureau, to State Medicaid Directors (May 26, 1993).
[51] *Id.*
[52] 28 C.F.R. § 35.130(d); CMS, Dear State Medicaid Director, Olmstead Update No. 4 (January 10, 2001); DOJ, Statement of the Department of Justice on Enforcement of the Integration Mandate of Title II of the ADA and *Olmstead v. L.C.* (June 22, 2011).

VI. SERVICES AVAILABLE UNDER OTHER FEDERAL AUTHORITIES

A. Home and Community Based Services Waivers

A state Medicaid program may offer services through home and community based services (HCBS) waiver programs. Such programs allow states to provide HCBS to individuals who would otherwise need long-term care in a nursing facility, intermediate care facility, or hospital. Waiver programs provide for coverage of services that are not otherwise available through the Medicaid program (including EPSDT) because they do not fit into one of the categories listed in section 1905(a). This includes habilitative services, respite services, or other services approved by CMS that can help prevent institutionalization. These programs are sometimes called 1915(c) waivers after the section of the Social Security Act that authorizes them.[53]

Children under age 21 who are enrolled in an HCBS waiver program are also entitled to all EPSDT screening, diagnostic, and treatment services. Because HCBS waivers can provide services not otherwise covered under Medicaid, waivers and EPSDT can be used together to provide a comprehensive benefit for children with disabilities who would otherwise need the level of care provided in an institutional setting. This enables those children to remain in their homes and communities while receiving medically necessary services and supports. The HCBS waiver services essentially "wrap-around" the EPSDT benefit. If a child enrolled in Medicaid is on a waiting list for HCBS waiver services, EPSDT requirements apply and necessary services that fit into the categories listed in 1905(a) must be covered.[54]

Children who are enrolled in an HCBS waiver program are also entitled to all EPSDT services.

States may also choose to offer services to children under section 1915(j) (self-directed personal assistance services), section 1915(k) (home and community-based attendant services and support) and section 1945 (coordinated care in

[53] Section 1915(c) of the Social Security Act.
[54] CMS, Dear State Medicaid Director, Olmstead Update No. 4, Att. 4-B (Jan. 10, 2001).

health homes for individuals with chronic conditions). Like services provided pursuant to a 1915(c) waiver, these services are not subject to EPSDT coverage provisions, but are instead available to supplement EPSDT services.

B. Alternative Benefit Plans

States must assure access to services available under the EPSDT benefit for all EPSDT-eligible children under age 21 enrolled in Alternative Benefit Plans (formerly known as benchmark plans and benchmark-equivalent plans).[55]

C. Role of Maternal and Child Health Services

Federal rules require state Medicaid agencies and Title V Maternal and Child Health (MCH) agencies and grantees to collaborate to assure better access to and receipt of the full range of screening, diagnostic, and treatment services covered under EPSDT.[56] Title V is administered by the Health Resources and Services Administration. Many state Medicaid agencies have entered into written agreements with their sister MCH programs and collaborate on improving access to EPSDT services in order to improve child health status. Among other things, cooperating MCH agencies can provide outreach, screening, diagnostic or treatment services, health education and counseling, case management and other assistance in achieving a comprehensive and effective child health benefit. MCH programs can also help Medicaid programs to enlist providers who can help deliver a broad array of services. In addition, they can inform potential and actual Medicaid recipients about EPSDT and refer them to necessary services.[57] CMS encourages such collaborations as MCH programs are crucial partners in the creation and delivery of a high quality, well-integrated child health benefit.

Many state Medicaid agencies have written agreements with their states' MCH programs and collaborate to improve access to EPSDT services.

[55] 42 C.F.R. § 440.345.
[56] 42 U.S.C. §§ 705(a)(5)(F), 709(a)(2); 42 C.F.R. § 441.61(c).
[57] CMS, State Medicaid Manual § 5230.

VII. ACCESS TO SERVICES

A. Access to Providers

Access to covered services is of course a critical component of delivering an appropriate health benefit to children. Accordingly, a number of Medicaid and EPSDT provisions are intended to assure that children have access to an adequate number and range of pediatric providers. For example, states are required to "make available a variety of individual and group providers qualified and willing to provide" services to children.[58] States must also "take advantage of all resources available" to provide a "broad base" of providers who treat children."[59] Some states may find it necessary to recruit new providers to meet children's needs.[60] In the event a child needs a treatment that is not coverable under the categories listed in section 1905(a), states are to provide referral assistance that includes giving the family or beneficiary the names, addresses, and telephone numbers of providers who have expressed a willingness to furnish uncovered services at little or no expense to the family.[61]

States are required to make available a variety of providers who are qualified and willing to treat EPSDT children.

A child is entitled to receive Medicaid services from any provider qualified to provide the service and willing to furnish it, unless CMS has decided that this "freedom of choice" requirement will not apply.[62] Most states have received permission from CMS to provide some services to some children through managed care arrangements that restrict the free choice of provider.

An appropriate level of reimbursement can be critical to ensuring adequate access to providers.[63] While the statute provides states with broad authority to set provider payment rates, it requires that payments to providers must be consistent with efficiency, economy, and quality care and be sufficient to enlist enough

[58] 42 C.F.R. § 441.61.
[59] CMS, State Medicaid Manual § 5220.
[60] *Id.*
[61] 42 C.F.R. § 441.61(a).
[62] Sections 1902(a)(23) and 1932(a) of the Social Security Act; 42 C.F.R. § 431.51(b).
[63] HCFA, Dear State Medicaid Director (Jan 18, 2001).

providers that care and services are available to Medicaid beneficiaries at least to the extent that they are available to the general population in the geographic area.[64]

Federal regulations provide that a Medicaid provider must agree to accept, as payment in full, the Medicaid payment for a covered service or item.[65] This means that a provider *may not* bill a Medicaid beneficiary for the difference between the provider's charge and the Medicaid payment (called "balance billing"). The payment in full requirement also prohibits Medicaid providers from billing beneficiaries for missed appointments. States may need to monitor compliance with this requirement.

Section 1905(a) lists coverable Medicaid services and some provider types. There are at least two means by which a state may cover a service by a provider type that is not specified in section 1905(a). Section 1905(a)(6) permits states to cover "medical care, or any other type of remedial care recognized under State law, furnished by licensed practitioners within the scope of their practice as defined by State law." Thus, a state may cover services performed by a class of providers (such as licensed dieticians) when the service they provide is not specified in section 1905(a) as long as the service is determined medically necessary for a child. Alternatively, a provider's services can be covered as a component of a section 1905(a) service. For example, in the case of a licensed social worker, the services could be provided through a federally qualified health center or a clinic, both of which are recognized providers under section 1905(a). The process for covering a provider for a service not specified in section 1905(a) varies depending on how the state intends to provide the service.

B. Managed Care

EPSDT benefits must be available to all children covered by Medicaid. As such, children enrolled in managed care plans, prepaid inpatient health plans, prepaid ambulatory health plans, primary care case management systems (collectively referred to as managed care entities) are entitled to the same EPSDT benefits they would have in a fee for service Medicaid delivery system. Properly implemented, managed care can enhance and promote EPSDT's goals of ensuring that care is provided in a coordinated way and with an emphasis on prevention.

States are responsible for assuring that the full EPSDT benefit is available to all Medicaid children in the state, even if the state contracts with a managed care entity to deliver some or all of the services available under EPSDT. The state's

[64] Section 1902(a)(30)(A) of the Social Security Act; Medicaid Program: Methods for Assuring Access to Covered Medicaid Services, 76 Fed. Reg. 26,342 (May 11, 2011) (proposed regulations).
[65] 42 C.F.R. § 447.15.

contracts with managed care entities should be drafted with sufficient precision so that the entity's responsibilities with respect to children are clearly delineated. A contract can provide that the managed care entities will be responsible for providing services under the EPSDT benefit to the same degree that the services are covered by the state. Or, if certain responsibilities are carved out of the managed care contract, those carve-outs must be explicit, and the state will retain the responsibility for ensuring that those carved-out services are provided to enrolled children. For example, the state may 'carve out' dental services from the managed care contract; nonetheless, the state must assure that children receive those services (through either fee for service or a specialized dental plan).

Managed care entities may not use a definition of medical necessity for children that is more restrictive than the state's definition.

Managed care entities may not use a definition of medical necessity for children that is more restrictive than the state's definition. One way to ensure this is for the state to include its definition of medical necessity in the entity's contract. States should review managed care entities' medical necessity definitions and criteria to ascertain whether they meet this requirement. As a further step to provide for consistency across the delivery system and proper implementation of the children's benefit package, it is the state's responsibility to educate its contracted managed care entities about EPSDT requirements, as well as to verify that managed care providers are informed about EPSDT requirements through trainings and provider manuals. Further, states are responsible for ensuring that managed care entities fulfill their contractual responsibilities to inform all families of the services available under EPSDT and how to access them.[66] Information made available to enrollees, usually included in a member handbook, should clearly explain which EPSDT services the managed care entity will provide and how any EPSDT services not within the scope of the contract can be accessed by enrollees. Managed care entities must make available to all enrolled children the entire scope of services included in the EPSDT benefit that is within their contract with the state.[67]

[66] Sections 1902(a)(5) and (a)(43) of the Social Security Act.
[67] 42 C.F.R. § 438.210(a)(4).

Managed care entities must demonstrate to the state that they have adequate provider capacity in the plan to serve enrolled children, including an appropriate range of pediatric and specialty services; access to primary and preventive care; and a sufficient number, mix and geographic distribution of providers.[68]

Monitoring managed care entities' compliance with EPSDT requirements is essential; a strong oversight framework ensures that states are meeting their responsibilities to children as well as Federal monitoring requirements.[69] There are several methods of exercising effective oversight in managed care systems.

First, states contracting with managed care organizations (MCOs) or prepaid inpatient health plans (PIHPs) are statutorily required to draft, implement, and maintain a managed care quality strategy.[70] The quality strategy is intended to provide a blueprint for states in assessing and improving the quality of care provided to managed care enrollees.[71] By means of this strategy, states can monitor and evaluate managed care entities' compliance with quality initiatives, track their performance on specified performance measures, and require them to design, implement and report the results of performance improvement projects.

Second, states are also required to ensure that external quality review of MCOs and PHIPs are performed by unbiased, external entities.[72] In this way, states can determine whether managed care entities are reporting accurate performance outcomes data and whether they are in compliance with state contract provisions.

Third, states can engage in an ongoing review of grievances and appeals related to children's services, as well as monitoring complaints filed with the state's enrollee and provider hotlines (if the state operates such hotlines). States could also require reports and perform data analysis of managed care entities' encounter data to detect underutilization of services by children.

In addition, all states are required to complete and file the Form 416 each year.[73] This reports the number of children receiving health screening services, dental and oral health services, and referrals for corrective treatment, as well as the state's rates of meeting EPSDT participation goals.

[68] 42 C.F.R. § 438.206.
[69] 42 C.F.R. § 438.240.
[70] Section 1932(c)(1) of the Social Security Act; 42 C.F.R. §§ 438.202, 438.204.
[71] 42 C.F.R. § 438.202.
[72] Section 1932(c)(2) of the Social Security Act; 42 C.F.R. § 438.350.
[73] Section 1902(a)(43)(D) of the Social Security Act.

C. Timeliness

Services under the EPSDT benefit, like all Medicaid services, must be provided with "reasonable promptness."[74] The state must set standards to ensure that EPSDT services are provided consistent with reasonable standards of medical and dental practice. The state must also ensure that services are initiated within a reasonable period of time. What is reasonable depends on the nature of the service and the needs of the individual child. Because states have the obligation to "arrang[e] for . . . corrective treatment" either directly or through referral to appropriate providers, a lack of providers does not automatically relieve a state of its obligation to ensure that services are provided in a timely manner. For example, as noted above, it may be necessary to cover services provided out of state.

Services under the EPSDT benefit, like all Medicaid services, must be provided with reasonable promptness.

[74] Section 1902(a)(8) of the Social Security Act.

VIII. NOTICE AND HEARING REQUIREMENTS

Children under age 21, like all other people enrolled in Medicaid, have the right to notice and an opportunity for a hearing. If a state or managed care entity takes an "action" – to deny, terminate, suspend, or reduce a requested treatment or service, it must give the beneficiary written notice of the action and of their right to a hearing (a pre-termination hearing, in instances where services are reduced or terminated), including instructions on how to request a hearing.[75] When services are being terminated or reduced, the notice must be sent at least ten days before the effective date of the action.[76] Under exceptional circumstances, the notice must be mailed no later than the day of the action, such as when the beneficiary's physician prescribes a change in treatment or the beneficiary has been admitted to an institution and is no longer eligible.[77] The notice must contain a statement of the intended action, the specific reasons and legal support for the action, and an explanation of the individual's hearing rights, rights to representation and to continued benefits.[78]

If a state or managed care entity takes an action to deny, terminate, suspend, or reduce a requested treatment or service, it must give the beneficiary written notice of the action and of their right to a hearing.

The beneficiary is entitled to a hearing before the state Medicaid agency, or, if a state's hearing process provides for it, an evidentiary hearing at the local level (for example at a county department of social services) with a right of appeal to the state agency.[79] The hearing must be conducted at a reasonable time, date, and place by an impartial hearing official. A beneficiary must be allowed to present his or her case to an impartial decision maker and present evidence and

[75] Section 1902(a)(3) of the Social Security Act; *Goldberg v. Kelly*, 397 U.S. 254 (1970).
[76] 42 C.F.R. § 431.211.
[77] 42 C.F.R. § 431.213.
[78] 42 C.F.R. §§ 431.206, 431.210.
[79] 42 C.F.R. § 431.205(b).

witnesses.[80] The beneficiary is also entitled to have representation, including legal counsel, a relative, or a friend.[81] Before the hearing, beneficiaries must have the right to examine the case file and all documents that will be used at the hearing.[82]

When a service is terminated or reduced, if the beneficiary requests a hearing within ten days of receiving notice of the termination or reduction, the beneficiary has the right to continued coverage of services pending a hearing decision.[83] This is sometimes called "aid paid pending." Once the agency issues a final decision, the beneficiary generally has the right to appeal that decision to state court.

Managed care enrollees must have access to in-plan grievance and appeal processes, in addition to the state fair hearing system.[84] Managed care plans must provide enrollees written notices that explain the action, the reason for the action, and the procedures for using the in-plan grievance and state fair hearing processes, including rights to continued benefits. Managed care plans must resolve complaints in a timely manner, including within three working days when the enrollee or provider indicates that delay could seriously jeopardize the enrollee's life, health or ability to attain, maintain, or retain maximum function.[85] The state can require enrollees to exhaust the plan's internal grievance process before obtaining a state fair hearing.

The state agency must issue and publicize its hearing decisions.[86] In addition, the public must have access to all fair hearing decisions, subject to regulatory requirements providing for safeguarding of confidential personal and health information.[87]

[80] 42 C.F.R. §§ 431.240, 431.242.
[81] 42 C.F.R. § 431.206(b)(3).
[82] 42 C.F.R. § 431.242.
[83] 42 C.F.R. § 431.230.
[84] 42 C.F.R. § 438.402.
[85] 42 C.F.R. § 438.408.
[86] 42 C.F.R. § 431.206(a).
[87] 42 C.F.R. § 431.244(g).

IX. CONCLUSION

The goal of EPSDT is to assure that all Medicaid-enrolled children under age 21 receive the health care they need. EPSDT covers not only medically necessary treatment to correct or ameliorate identified conditions, but also preventive, and maintenance services. In addition, EPSDT covers age-appropriate medical, dental, vision and hearing screening services at specified times, and when health problems arise or are suspected.

The broad scope of EPSDT provides states with the tools necessary to offer a comprehensive, high-quality health benefit. To fully realize EPSDT's potential, however, attention is needed on issues affecting access to services, including supply of providers, the presence of managed care, linguistic and disability access, and transportation. CMS is available to help states address these issues to ensure that EPSDT coverage meets the needs of children under age 21 who depend on Medicaid for their health care.

X. WHAT YOU NEED TO KNOW ABOUT EPSDT

EARLY: Assessing and identifying problems early

Children covered by Medicaid are more likely to be born with low birth weights, have poor health, have developmental delays or learning disorders, or have medical conditions (e.g., asthma) requiring ongoing use of prescription drugs. Medicaid helps these children and adolescents receive quality health care.

EPSDT is a key part of Medicaid for children and adolescents. EPSDT emphasizes preventive and comprehensive care. Prevention can help ensure the early identification, diagnosis, and treatment of conditions before they become more complex and costly to treat. It is important that children and adolescents enrolled in Medicaid receive all recommended preventive services and any medical treatment needed to promote healthy growth and development.

PERIODIC: Checking children's health at age-appropriate intervals

As they grow, infants, children and adolescents should see their health care providers regularly. Each state develops its own "periodicity schedule" showing the check-ups recommended at each age. These are often based on the American Academy of Pediatrics' Bright Futures guidelines: Recommendations for Preventive Pediatric Health Care. Bright Futures helps doctors and families understand the types of care that infants, children and adolescents should get and when they should get it. The goal of Bright Futures is to help health care providers offer prevention-based, family-focused, and developmentally-oriented care for all children and adolescents. Children and adolescents are also entitled to receive additional check-ups when a condition or problem is suspected.

SCREENING: Providing physical, mental, developmental, dental, hearing, vision and other screening tests to detect potential problems

All infants, children and adolescents should receive regular well-child check-ups of their physical and mental health, growth, development, and nutritional status. A well-child check-up includes:

- A comprehensive health and developmental history, including both physical and mental health development assessments;
- Physical exam;
- Age-appropriate immunizations;
- Vision and hearing tests;
- Dental exam;
- Laboratory tests, including blood lead level assessments at certain ages; and
- Health education, including anticipatory guidance.

DIAGNOSTIC: Performing diagnostic tests to follow up when a health risk is identified

When a well-child check-up or other visit to a health care professional shows that a child or adolescent might have a health problem, follow up diagnostic testing and evaluations must be provided under EPSDT. Diagnosis of mental health, substance use, vision, hearing and dental problems is included. Also included are any necessary referrals so that the child or adolescent receives all needed treatment.

TREATMENT: Correct, reduce or control health problems found

EPSDT covers health care, treatment and other measures necessary to correct or ameliorate the child or adolescent's physical or mental conditions found by a screening or a diagnostic procedure. In general, States must ensure the provision of, and pay for, any treatment that is considered "medically necessary" for the child or adolescent. This includes treatment for any vision and hearing problems, including eyeglasses and hearing aids. For children's oral health, coverage includes regular preventive dental care and treatment to relieve pain and infections, restore teeth, and maintain dental health. Some orthodontia is also covered.

XI. RESOURCES

CMS Resources

- CMS, *State Medicaid Manual §§ 2700.4 and 5010-5360*
- CMS, *Early and Periodic Screening Diagnostic and Treatment Resources*

Adolescent Health

- CMS, *Paving the Road to Good Health: Strategies for Increasing Medicaid Adolescent Well-Care Visits (Feb. 2014)*

Oral Health

- CMS, *Keep Kids Smiling: Promoting Oral Health Through the Medicaid Benefit for Children and Adolescents* (September 2013)
- CMS, *Improving Access to and Utilization of Oral Health Services for Children in Medicaid and CHIP Programs,* CMS Oral Health Strategy (April 11, 2011)
- CMS, *CMCS Informational Bulletin, CMS Oral Health Initiative and Other Dental Related Issues* (April 18, 2013)
- *Improving Oral Health Care Delivery in Medicaid and CHIP: A Toolkit for States* (February 2014)

Mental Health

- CMS, *CMCS Informational Bulletin, Prevention and Early Identification of Mental Health and Substance Use Conditions* (March 27, 2013)
- CMS, *Joint CMCS and SAMHSA Informational Bulletin, Coverage of Behavioral Health Services for Children, Youth, and Young Adults with Significant Mental Health Conditions* (May 7, 2013)

Screening Services

- CMS, *Guide for States Interested in Transitioning to Targeted Blood Lead Screening for Medicaid-eligible Children* (May 2012)

Accessibility

- CMS, *CMCS Informational Bulletin* (April 26, 2011) (federal funding for interpretation and translation services)
- CMS, *Dear State Medicaid Director* (Aug. 31, 2000) (Limited English Proficiency)
- CMS, *Dear State Medicaid Director, Olmstead Update No. 4*, Att. 4-B EPSDT (Jan. 10, 2001)
- CMS, *Medicaid School-Based Administrative Claiming Guide* (May 2003)

Other Federal Resources

- CDC, Vaccine Recommendations of the ACIP
- HRSA, *EPSDT & Title V Collaboration to Improve Child Health*
- Health Resources and Services Administration EPSDT website
- HHS Office of Minority Health's *Think Cultural Health: Advancing Health Equity at Every Point of Contact*
- HHS Office of Minority Health's *A Physician's Practical Guide to Culturally Competent Care*
- HHS Office of Minority Health's *Culturally Competent Nursing Care: A Cornerstone of Caring*
- HHS Office of Minority Health's *Cultural Competency Curriculum for Disaster Preparedness and Crisis Response*
- HHS Office of Minority Health's *Cultural Competency Program for Oral Health Professionals*
- HHS Office of Minority Health's *National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care (the National CLAS Standards)*
- HHS Office of Minority Health's *A Blueprint for Advancing and Sustaining CLAS Policy and Practice (The Blueprint)*

Other Resources

- American Academy of Pediatrics, *Bright Futures* (2014)
- American Academy of Pediatrics, *Bright Futures Recommendations for Pediatric Preventive Care* (2014)
- American Academy of Pediatric Dentistry, *Guideline on Periodicity of Examination, Preventive Dental Services, Anticipatory Guidance/Counseling, and Oral Treatment for Infants, Children, and Adolescents* (2013)
- Association of Maternal and Child Health Programs, *Standards for Systems of Care for Children and Youth with Special Health Care Needs* (March 2014)
- George Washington University, Health Information & The Law, *Understanding the Interaction Between EPSDT and Federal Health Information Privacy and Confidentiality Laws* (2013)
- National Academy of State Health Policy, Managing the "T" in EPSDT Services (2010)
- National Academy of State Health Policy, Resources to Improve Medicaid for Children and Adolescents
- National Health Law Program, Toward a Healthy Future: Medicaid EPSDT Services for Poor Children and Youth
- National Health Law Program, Annotated Federal Documents

TAB 176-23

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES
Center for Medicaid & CHIP Services

CMCS Informational Bulletin

DATE: July 21, 2022

FROM: Daniel Tsai, Deputy Administrator and Director
Center for Medicaid and CHIP Services

SUBJECT: Beneficiary Protections and Medicaid Drug Coverage - Under Value Based Purchasing (VBP) and Other Innovative Payment Arrangements

The purpose of this Center for Medicaid and CHIP Services (CMCS) Informational Bulletin (CIB) is to remind states and stakeholders of existing federal beneficiary protections that help ensure appropriate beneficiary access to prescription medications, especially as state programs and stakeholders continue to negotiate novel payment arrangements with drug manufacturers.

The Centers for Medicare & Medicaid Services (CMS) understand the challenges that states face managing pharmacy costs, especially as new, innovative gene and cell therapies are brought to market. We are taking several steps to help states meet these challenges. We have approved 13 state plan amendments (SPAs) that authorize states to negotiate with manufacturers for value-based supplemental rebates for a drug, and several more states' SPAs are under review. Moreover, we are issuing this CIB to coincide with the start of the new flexibilities that allow manufacturers to report to the agency multiple best prices for a drug that are connected to a VBP arrangement (as defined at 42 CFR 447.502) and made available to all states. These VBP arrangements will hold manufacturers more accountable for the clinical outcomes of their drugs, while giving more states the opportunity to earn additional rebates depending on how a drug works for patients. In addition, we look forward to working with states through a learning collaborative that will be launched in the fall of 2022 to help states better manage their pharmacy costs, especially for these high cost drugs. We hope this work will lead to productive negotiations between states and manufacturers regarding the cost of these drugs for Medicaid beneficiaries.

Introduction

Alternative VBP arrangements for drugs, such as outcomes-based models and supplemental rebate agreements, have become more commonplace. These arrangements allow state Medicaid agencies to receive additional discounts or rebates from manufacturers on a drug when a drug does not meet certain observed or expected therapeutic or clinical values in a select population, based on applicable evidence-based or outcomes-based measures. As a result of these new payment arrangements, we believe it is important that beneficiaries, states, and manufacturers understand the beneficiary protections currently in

place to ensure access to medications under both traditional pharmacy programs and alternative payment arrangements.

In the December 31, 2020 issue of the *Federal Register*, the CMS published the final rule entitled: *Medicaid Program; Establishing Minimum Standards in Medicaid State Drug Utilization Review (DUR) and Supporting Value-Based Purchasing (VBP) for Drugs Covered in Medicaid, Revising Medicaid Drug Rebate and Third Party Liability (TPL) Requirements* (hereinafter referred to as the December 2020 final rule) (85 Fed. Reg. 87000; CMS 2482-F2). This new regulation permits manufacturers to report multiple best prices for a covered outpatient drug in certain cases. More specifically, it provides that if a manufacturer offers a VBP arrangement to all states, the lowest price available from a manufacturer may include varying best price points for a single dosage form and strength as a result of that VBP arrangement. These arrangements offered by manufacturers to states must meet the definition of a VBP arrangement as specified in 42 CFR § 447.502 and allow the state to collect additional rebates based on a patient's outcomes beyond those that the state will already receive under the Medicaid Drug Rebate Program (MDRP).

We note that states are not required to participate in these VBP arrangements in order for manufacturers to report multiple best prices. In addition to the states' voluntary participation in commercially-available VBP arrangements, states have also been actively negotiating other types of payment arrangements with manufacturers, such as through CMS-authorized supplemental rebate agreements, pay-over-time models, and "subscription" model arrangements under which the manufacturer charges a payer a fixed amount for an unlimited supply of a drug (resulting in a lower per unit price as utilization of the drug increases). Regardless of the type of arrangement, CMS is providing this guidance to ensure that stakeholders are aware of laws and regulations regarding beneficiaries' access to medically necessary medications.

Medicaid Requirements that Protect Beneficiary Access to Drugs

CMS believes it is important to reiterate to states and manufacturers the current federal protections that are in place under the Medicaid program to help ensure appropriate beneficiary access to drugs. States must generally apply these existing broad statutory requirements to Medicaid coverage of prescription drugs, regardless of any type of payment arrangement the state may have with manufacturers, unless an exception applies, such as a waiver.

1. States must cover all covered outpatient drugs subject to a rebate agreement with the Secretary: States must cover all covered outpatient drugs of a manufacturer that has entered into and has in effect a Medicaid drug rebate agreement, and may only restrict or exclude coverage of drugs as expressly described in section 1927(d) of the Social Security Act (the Act). Subject to these permissible restrictions, covered outpatient drugs that are prescribed for a medically accepted indication must be covered. States are permitted to subject any drug to prior authorization as long as it meets the requirements of section 1927(d)(5).

   Section 1927(d)(1)(B) of the Act permits states to restrict or exclude coverage of a covered outpatient drug only if the prescribed use is not for a medically accepted indication, the drug is included in the list of drugs or drug classes (or their medical uses) that may be excluded or otherwise restricted by the state (e.g., agents when used for cosmetic purposes or to promote fertility), the drug is subject to restrictions

pursuant to an authorized agreement between the manufacturer and state under a permissible prior authorization program or formulary, or pursuant to a state established formulary that is consistent with federal law.

Section 1927(d)(6) permits states to impose limitations with respect to all such drugs in a therapeutic class, on minimum or maximum quantities per prescription or on the number of refills, if such limitations discourage waste, and may address instances of fraud and abuse. The statute also further provides an enumerated list of non-excludable drugs, classes of drug, or their medical uses at section 1927(d)(7), which a state may not exclude from coverage. In summary, a state must ensure the covered outpatient drugs of a manufacturer with an effective Medicaid drug rebate agreement are covered and available when the covered outpatient drug is prescribed for a medically accepted indication, unless certain exclusions or restrictions apply.

2. State Alternative Benefit Plans (ABP) must follow Essential Health Benefit (EHB) standards when providing prescription drug coverage: When providing coverage under alternative benefit plans to a Medicaid population, states are required to provide prescription drug coverage that meets certain specific drug formulary standards, and to have a process in place such that the Medicaid beneficiary can access clinically appropriate drugs not covered on the state's drug formulary. Specifically, under 42 CFR § 440.347(a)(6), states must provide prescription drug coverage that meets the Essential Health Benefits (EHB) standards described in 45 CFR § 156.122, including a formulary that meets the standards at 45 CFR § 156.122(a), and that includes a process in place that allows the Medicaid beneficiary (or their designee) to request and gain access to clinically appropriate drugs not otherwise covered by the formulary consistent with the EHB standard at 45 CFR § 156.122(c). As specified at 42 CFR § 440.347(e), EHBs cannot be based on a benefit design or implementation of a benefit design that discriminates based on an individual's age, expected length of life, present or predicted disability, degree of medical dependency, quality of life or other health conditions.

3. States generally cannot limit beneficiary access to certain providers because of a specific payment arrangement: In general, section 1902(a)(23)(A) of the Act and 42 CFR § 431.51(b) require that any Medicaid beneficiary may obtain Medicaid services (including covered outpatient drugs) from any institution, agency, pharmacy, person, or organization that is qualified to furnish the service or services, and willing to furnish them to that particular beneficiary. CMS can waive this requirement under section 1915(b) or section 1115 of the Act, and this requirement also would not generally apply under state plan Medicaid managed care programs. Therefore, unless this requirement has been waived, is not applicable, or an exception applies, a state may not limit coverage of drugs to those obtained from a limited list of Medicaid providers or pharmacies. Additionally, under certain circumstances specified in 42 CFR § 431.52, states are required to cover Medicaid services provided out of state to their residents who are Medicaid beneficiaries and who are absent from the state.

4. States generally must comply with the Medicaid comparability requirement: Unless an exception applies or this requirement is waived under section 1115 of the Act, section 1902(a)(10)(B) of the Act and 42 CFR § 440.240 require states to ensure that the services available to any categorically needy beneficiary under the Medicaid state plan are not less in amount, duration, and scope than those services available to a medically needy beneficiary. Also, unless an exception applies or the requirement is waived, these provisions require states to ensure that the services available to any

individual in the following groups are equal in amount, duration, and scope for all beneficiaries within the group: (1) the categorically needy; and (2) a covered medically needy group. Therefore, any payment arrangement a state enters into must result in compliance with these comparability requirements, unless an exception applies or the requirements have been waived.

5. States must adhere to Early and Periodic Screening, Diagnostic and Treatment (EPSDT) requirements: Under section 1905(a)(4)(B) and (r) of the Act, states are required to cover all medically necessary services described in section 1905(a) of the Act for children under the age of 21 who are eligible for EPSDT, including prescribed drugs, regardless of any payment arrangement. What this means is that any prescribed drug covered under Medicaid EPSDT requirements is eligible for federal financial participation (FFP), regardless of the applicability of section 1927. In other words, even if the drug is not a covered outpatient drug in accordance with section 1927(k)(2) of the Act or the drug is a covered outpatient drug and a manufacturer does not have in effect a drug rebate agreement, the drug is covered under Medicaid and is eligible for FFP if prescribed under EPSDT requirements.

6. States must continue to have Drug Utilization Review (DUR) Programs in place: As required under section 1927(g) of the Act, a state must continue to have a DUR program targeted, in part, at reducing abuse and misuse of outpatient prescription drugs covered under the state's Medicaid program. The DUR program operates to help ensure that prescriptions are appropriate, medically necessary, and are not likely to result in adverse medical results for Medicaid beneficiaries. Each state DUR program must consist of prospective drug use review, retrospective drug use review, data assessment of drug use against predetermined standards, and ongoing educational outreach activities. States must continue to apply DUR requirements to covered outpatient drugs regardless of how the state pays for the drug.

Other Federal Laws and Regulations Protecting Medicaid Beneficiaries

There are other federal laws and regulations that states and manufacturers must review and follow in addition to the specific Medicaid statutory and regulatory requirements discussed above. Below, we identify some federal laws that provide additional protection to beneficiaries that states and manufacturers should remain mindful of as they pursue any payment arrangement, however, this does not constitute an exhaustive list of all applicable federal laws and regulations.

1. All parties must comply with the federal fraud and abuse laws: For example, federal anti-kickback provisions at section 1128B(b) of the Act makes it a criminal offense to knowingly and willfully offer, pay, solicit, or receive any remuneration to induce, or in return for, the referral of an individual to a person for the furnishing of, or arranging for the furnishing of, any item or service reimbursable under a federal health care program. The statute's prohibition also extends to remuneration to induce, or in return for, the purchasing, leasing, or ordering of, or arranging for or recommending the purchasing, leasing, or ordering of, any good, facility, service, or item reimbursable by a federal health care program. For purposes of the federal anti-kickback statute, "remuneration" includes the transfer of anything of value, directly or indirectly, overtly or covertly, in cash or in kind. The federal anti-kickback statute has been interpreted to cover any arrangement where one purpose of the remuneration is to induce referrals for items or services reimbursable by a federal health care program. The Office of Inspector General (OIG), Department of Health and Human Services (HHS) has promulgated certain

safe harbors potentially applicable to certain value based arrangements, *see, e.g., Medicare and State Health Care Programs: Fraud and Abuse; Revisions to Safe Harbors Under the Anti-Kickback Statute, and Civil Monetary Penalty Rules Regarding Beneficiary Inducements* (https://www.govinfo.gov/content/pkg/FR-2020-12-02/pdf/2020-26072.pdf). In addition, parties may request an advisory opinion[1] from HHS-OIG regarding the application of HHS-OIG's fraud and abuse authorities, including those related to the federal anti-kickback statute, to the party's existing or proposed arrangement.

2. States must comply with federal civil rights laws: Civil rights laws that prohibit discrimination on the basis of race, color, national origin, sex (including pregnancy, sexual orientation and gender identity), age, and disability continue to apply when states participate in any payment arrangement. These laws include Section 1557 of the Affordable Care Act, 42 U.S.C. § 18116 (race, color, national origin, sex (including pregnancy, sexual orientation and gender identity), age, and disability in health programs and activities), Title VI of the Civil Rights Act of 1964, 42 U.S.C. §§ 2000d *et seq*. (race, color, national origin), Title IX of the Education Amendments of 1972, 20 U.S.C. §§ 1681 *et seq*. (sex (including pregnancy, sexual orientation, and gender identity) in education programs and activities), the Age Discrimination Act of 1975, 42 U.S.C. §§ 6101 *et seq*. (age), Section 504 of the Rehabilitation Act of 1973, 29 U.S.C. § 794 (disability), and the Americans with Disabilities Act, 42 U.S.C. §§ 12101 *et seq*. (disability). In accordance with these legal obligations, we noted in the December 2020 rule (85 FR 87014) that manufacturers and payers, including state Medicaid agencies, may not make use of measures that would unlawfully discriminate on the basis of disability or age, among other bases, when designing or participating in VBP arrangements. We further noted at 85 FR 87016, that VBP measures should not endanger certain patients, providers, or impede access to other available medications and treatments, or interfere with the practice of medicine generally.

3. States must comply with applicable privacy and security laws: Privacy and security laws and regulations, such as those under the Health Insurance Portability and Accountability Act of 1996 (HIPAA; P.L. 104-191), must be considered when states participate in arrangements that require reporting and recording of patient-specific outcomes data for evaluation to determine payment when payment is tied to outcomes. This is especially important with respect to lower-utilized drugs when disclosure of individually identifiable health information may lead to privacy concerns. Such information should only be used or disclosed in accordance with applicable privacy and security laws, which may limit use or disclosure to the minimum necessary data.

Available Enforcement Mechanisms for CMS

If CMS becomes aware of potential state compliance concerns related to the specific Medicaid requirements discussed above, CMS will first work with the state to help its Medicaid program come into compliance with the applicable laws and regulations. As a next step, when necessary, CMS may review state and local administration of Medicaid programs through an analysis of the state's policies and procedures, on-site review of selected aspects of agency operations, and examination of samples of

[1] Advisory Opinion Process | Office of Inspector General | Government Oversight | U.S. Department of Health and Human Services (hhs.gov)

individual case records, in accordance with 42 CFR § 430.32. If these reviews reveal serious problems with respect to state compliance with any federal requirement, or with the state's approved state plan, CMS will request the state to correct its practice. After CMS provides a *notice of non-compliance,* with a request to the state to develop a corrective action plan, if the state fails to comply after being notified and given an opportunity for a hearing, CMS may withhold FFP for non-compliance. The withholding may continue until CMS is satisfied that the state's practices are in compliance with federal requirements (see 42 CFR § 430.35).

CMS does not enforce the non-Medicaid related federal requirements summarized above and will work with the HHS-OIG or the HHS Office for Civil Rights if we believe there are potential compliance issues. CMS may also refer any findings specific to manufacturer drug pricing and drug product related reporting activity to the HHS-OIG.

Conclusion

CMS' policy goal with respect to the MDRP, and state adoption of manufacturers' VBP arrangements, as well as participation in other novel payment arrangements, is to further increase access to high cost therapies for underserved populations, and reduce health disparities. This bulletin reminds states that choose to enter into these arrangements of the range of federally-based protections available to Medicaid beneficiaries. CMS will continue to monitor state Medicaid drug coverage under such arrangements to ensure it remains consistent with the Medicaid statutory and regulatory requirements and that Medicaid beneficiaries can access all medically necessary prescription medications.

For further information regarding this CIB, you may contact John M. Coster, Director of the Division of Pharmacy, at John.Coster@cms.hhs.gov.

TAB 176-29

April 18, 2016

The U.S. Commission on Civil Rights Statement Condemning Recent State Laws and Pending Proposals Targeting the Lesbian, Gay, Bisexual, and Transgender Community

The United States Commission on Civil Rights, by a majority vote, strongly condemns recent state laws passed, and proposals being considered, under the guise of so-called "religious liberty" which target members of the lesbian, gay, bisexual, and transgender ("LGBT") community for discrimination.

North Carolina Governor Pat McCrory recently signed into law H.B. 2, legislation blocking local governments from passing anti-discrimination rules that grant protections to gay and transgender persons. The law also repeals existing municipal anti-discrimination laws which protected LGBT people from bias in housing and employment. Critically, the new legislation also forces transgender people to utilize public bathrooms and changing facilities based on the sex issued on their birth certificates, and not according to their gender identities. This jeopardizes not only the dignity, but also the actual physical safety, of transgender people whose appearances may not match societal expectations of the sex specified on their identification documents.

In Mississippi, Governor Phil Bryant recently signed HB 1523 into law. The new statute is far- reaching and allows people with "religious objections" to deny wedding services to same-sex couples. It also clears the way for employers to cite religion in determining workplace policies on dress code, grooming and bathroom access. The physical safety concerns for transgender people are the same as in North Carolina.

The laws enacted in North Carolina and Mississippi are not isolated, but are part of a larger, alarming trend to limit the civil rights of a class of people using religious beliefs as the excuse. Similar laws were passed by the legislatures in Georgia and Virginia, but those were vetoed

after significant public pressure. The Tennessee legislature just passed a bill which, if signed by Governor Bill Haslam, will permit mental health professionals to deny counseling services to LGBT people based upon "sincerely held religious beliefs." Kansas is considering a non-legislative, administrative policy change which would make it more difficult for transgender people to change the sex listed on their birth certificates. These laws and policies can be found to violate the Equal Protection and Due Process clauses of the Fourteenth Amendment. These laws can also be found to violate Title IX of the Education Amendments of 1972, which forbids discrimination against transgender students in any school that receives federal funding.

The Commission recently approved a report, which will be released shortly, on the issue of religious liberty. In our findings and recommendations the Commission makes clear:

- Civil rights protections ensuring nondiscrimination, as embodied in the Constitution, laws, and policies, are of preeminent importance in American jurisprudence.
- Religious exemptions to the protections of civil rights based upon classifications such as race, color, national origin, sex, disability status, sexual orientation, and gender identity, when they are permissible, significantly infringe upon these civil rights.
- Overly broad religious exemptions unduly burden nondiscrimination laws and policies. Federal and state courts, lawmakers, and policy-makers at every level must tailor religious exceptions to civil liberties and civil rights protections as narrowly as applicable law requires.

Commission Chairman Martin R. Castro stated on behalf of the Commission, "Religious freedom is an important foundation of our nation. However, in the past, 'religious liberty' has been used to block racial integration and anti-discrimination laws. Those past efforts failed and this new attempt to revive an old evasive tactic should be rejected as well. The North Carolina and Mississippi laws, and similar legislation proposed in other states, perverts the meaning of religious liberty and perpetuates homophobia, transphobia, marginalizes the transgender and gay community and has no place in our society.

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The U.S. Commission on Civil Rights is an independent, bipartisan agency charged with advising the President and Congress on civil rights matters and issuing a federal civil rights enforcement report. For information about Commission's reports and meetings, visit http://www.usccr.gov.

TAB 176-31

Department of Health and Human Services
DEPARTMENTAL APPEALS BOARD
Appellate Division

NCD 140.3, Transsexual Surgery
Docket No. A-13-87
Decision No. 2576
May 30, 2014

DECISION

The Board has determined that the National Coverage Determination (NCD) denying Medicare coverage of all transsexual surgery as a treatment for transsexualism is not valid under the "reasonableness standard" the Board applies. The NCD was based on information compiled in 1981. The record developed before the Board in response to a complaint filed by the aggrieved party (AP), a Medicare beneficiary denied coverage, shows that even assuming the NCD's exclusion of coverage at the time the NCD was adopted was reasonable, that coverage exclusion is no longer reasonable. This record includes expert medical testimony and studies published in the years after publication of the NCD. The Centers for Medicare & Medicaid Services (CMS), which is responsible for issuing and revising NCDs, did not defend the NCD or the NCD record in this proceeding and did not challenge any of the new evidence submitted to the Board.

Effect of this decision

Since the NCD is no longer valid, its provisions are no longer a valid basis for denying claims for Medicare coverage of transsexual surgery, and local coverage determinations (LCDs) used to adjudicate such claims may not rely on the provisions of the NCD. The decision does not bar CMS or its contractors from denying individual claims for payment for transsexual surgery for other reasons permitted by law. Nor does the decision address treatments for transsexualism other than transsexual surgery. The decision does not require CMS to revise the NCD or issue a new NCD, although CMS, of course, may choose to do so. CMS may not reinstate the invalidated NCD unless it has a different basis than that evaluated by the Board. 42 C.F.R. § 426.563.

CMS must implement this Board decision within 30 days and apply any resulting policy changes to claims or service requests made by Medicare beneficiaries other than the AP for any dates of service after that implementation. With respect to the AP's claim in

particular, CMS and its contractors must "adjudicate the claim without using the provision(s) of the NCD that the Board found invalid." 42 C.F.R. § 426.560(b)(1).[1]

Legal background

With exceptions not relevant here, section 1862(a)(l)(A) of the Social Security Act (Act) (42 U.S.C. § 1395y(a)(l)(A)) bars Medicare payment for items or services "not reasonable and necessary for the diagnosis or treatment of illness or injury[.]"[2] CMS refers to this requirement as the "medical necessity provision." 67 Fed. Reg. 54,534, 54,536 (Aug. 22, 2002). An NCD is "a determination by the Secretary [of Health and Human Services] with respect to whether or not a particular item or service is covered nationally under [title XVIII (Medicare)]." Act §§ 1862(l)(6)(A),1869(f)(1)(B); *see also* 42 C.F.R. § 400.202 (NCD "means a decision that CMS makes regarding whether to cover a particular service nationally under title XVIII of the Act."). NCDs "describe the clinical circumstances and settings under which particular [Medicare items and] services are reasonable and necessary (or are not reasonable and necessary)." 67 Fed. Reg. at 54,535. When CMS issues NCDs, they apply nationally and are binding at all levels of administrative review of Medicare claims. 42 C.F.R. § 405.1060. CMS and its contractors use applicable NCDs in determining whether a beneficiary may receive Medicare reimbursement for a particular item or service. 42 C.F.R. §§ 405.920, 405.921.

A Medicare beneficiary "in need of coverage for a service that is denied based on … an NCD" is an "aggrieved party" who may challenge the NCD by filing a "complaint" with the Board.[3] Act § 1869(f)(1); 42 C.F.R. §§ 426.110, 426.320. The complaint must comply with the requirements for a valid complaint in 42 C.F.R. § 426.500 in order to be accepted by the Board. 42 C.F.R. §§ 426.510(b)(2), 426.505(c)(2). After the Board notifies CMS of the receipt of a complaint that is acceptable under the regulations, CMS produces the "NCD record," which "consists of any document or material that CMS

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[1] *See generally* 42 C.F.R. § 426.560(b) (setting out the effects of a Board NCD decision); 42 C.F.R. § 426.555 (specifying what the Board's decision "may not do"). This decision has no effects beyond those set out in 42 C.F.R.§ 426.560(b) and does not impose on CMS or its contractors any orders or requirements prohibited by 42 C.F.R. § 426.555.

[2] The table of contents to the current version of the Social Security Act, with references to the corresponding United States Code chapter and sections, can be found at http://www.socialsecurity.gov/OP_Home/ssact/ssact-toc.htm.

[3] The regulations also provide that a person other than the aggrieved party with an interest in the issues may petition to participate in the review process as an amicus curiae. 42 C.F.R. §§ 426.510(f), 426.513. The Board posts on its website notice of the NCD complaint specifying a time period for requests to participate in the review. 42 C.F.R. § 426.510(f).

considered during the development of the NCD" including "medical evidence considered on or before the date the NCD was issued . . . ." 42 C.F.R. §§ 426.510(d)(3), 426.515, 426.518(a). The aggrieved party submits a statement "explaining why the NCD record is not complete, or not adequate to support the validity of the NCD under the reasonableness standard," and CMS may submit a response "in order to defend the NCD." 42 C.F.R. § 426.525(a), (b). If the Board determines that the NCD record "is complete and adequate to support the validity of the NCD," the review process ends with the Board's "[i]ssuance of a decision finding the record complete and adequate to support the validity of the NCD . . . ." 42 C.F.R. § 426.525(c)(1), (2). If the Board determines that the record is *not* complete and adequate to support the validity of the NCD, the Board "permits discovery and the taking of evidence . . . and evaluates the NCD" in accordance with the requirements of Part 426, including conducting a hearing, unless the matter can be decided on the written record. 42 C.F.R. §§ 426.525(c)(3), 426.531(a)(2).

Prior to issuing a decision, the Board must review any "new evidence" admitted to the record before the Board and determine whether it "has the potential to significantly affect" the Board's evaluation. 42 C.F .R. §§ 426.340(a), (b), 426.505(d)(3). "New evidence" is defined as "clinical or scientific evidence that was not previously considered by … CMS before the … NCD was issued." 42 C.F.R. § 426.110. If the Board so concludes, the Board stays proceedings for CMS "to examine the new evidence, and to decide whether [to] initiate[] … a reconsideration" of the NCD. 42 C.F.R. § 426.340(d). If CMS does not reconsider the NCD, or reconsiders it but does not change the challenged provision, the Board lifts the stay and the NCD challenge process continues. 42 C.F.R. § 426.340(f). At the end of that process, the Board closes the record and issues a decision that the challenged "provision of the NCD is valid" or "is not valid under the reasonableness standard."[4] 42 C.F.R. § 426.550. The Board's decision "constitutes a final agency action and is subject to judicial review" on appeal by an aggrieved party. 42 C.F.R. § 426.566.

[4] Section 426.547(b) states that the Board must make the decision available at the HHS Medicare Internet site and that "the posted decision does not include any information that identifies any individual, provider of service, or supplier." CMS has indicated in the preamble to the Part 426 regulations that this provision was meant to protect the privacy of Medicare beneficiaries such as the AP. *See, e.g.*, 68 Fed. Reg. 63,692, 63,708 (Nov. 7, 2003) ("Board decisions regarding NCDs will be made available on the Medicare Internet site, without beneficiary identifying information").

Case background

The NCD and the NCD record

The challenged NCD, titled "140.3, Transsexual Surgery," states:[5]

> **Item/Service Description**
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> Transsexual surgery, also known as sex reassignment surgery or intersex surgery, is the culmination of a series of procedures designed to change the anatomy of transsexuals to conform to their gender identity. Transsexuals are persons with an overwhelming desire to change anatomic sex because of their fixed conviction that they are members of the opposite sex. For the male-to-female, transsexual surgery entails castration, penectomy and vulva-vaginal construction. Surgery for the female-to-male transsexual consists of bilateral mammectomy, hysterectomy and salpingo-oophorectomy, which may be followed by phalloplasty and the insertion of testicular prostheses.
>
> **Indications and Limitations of Coverage**
>
> Transsexual surgery for sex reassignment of transsexuals is controversial. Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental. Moreover, there is a high rate of serious complications for these surgical procedures. For these reasons, transsexual surgery is not covered.

NCD Record at 93. CMS's predecessor, the Health Care Financing Administration (HCFA), published the NCD in the Federal Register on August 21, 1989.[6] 54 Fed. Reg. 34,555, 34,572 (Aug. 21, 1989); NCD Record at 76, 78, 93, 128. The NCD quotes or paraphrases portions of an 11-page report that the former National Center for Health Care Technology (NCHCT) of the HHS Public Health Service (PHS) issued in 1981, titled

[5] NCDs are available at http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx?list_type=ncd.

[6] The Federal Register notice stated, "This notice lists those current Medicare national coverage decisions which have been issued in the Medicare Coverage Issues Manual (HCFA Pub. 6)." 54 Fed. Reg. at 34,555.

"Evaluation of Transsexual Surgery" (1981 report).[7] NCD Record at 13-23. The NCHCT forwarded the 1981 report to HCFA with a May 6, 1981 memorandum stating that the 1981 report "concludes that transsexual surgery should be considered experimental because of the lack of proven safety and efficacy of the procedures for the treatment of transsexualism" and recommending "that transsexual surgery not be covered by Medicare at this time." *Id.* at 12.

The NCD record includes three April 1982 letters from the American Civil Liberties Union (ACLU) of Southern California disagreeing with HCFA's noncoverage determination. *Id.* at 24-25, 26, 41-42. The ACLU submitted letters and affidavits from physicians and therapists supporting the medical necessity of transsexual surgery and taking issue with the non-coverage determination. *Id.* at 27-75. On May 11, 1982, the HCFA physicians panel, by a vote of five to two, recommended against referring the ACLU's submissions to PHS, "on the basis that it does not contain information about new clinical studies or other medical and scientific evidence sufficiently substantive to justify reopening the previous PHS assessment." *Id.* at 7, 9. Thus, although the NCD was issued in 1989, it was based on the analysis of medical and scientific publications in the 1981 report.

The NCD complaint

The AP in this case, a Medicare beneficiary whose insurer denied a physician's order for sex reassignment surgery (transsexual surgery), filed an acceptable NCD complaint and supporting materials. CMS submitted the NCD record on May 15, 2013, and the AP submitted a statement of why the NCD record is not complete or adequate to support the validity of the NCD under the reasonableness standard (AP Statement) on June 14, 2013. The Board granted unopposed requests by six advocacy organizations to participate as amici curiae in the NCD review by filing written briefs arguing that the NCD was invalid. (Four of the amici submitted a joint brief.)[8]

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[7] The concluding summary of the 1981 NCHTC report stated in relevant part:

> Transsexual surgery for sex reassignment of transsexuals is controversial. There is a lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism. There is evidence of a high rate of serious complications of these surgical procedures. The safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned. Therefore, transsexual surgery must be considered still experimental.

NCD Record at 19.

[8] The six amici are the Human Rights Campaign (HRC) and the World Professional Association for Transgender Health (WPATH), which each submitted briefs, and the FORGE Transgender Aging Network, the National Center for Transgender Equality, the Sylvia Rivera Law Project, and the Transgender Law Center, which submitted a joint brief.

On June 26, 2013, CMS notified the Board that it "declines to submit a response" to the AP's statement. On December 2, 2013, the Board ruled that the NCD record "is not complete and adequate to support the validity of the NCD[.]" *NCD 140.3, Transsexual Surgery*, NCD Ruling No. 2 (Dec. 2, 2013) (NCD Ruling).[9] The parties then jointly reported that they did not intend to submit additional evidence (except for curricula vitae (CVs) of the AP's witnesses) or cross-examine any witness and asked the Board to close the NCD review record to the taking of evidence and decide the case based on the written record.

The Board determined that the new evidence in the record had the potential to significantly affect its review of the NCD and, as required, stayed proceedings for 10 days for CMS to examine the new evidence and decide whether to reconsider the NCD.[10] *Order Closing Record & Staying Proceedings for CMS to Determine Whether to Reconsider NCD* (Feb. 25, 2014) (Order); 42 C.F.R. §§ 426.340(d), 426.505(d)(3). Two days later, CMS informed the Board by email that it "does not wish to reconsider the NCD." On February 28, 2014, the Board lifted the stay and informed the parties that it would proceed to decision.

The record developed before the Board

The record before the Board consists of the NCD record, the briefs submitted by the AP and the amici and evidence submitted by the AP and one of the amici, the Human Rights Campaign. Since neither party submitted argument or evidence (except for the CVs) after the Board's Ruling, the Board treats the AP statement as the AP's brief in this appeal.[11] The AP submitted written declarations made under penalty of perjury from a clinical psychologist and a physician, and two notarized physician letters submitted to an Administrative Law Judge in the Department of Health and Human Services Office of Medicare Hearings and Appeals in another matter. The AP described the witnesses, who are active in the field of treating transgender persons, as experts and submitted their resumes or CVs. AP Statement at 9; AP complaint; AP/CMS e-mail (Jan. 7, 2014).

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[9] The NCD Ruling is at http://www.hhs.gov/dab/decisions/dabdecisions/ncd1403.pdf.

[10] The Board also published on its website notice providing an additional time period for interested parties to submit participation requests; none were received.

[11] Most of the AP's evidence other than witness statements is an appendix of sources the clinical psychologist cited in her declaration. We refer to these materials as the AP's exhibits (AP Exs.) and cite to the page numbers used in the publications in which they appeared. In addition, the physician's declaration includes an appendix of 20 unnumbered pages of insurance regulations from four states and the District of Columbia barring exclusion of sex reassignment surgery as medically necessary treatment for severe gender dysphoria. One of the amici, the Human Rights Campaign, submitted 62 exhibits with its brief ("HRC Exs.").

CMS did not challenge the witnesses' qualifications as experts or seek to cross-examine them. We summarize their qualifications when we address their testimony below. In this decision we use the term "new evidence" to refer to the evidence submitted to us by the AP and amici to distinguish it from the evidence used to support the NCD which, as noted, consists principally of the 1981 report. Under the regulatory definition in 42 C.F.R. § 426.110, "new evidence" would also include any evidence submitted by CMS in response to an NCD complaint that was not considered by CMS before the NCD was issued. In this case, however, as we discuss below, CMS submitted no "new evidence."

Standard of review

The Board "evaluate[s] the reasonableness" of an NCD by determining whether it "is valid [or] is not valid under the reasonableness standard," which requires us to uphold the NCD "if the findings of fact, interpretations of law, and applications of fact to law by … CMS are reasonable" based on the NCD record and the relevant record developed before us. Act § 1869(f)(1)(A)(iii); 42 C.F.R. §§ 426.110, 426.531(a), 426.550(a). The Board "defer[s] only to the reasonable findings of fact, reasonable interpretations of law, and reasonable applications of fact to law by the Secretary." Act § 1869(f)(1)(A)(iii); 42 C.F.R. § 426.505(b).

During the review, the aggrieved party bears the burden of proof and the burden of persuasion for the issues raised in an NCD complaint; the burden of persuasion is judged by a preponderance of the evidence. 42 C.F.R. § 426.330. CMS has explained that "[s]o long as the outcome [in the NCD] is one that could be reached by a rational person, based on the evidence in the record as a whole (including logical inferences drawn from that evidence), the determination must be upheld," and that if CMS "has a logical reason as to why some evidence is given more weight than other evidence," the Board "may not overturn the determination simply because they would have accorded more weight to the evidence in support of coverage." 68 Fed. Reg. at 63,703.

Analysis

The NCD is invalid because a preponderance of the evidence in the record as a whole supports a conclusion that the NCD's stated bases for its blanket denial of coverage for transsexual surgery are not reasonable.

As previously stated, the NCD was based principally on the 1981 report findings that the safety and effectiveness of transsexual surgery had not been proven. The AP argues that these findings are not "supportable by the current state of medical science" and "not reasonable in light of the current state of scientific and clinical evidence and current medical standards of care" and are contradicted by studies conducted in the 32 years since the 1981 report. AP Statement at 6-7, 14. The amici made similar arguments. *See, e.g.*, WPATH Br. at 13 ("since [the NCD] was issued, it has been repeatedly

demonstrated that SRS [sex reassignment surgery] is safe, effective, and indisputably necessary treatment for certain individuals with severe GID [gender identity disorder]"). As we discuss below, the new evidence, which is unchallenged, indicates that the bases stated in the NCD and the NCD record for denying coverage, even assuming they were reasonable when the NCD was issued, are no longer reasonable.

A. The fact that the new evidence is unchallenged and the NCD record undefended is significant.

As we stated earlier, the AP has the burden of proof by a preponderance of the evidence that an NCD is invalid under a reasonableness standard. In deciding whether the AP has met this burden, we must weigh the evidence in the record before us. Thus, we consider it important to note at the outset that the only evidence before us, other than the record for the NCD, which consists principally of the 1981 report, is the new evidence submitted by the AP and the amicus HRC. CMS submitted the NCD record, as it was required to do, but has not argued that that record or any other evidence supports the NCD. CMS also did not elect to cross-examine the AP's witnesses, has not challenged their testimony or professional qualifications and joined the AP in asking the Board to decide the appeal based on the written record. *See* AP/CMS e-mail (Jan. 7, 2014). The preamble to the regulations that implement the NCD statute states that the "reasonableness standard . . . recognizes the expertise of … CMS in the Medicare program—specifically, in the area of coverage requiring the exercise of clinical or scientific judgment." 68 Fed. Reg. at 63,703 (emphasis added). Accordingly, in determining whether the NCD is valid under the reasonableness standard, we must accord some deference to CMS's position, and its decision not to defend the NCD or challenge the new evidence in this case has some significance for our decision-making.

Apart from the absence of any challenge to the new evidence or defense of the NCD record, we find the new evidence credible and persuasive on its face.[12] We have no difficulty concluding that the new evidence, which includes medical studies published in the more than 32 years since issuance of the 1981 report underlying the NCD, outweighs the NCD record and demonstrates that transsexual surgery is safe and effective and not experimental. Thus, as we discuss below, the grounds for the NCD's exclusion of coverage are not reasonable, and the NCD is invalid.

[12] For this reason, we found it unnecessary to exercise our independent authority to "consult with appropriate scientific or clinical experts concerning clinical and scientific evidence." *See* 42 C.F.R. § 426.531(b).

B. The new evidence indicates acceptance of criteria for diagnosing transsexualism.

Transsexual surgery is a treatment option for the medical condition of transsexualism. The NCD recognized that transsexualism is a diagnosed medical condition. The 1981 report stated that transsexualism "is defined as an overwhelming desire to change anatomic sex stemming from the fixed conviction that one is a member of the opposite sex." NCD Record at 13, citing Dorland's Illustrated Medical Dictionary, 25th ed. The 1981 report recognized that the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders issued in 1980 (DSM III) had "included for the first time the diagnostic category of 'Transsexualism.'" NCD Record at 13. Nonetheless, the 1981 report expressed concern that diagnosing transsexualism was "problematic" because, the report contended, the criteria for establishing the diagnosis "vary from center to center and have changed over time." NCD Record at 14.

One of the AP's expert witnesses, Randi Ettner, Ph.D., a clinical psychologist, testified that the expressed basis for this concern is "completely untrue now." Ettner Supp. Decl. at ¶ 5. Dr. Ettner stated that "Gender Identity Disorder is a serious medical condition codified in the International Classification of Diseases (10th revision; World Health Organization) and the [DSM]."[13] Ettner Decl. at ¶ 10; *see also* Ettner Supp. Decl. at ¶ 6 (similar testimony). She described the condition as follows:

> The disorder is characterized by intense and persistent discomfort with one's primary and secondary sex characteristics—one's birth sex. The suffering that arises is often described as "being trapped in the wrong body." The psychiatric term for this severe and unremitting emotional pain is "gender dysphoria."

Ettner Decl. at ¶ 10. Dr. Ettner's declaration and CV state that she has a doctorate in psychology, has evaluated or treated between 2,500 and 3,000 individuals with GID and mental health issues related to gender variance, has published three books, including *Principles of Transgender Medicine and Surgery*, has authored articles in peer-reviewed journals, and is a member of the board of directors of the World Professional Association for Transgender Health (WPATH) and an author of the WPATH Standards of Care for

[13] The record indicates that the term "transsexualism" that was used in the NCD and the DSM-III was succeeded in the DSM-IV and DSM-V by the terms "Gender Identity Disorder" (GID) and "gender dysphoria." AP Statement at 1 n.1; Ettner Supp. Decl. at ¶ 6; Hsiao Decl. at ¶ 11; AP Ex. 7, at 208; WPATH Br. at 2 n.3. In this decision, we use the term "transsexualism" because it is used in the NCD, but our decision should be read as encompassing the successor terminology as well.

the Health of Transsexual, Transgender, and Gender-Nonconforming People. *Id.* at ¶¶ 3-6; *see also Sundstrom v. Frank*, 630 F. Supp. 2d 974, 986-87 (E.D.Wis. 2007) ("Dr. Ettner's experience speaks for itself … the doctor has conducted research and has been an instructor specializing in the etiology, diagnosis and treatment of GID [and] is the editor of a medical textbook in which she wrote the chapter of that book on the etiology of GID. The court finds that Dr. Ettner is sufficiently qualified to provide expert testimony.").

We find nothing in the new evidence that would undercut Dr. Ettner's statement. The DSM-IV-TR (text revision), published in 2000, continues to recognize "transsexualism" as a diagnosed medical condition, although it refers to the same disorder as GID and identifies criteria for diagnosing GID in adolescents and adults that are consistent with Dr. Ettner's description, albeit more detailed. The criteria include "strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex)" that is "manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex;" "[p]ersistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex" that is "manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex;" and "[t]he disturbance is not concurrent with a physical intersex condition." AP Ex. 4, at 581. The DSM-IV-TR states that if GID is present in adults, "[t]he disturbance can be so pervasive that the mental lives of some individuals revolve only around those activities that lessen gender distress." *Id.* at 576, 78. The WPATH brief indicates that transsexualism or GID remains a diagnostic category in the fifth edition of the DSM issued in 2013 (DSM-V), which uses the term "Gender Dysphoria." WPATH Br. at 2, n.3.

The DSM has been recognized as a primary diagnostic tool of American psychiatry. *See O'Donnabhain v. Comm'r of Internal Revenue*, 134 T.C. 34, at 60 (2010) (stating "all three experts agree [that the DSM-IV-TR] is the primary diagnostic tool of American psychiatry"); *see also* AP Ex. 3, at 1[14] (resolution of American Medical Association House of Delegates noting the DSM description of GID as "a persistent discomfort with one's assigned sex and with one's primary and secondary sex characteristics, which causes intense emotional pain and suffering" that "if left untreated, can result in clinically significant psychological distress, dysfunction, debilitating depression and, for some people without access to appropriate medical care and treatment, suicidality and death").

[14] American Medical Association House of Delegates, *Resolution 122 (A-08)*, *Removing Financial Barriers to Care for Transgender Patients* (2008).

We conclude that to the extent the NCD was based on concerns expressed in the NCD record about problems diagnosing transsexualism, that concern is unreasonable based on the new evidence.

C. The new evidence indicates that transsexual surgery is safe.[15]

The 1981 report stated that transsexual surgery "cannot be considered safe because of the high complication rates." NCD Record at 18. The 1981 report identified surgical complications including "rectovaginal fistulas, perineal abscesses, introital and deep vaginal stenosis, and vaginal shortening" in male-to-female (MF) patients, and "rejection of the testicular implants, scrotal fusion, and phalloplasty infections" in female-to-male (FM) patients, and states that "[m]ultiple complications for individual patients and secondary surgeries to correct complications or to improve on undesirable results are not uncommon." *Id.* at 15 (citations omitted). The AP argues that "advancements in surgical techniques have dramatically reduced the risk of complications from sex reassignment surgery and the rates of serious complications from such surgeries are low" and that the studies cited in the 1981 report "evaluated outdated surgical techniques that have been replaced with improved, safer procedures." AP Statement at 7, 10. The new evidence supports the AP.

Expert witness Katherine Hsiao, M.D., testified that hysterectomies and mastectomies are common procedures used to treat gender GID in transgender men (FM) and "are routinely performed in other contexts, such as in cases of breast cancer, ovarian cancer, uterine cancer and/or cervical cancer . . . ." Hsiao Decl. at ¶ 11. These procedures, she stated, "have low rates of complications" and are "generally identical whether performed on transgender men to treat gender dysphoria or to treat women for these other conditions."[16] *Id.* Dr. Hsiao also stated that "insurance companies routinely cover the costs associated" with hysterectomies. *Id.* Dr. Hsiao testified that based on her own practice of providing surgery to transgender men, "gender affirming surgeries for transgender men are extremely safe and have very low rates of serious complications,"

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[15] We are unable to discuss in the space of this decision all of the new evidence and see no need to do so since it is all unchallenged. However, we find nothing in the new evidence not discussed that would alter our conclusion that the NCD is invalid, at least absent argument or counter-evidence from CMS. We have attached to this decision an Overview of the Scientific Literature in the New Evidence.

[16] Dr. Hsiao testified without contradiction that a "serious complication" of surgery–

> is generally understood among surgeons to include death, conditions requiring an unplanned admission to the Intensive Care Unit or unplanned readmission to the hospital within 30 days, severe hemorrhage requiring transfusion of several units of blood product, permanent disability, an intraoperative injury requiring an unplanned intervention during the surgical procedure, permanent brain damage, or cardiac arrest.

Hsiao Decl. at ¶ 9.

that she has performed hysterectomies for transgender men for the past ten years and that those procedures "are generally identical to the ones I perform on women to treat early cancer or other conditions." *Id.* at ¶ 20. Dr. Hsiao reports having "typically performed multiple obstetrical, gynecologic, or other pelvic surgeries every week, including but not limited to hysterectomies and other advanced pelvic surgeries targeting the reproductive system and adjacent organs . . . ." *Id.* at ¶ 6. Dr. Hsiao's declaration and CV indicate that she is certified by the American Board of Obstetrics and Gynecology, is the chief of the division of gynecology and the director of Ob/Gyn resident education at a California medical center and an assistant clinical professor in the department of obstetrics, gynecology and reproductive medicine at the University of California at San Francisco. *Id.* at ¶¶ 3-6; CV.

Dr. Hsiao further stated, regarding MF transsexual surgery, that she has been part of a surgical team that performed surgery to create a neovagina in women born with a congenital "complete or partial absence of a vagina, cervix, and uterus," a condition called Mayer-Rokitansky-Kuster-Hauser syndrome, or MRKH. Hsiao Decl. at ¶ 12. She stated that this procedure has "a low rate of complications," and that the associated surgical costs are, in her experience, "routinely cover[ed]" by insurance companies for women born with MRKH. She stated that while women with MRKH "can never have biological children … the role of surgery is essential to affirm their gender identity and to align their anatomy with that identity." *Id.*

Dr. Ettner stated that "[t]here is no scientific or medical basis" for the NCD's statement that sex reassignment surgery has not been proven safe and has a high rate of serious complications; that the "[r]ates of complications during and after sex reassignment surgery are relatively low, and most complications are minor;" and that the risk of complications "has, moreover, been dramatically reduced since 1985." Ettner Decl. at ¶¶ 32, 34. Dr. Ettner testified that during eight years at the Chicago Gender Clinic she "regularly consulted with our surgeon" and is "aware of only two major surgical complications, both of which were immediately repaired." *Id.* at ¶ 36. She stated that the clinic "as a whole has a 12 percent complication rate for genital surgery" and that "the vast majority of those complications [were] minor, all were easily corrected, and none involved surgical site infection or readmission." *Id.* Dr. Ettner stated the 1981 report's discussion of surgical complication rates was "outdated and irrelevant based on current medical practices and procedures." Ettner Supp. Decl. at ¶ 9. In particular, she stated that one of the studies cited in the 1981 report's discussion of complications (Laub & Fisk 1974) reflected the use of a MF surgical technique that "led to unacceptably high rates of fistulae and other complications" and was later abandoned by the study's authors. *Id.* at ¶ 10.

Another of the AP's expert witnesses, Marci L. Bowers, M.D., stated in her notarized letter that in her experience of performing gender-related surgeries, transsexual surgery "does not have a higher rate of complication than any other surgery, and in fact has very

few complications, which are mainly minor in nature." Bowers Letter at 1 (Mar. 5, 2013), Att. to AP Statement. Dr. Bowers stated that she performs approximately 220 gender-related surgeries annually and has performed over 1000 "Male to Female Gender Corrective Surgeries." *Id.* Her CV indicates that she has served as the Chair of the Department of Obstetrics and Gynecology at the Swedish (Providence) Medical Center in Seattle.

The fourth expert witness, Sherman N. Leis, M.D., stated that he personally "perform[s] several gender reassignment procedures each week" and has "seen only relatively minor complications which are easily treated" and has "thus far seen no life threatening complications from any of the transgender surgeries" he has performed. Leis Letter at 2 (Feb. 28, 2013), Att. to AP Statement. Dr. Leis's letter and CV indicate that he is Board-certified in plastic and reconstructive surgery and in general surgery. *Id.* at 1.

The testimony of Drs. Ettner and Hsiao is based on studies as well as personal experience. Dr. Hsiao testified that she reviewed five studies in the AP exhibits "that include complication rate data and information for gender affirming surgeries performed in recent years" and that "[n]one of these five studies reported high rates of serious complications." Hsiao Decl. at ¶¶ 13-14, citing studies at AP Exs. 2, 9, 14, 21, 28. She stated that "almost all of the complications listed in these studies, such as urinary incontinence or retention, stenosis or stricture, bleeding, recto-vaginal fistula, and partial necrosis, are not specific to sex reassignment surgeries, but rather are known potential side effects of any type of urogenital surgery which are covered by Medicare." *Id.* at ¶ 15. She further testified that "every complication tracked in [Jarolim, et al. (2009)] for instance, falls into this category and none of them are serious;" that "[t]he Spehr (2007) study includes similar types of complications at very low rates;" and that "none of the complications listed in Lawrence (2006) are serious and many of them are consistent with what would be potential, expected outcomes for any urogenital surgery." *Id.* at 15-17, citing studies at AP Exs. 14,[17] 21,[18] 28.[19] She also stated that of the four "potentially serious" complications noted in the Amend (2013) study of 24 MF patients, none "were serious as that term is generally understood." *Id.* at ¶ 14, citing study at AP Ex. 2.[20]

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[17] Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009).

[18] Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006).

[19] Christiane Spehr, *Male-to-Female Sex Reassignment Surgery in Transsexuals*, 10 Int'l J. Transgenderism 25-37 (2007).

[20] Bastian Amend, et al., *Surgical Reconstruction for Male-to-Female Sex Reassignment*, 64 Eur. Urol. 1-9 (2013).

Dr. Hsiao further stated that Eldh et al. (1997) compared complication rates for surgeries performed before and after 1986 and showed that "[n]early all of the surgical complication rates decreased significantly over time." Hsiao Decl. at ¶ 18, citing study at AP Ex. 9.[21] Dr. Hsiao stated that "fistulas, in particular, which are a risk of many urogenital surgeries, decreased from 18 percent in surgeries before 1986 to only 1 percent between 1986 and 1995," and that "the only fistula that occurred after 1985 'closed spontaneously,' meaning without the need for any medical intervention." *Id.* Eldh, Dr. Hsiao stated, showed that "[t]here is not a high rate of serious complications in any of the surgeries performed after 1986" and she noted that "there have been nearly 20 years of additional surgical progress since the last surgery tracked." *Id.*

Dr. Ettner cited the same five studies as showing that surgical outcomes were "far superior" after 1985 due to "improvements in technique, shortened hospital stays and improvements in postoperative care;" that significant surgical complications were uncommon; that only a low percentage of patients experienced complications, which were successfully resolved; and that "the complication rate is low and most complications can be overcome by adequate correctional interventions." Ettner Decl. at ¶¶ 34-35.

We find no reason to discount the opinions of these experts or their representations regarding the findings in the studies they cite. We have conducted our own review of the studies cited by Dr. Hsiao and Dr. Ettner and find them consistent with these opinions and representations. We note, for example, that Eldh, which divided the study group into those operated on before 1986 and those operated on from 1986–1995, made findings tending to support these expert opinions. The Eldh study states:

> After 1985 the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment. Total time spent in hospital decreased dramatically after 1985 because the number of procedures was less and the rate of early and late postoperative complications dropped. Haemorrhage and haematoma were common in both groups, predominantly originating from the spongious tissue of the urethra. Infections occurred less often in the late group perhaps as a result of peroperative antibiotic prophylaxis. Serious complications like fistula formation and partial flap necrosis were rare after 1985, though they were common before then. The reason for the lower fistula rate in the later group may be ascribed to better anatomical knowledge of this region and a more precise surgical technique. There was only one rectovaginal fistula after 1985 and this fistula closed spontaneously.

[21] Jan Eldh, *et al.*, *Long-Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997).

AP Ex. 9, at 44. Dr. Hsiao stated that those findings are "consistent with what I would expect to find when comparing surgeries, and surgical techniques, over a long period of time." Hsiao Decl. at ¶ 18; *see also* WPATH Br. at 9-10 (citing Eldh and stating that "while early sex reassignment surgeries were sometimes accompanied by serious complications like fistulas or necrotic tissue, the rate of such complications has dropped dramatically with the advent of more sophisticated surgical techniques, among other reasons").

We conclude that the AP has shown that the NCD's statement that transsexual surgery is unsafe and has a high rate of complications is not reasonable in light of the evolution of surgical techniques and the studies of outcomes discussed in the unchallenged new evidence presented here.

D. The new evidence indicates that transsexual surgery is an effective treatment option in appropriate cases.[22]

1. The expert testimony and studies on which the experts rely support the surgery's effectiveness.

The AP argues that studies conducted after the 1981 report was issued confirm that transsexual surgery is an effective treatment for persons with severe gender dysphoria, and the expert testimony and studies support that argument. AP Statement at 7-8.

Dr. Ettner testified that "[b]ased on decades of extensive scientific and clinical research, the medical community has reached the consensus that altering a transsexual individual's primary and secondary sex characteristics is a safe and effective treatment for persons with severe Gender Identity Disorder." Ettner Decl. at ¶ 13.[23] With regard to effectiveness in particular, Dr. Ettner testified that "more than three decades of research confirms that sex reassignment surgery is therapeutic and therefore an effective treatment for Gender Identity Disorder" and that "for many patients with severe Gender Identity

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[22] We use the term "appropriate cases" because we do not read the new evidence as necessarily stating that transsexual surgery is appropriate in all cases of transsexualism, and our conclusion that the NCD's blanket preclusion of Medicare coverage for transsexual surgery is invalid does not require a finding to that effect. However, it is worth noting that WPATH has developed, in its standards of care, criteria for the use of different transsexual surgical procedures. *See, e.g.*, WPATH "[c]riteria for hysterectomy and salpingooophorectomy in [FM] patients and for orchiectomy in [MF] patients." AP Ex. 7, at 202 (E. Coleman, et al., *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7, 13 Int'l J. Transgenderism 165–232 (2011)).

[23] Dr. Ettner in her declaration focuses on genital surgery for the male-to-female (MF) transsexual. *See* Ettner Decl. at ¶ 8. Dr. Hsiao's testimony addressed procedures performed on FM patients. Hsiao Decl. at ¶¶ 7, 11, 20-21.

Disorder, sex reassignment surgery is the only effective treatment." *Id.* at ¶ 19. She concluded that "[t]he NCD's determination regarding efficacy is not reasonably supported by scientific or clinical evidence, or standards of professional practice, and fails to take into account the robust body of research establishing that surgery relieves, and very often completely eliminates, gender dysphoria." *Id.* at ¶ 31.

Dr. Bowers stated that "[m]any patients report a dramatic improvement in mental health following surgery, and patients have been able to become productive members of society, no longer disabled with severe depression and gender dysphoria." Bowers Letter at 1. She concluded that "Gender Corrective Surgery has been shown to be a life-saving procedure, and is unequivocally medically necessary." *Id.* Dr. Leis stated that "[m]edical literature reports a dramatic drop in the incidence of depression and suicide attempt[s] by individuals who have undergone gender reassignment, indicating that many lives have been saved because of this surgery," that "there is a very low incidence of 'regret'" of "only about 1% of patients who have had gender reassignment surgery" and that "I personally have never had a single patient who has regretted having this surgery." Leis Letter at 2.

Dr. Ettner cited 20 studies published between 1987 and 2010 as showing the effectiveness of transsexual surgery. Ettner Decl. at ¶¶ 20-26, 28-30. She emphasized three studies, two of which were published in 1998 and 2007 and analyze other studies of the treatment of transsexuals published during the years 1961 to 1991 and 1990 to 2007, respectively. *Id.* at ¶¶ 20-22, citing studies at AP Exs. 10, 25, 27; *see also* WPATH Br. at 7-8 (discussing the same three studies). The 1998 study (Pfafflin & Junge) reviewed "30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery" including more than 70 individual studies and eight published reviews from four continents. AP Ex. 25 at unnumbered page 1.[24] As "general results," the researchers in the 1998 study stated that the studies they reviewed concluded "that gender reassigning treatments are effective," that positive, desired results outweigh the negative or non-desired effects, and that "[p]robably the most important change that is found in most research is the increase of subjective satisfaction [which] contrasts markedly to the subjectively unsatisfactory start position of the patients." *Id.* at 45, 49. The study's summary, which it qualified as a "simplification," stated that the studies reviewed show that "[i]n over 80 qualitatively different case studies and reviews from 12 countries, it has been demonstrated during the last 30 years that the treatment that includes the whole process of gender reassignment is effective." *Id.* at 66. The summary stated that all "follow-up studies mostly found the desired effects" the most important of

[24] Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992) (http://web.archive.org/web/20061218132346/http://www.symposion.com/ijt/pfaefflin/1000.htm, accessed May 29, 2014).

which the patients felt were "the lessening of suffering" and "desired changes in the areas of partnership and sexual experience, mental stability and socio-economic functioning level." *Id.* at 66-67.

The 2007 study, Gijs & Brewaeys, which examined the results of 18 studies published between 1990 and 2006, states that sex reassignment "is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals" and that "96% of the persons who underwent [surgery] were satisfied and regret was rare." AP Ex. 10, at 215, cited in Ettner Decl. at ¶ 22, WPATH Br. at 7.[25] Two of the reviewed studies showed that "[s]uicidality was significantly reduced postoperatively" and that in MF patients there were no suicide attempts after surgery as opposed to three attempts before surgery. AP Ex. 10, at 188, 192.

Dr. Ettner and WPATH also cited what Dr. Ettner described as "a large-scale prospective study" finding "that after surgery there was 'a virtual absence of gender dysphoria' in the cohort and that the 'results substantiate previous conclusions that sex reassignment is effective.'" Ettner Decl. at ¶ 21, citing Smith et al. (2005), AP Ex. 27;[26] WPATH Br. at 8. Dr. Ettner concluded that Smith et al. and other studies have, variously, "shown that by alleviating the suffering and dysfunction caused by severe gender dysphoria, sex reassignment surgery improves virtually every facet of a patient's life," including "satisfaction with interpersonal relationships and improved social functioning," "improvement in self-image and satisfaction with body and physical appearance," and "greater acceptance and integration into the family[.]" Ettner Decl. at ¶ 24, citing studies at AP Exs. 1, 12, 15, 19, 22, 26, 27, 30. She also cited nine studies as having "shown that surgery improves patients' abilities to initiate and maintain intimate relationships." *Id.* at ¶ 25, citing studies at AP Exs. 8, 13, 14, 16, 20-22, 26, 27.

Based on our own review of the cited studies, we find no reason to question the expert testimony about them. In general, the studies included interviewing post-operative patients with a variety of surveys or questionnaires to assess changes in different aspects of their lives and psychological symptoms following surgery. The studies also generally used statistical techniques to assess the results. The studies were conducted in countries including the United States, Canada, Sweden, the Czech Republic, Israel, Brazil, The Netherlands, and Belgium.

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[25] Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges,* 18 Ann. Rev. Sex Res. 178-224 (2007).

[26] Yolanda L.S. Smith et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals,* 35 Psychol. Med. 89-99 (2005).

We note that these studies are scientific writings and do not make sweeping pronouncements or claim discoveries beyond possible doubt. Indeed, the authors sometimes qualify the results and caution against drawing overly broad and simplistic conclusions. *See, e.g.*, AP Ex. 25, at 66 (Pfafflin & Junge, qualifying the study's summary of its conclusion as a simplification). This, in our view, enhances their facial credibility. Nonetheless, even keeping in mind the possible limitations of these studies, they support the AP's position that transsexual surgery has gained broad acceptance in the medical community.

2. *The 1981 report's expressed concern about an alleged lack of controlled, long-term studies is not reasonable in light of the new evidence.*

The 1981 report summarized the findings of nine studies on "[t]he result or outcome of" transsexual surgery. NCD record at 15-18. With respect to those studies, the report stated that "surgical complications are frequent, and a very small number of post-surgical suicides and psychotic breakdowns are reported." *Id.* at 17-18. However, the report also acknowledged that eight of those nine studies "report that most transsexuals show improved adjustment on a variety of criteria after sex reassignment surgery, and that "[i]n all of these studies the large majority of those who received surgery report that they are personally satisfied with the change[.]" NCD Record at 17. Notwithstanding its discussion of these studies, the 1981 report (and the NCD) cited an alleged "lack of well controlled, long term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism" as a ground for finding the procedures "experimental." *Id.* at 19. The 1981 report did not define "long term" for the purpose of assigning weight to study results and the NCD record provided no clarification of that phrase. The 1981 report noted "post-operative followup" and "followup" times for eight of the nine studies on the outcomes of surgery, with "average," "mean" or "median" periods ranging from 25 months to over eight years, and individual periods from three months to 13 years. NCD Record at 15-17. If these studies do not qualify as acceptable long-term studies, the basis for such a conclusion is not adequately explained in the NCD record.

Even assuming the studies cited in the 1981 report could be viewed as not sufficiently "long-term," Dr. Ettner stated that "there are numerous long-term follow-up studies on surgical treatment demonstrating that surgeries are effective and have low complication rates" and, as discussed above, her testimony cited some of those studies. Ettner Decl. at ¶ 26. CMS does not challenge this statement, and we find no reason to question it. We note that the participants in one study Dr. Ettner cited had a mean interval since

vaginoplasty of 75.46 months. AP Ex. 30, at 754.[27] We also note that the 18 studies published between 1990 and 2006 and encompassing 807 MF and FM patients analyzed in Gijs & Brewaeys (2007) had mean follow-up durations ranging from six months to as long as (in one study) 168 months. AP Ex. 10, at 186-87.[28] Additionally, two studies Dr. Ettner cited appear to be long term in that they studied patients who had undergone surgery during periods of 14 and 20 years, respectively. AP Exs. 13,[29] 29.[30] Those studies reported favorable overall results.

Dr. Ettner also testified that two studies from 1987 and 1990 used control groups and found improved psychosocial outcomes in surgery patients. Ettner Decl. at ¶¶ 28-30. In the 1990 study, she stated, MF patients were "matched for family and psychiatric histories and severity of the [GID] diagnosis" and "randomly assigned either to immediately undergo surgery, or be placed on a waiting list for two years." *Id.* at ¶ 29, citing study at AP Ex. 23.[31] The study found that patients who underwent surgery "demonstrated dramatically improved psychosocial outcomes, compared to the still-waiting controls" and "were more active socially and had significantly fewer psychiatric symptoms." *Id.*; *see also* WPATH Br. at 8 (study found "comparative improvements in neurotic symptoms and social activity for the group receiving surgery"). Dr. Ettner described the 1990 study as the "best example of a well-controlled investigation." Ettner Decl. at ¶ 29. Dr. Ettner also described a 1987 study comparing transsexuals who had undergone surgery with "those who had not, but were otherwise matched (control group)" as finding that "the patients who underwent surgery were better adjusted psychosocially, had improved financial circumstances, and reported increased satisfaction with sexual experiences, as compared to the unoperated group." *Id.* at ¶ 30, citing study at AP Ex. 17.[32]

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[27] Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009).

[28] Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges,* 18 Ann. Rev. Sex Res. 178-224 (2007).

[29] Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute's 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009).

[30] Svetlana Vujovic, M.D. Ph.D., *et al.*, *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009).

[31] Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change After Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990).

[32] G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study*, 16 Archives of Sexual Behavior 511-22 (1987).

Nothing in the record puts into question the authoritativeness of the studies cited in the new evidence based on methodology (or any other ground). Even if questions about methodology had been raised, we would be hard pressed to find that this alone would justify our not crediting the new evidence that transsexual surgery is effective and safe. This is particularly true since the 1981 report itself suggested it might be impossible to find the kind of adequate control groups needed to assuage this criticism. *See* NCD Record at 18 (stating the need for adequate control groups and stating "perhaps this is impossible."). We note that in the local coverage determination (LCD) context, CMS guidance for contractors states that the determinations "shall be based on the strongest evidence available." CMS Medicare Program Integrity Manual (MPIM), CMS Pub. 100-08, Ch. 13, § 13.7.1.[33] While the guidance states a "preference" for "[p]ublished authoritative evidence derived from definitive randomized clinical trials or other definitive studies . . .," it also includes as evidence meeting that standard, "[g]eneral acceptance by the medical community (standard of practice), as supported by sound medical evidence . . . ."[34] *Id.* In *LCD Complaint: Homeopathic Med. & Transfer Factor*, DAB No. 2315 (2010), the Board relied on that guidance when rejecting the argument that a certain type of controlled study was the sole basis on which a determination of medical necessity could be supported. The Board stated, "[a]s the [CMS guidance] explains, general acceptance in the medical community may be sufficient if it has scientific support." DAB No. 2315, at 34. While the guidance applies to contractors, who develop LCDs but not NCDs, it is instructive here as representing CMS's determination of the type of evidence that may support Medicare coverage. Regardless of whether the new evidence here meets the first option for meeting the evidentiary standard set forth in the guidance (and CMS does not assert that it does not), it clearly meets the second option because it indicates a consensus among researchers and mainstream medical organizations that transsexual surgery is an effective, safe and medically necessary treatment for transsexualism.

Based on the record as a whole, including the new evidence discussed above, we conclude that the AP has shown that transsexual surgery is an effective treatment option for transsexualism in appropriate cases.

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[33] CMS Manuals are available at http://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs.html, accessed May 14, 2014.

[34] The guidance further provides that the "sound medical evidence" supporting this "general acceptance" should be based on "[s]cientific data or research studies published in peer-reviewed medical journals; … [c]onsensus of expert medical opinion (i.e., recognized authorities in the field); or … [m]edical opinion derived from consultations with medical associations or other health care experts." MPIM § 13.7.1.

E. The new evidence indicates that the NCD's rationale for considering the surgery experimental is not valid.

The NCD asserted that transsexual surgery was considered experimental because it had not been shown to be safe and effective.[35] The 1981 report stated that transsexual surgery "must be considered still experimental" because "[t]he safety and effectiveness of transsexual surgery as a treatment of transsexualism is not proven and is questioned." NCD Record at 19. As discussed above, the unchallenged new evidence indicates that transsexual surgery is a safe and effective treatment option for transsexualism in appropriate cases. Accordingly, the NCD's reasons for asserting that transsexual surgery was experimental are no longer valid.

In addition, the new evidence independently indicates that transsexual surgery is not considered experimental in a broader sense relating to its acceptance as a treatment for transsexualism. Dr. Bowers stated that "[m]any thousands of gender corrective surgeries have been performed worldwide for decades, and this treatment is in no way experimental." Bowers Letter at 1. Dr. Hsiao testified that there is "no scientific or medical basis for [the NCD's] description of gender affirming surgeries as 'experimental.'" Hsiao Decl. at ¶ 22. Dr. Hsiao, as noted, stated that some of the procedures involved in transsexual surgery are routinely performed in other contexts, and that surgery to create a neovagina is performed on women born MRKH. Hsiao Decl. at ¶¶ 11, 12; *see* Ettner Supp. Decl. at ¶ 15 ("mastectomies, hysterectomies and salpingo-oophorectomies, which are … excluded from coverage under [the NCD] are performed frequently… when indicated for medical conditions other than gender dysphoria").

Dr. Hsiao cited the "increasing coverage of sex affirming surgeries by private and public medical plans" and the inclusion of those surgeries "in prominent surgical text books" as showing that "gender affirming surgeries … are the standard of care and are not experimental." *Id.* at ¶¶ 23, 24. Dr. Hsiao cited California managed care guidance "clarifying that any attempt 'to exclude insurance coverage of [] transsexual surgery'" would violate California law, and she stated that Vermont, Colorado, Oregon, and Washington, D.C. "have issued similar insurance directives prohibiting discrimination based on gender identity with respect to healthcare policies." *Id.* at ¶ 25, citing Letter No. 12-K: Gender Nondiscrimination Requirements, Calif. Dep't of Managed Health Care

[35] "Because of the lack of well controlled, long-term studies of the safety and effectiveness of the surgical procedures and attendant therapies for transsexualism, the treatment is considered experimental." NCD Record at 93.

(Apr. 9, 2013), Ex. A to Hsiao Decl.[36] "These events in the private and public sector," Dr. Hsiao stated, "solidify what the medical community has known for years—that gender affirming surgeries to treat gender dysphoria are evidence-based, medically necessary, and the standard of care for these patients." *Id.* at ¶ 26.

Dr. Leis stated that gender reassignment surgery "is not experimental and has been performed thousands of times with surgeons around the world and has been proven to be a medically necessary and successful treatment, saving many lives and significantly improving the lives of those who undergo this surgery." Leis Letter at 2. Dr. Leis also stated that "[m]edical and mental health professionals who are knowledgeable and experienced in this field recognize that counseling or psychotherapy, hormone therapy and genital reassignment surgery are medically necessary treatment modalities for many individuals with [GID]" and that those therapies "are widely accepted treatments for individuals with significant [GID] in the United States and in many other countries." *Id.* at 1. Dr. Leis also pointed to the acceptance of transsexual surgery procedures "as standard therapy by leading medical and mental health organizations" including the American Medical Association, the National Association of Social Workers, the American Psychological Association, the American Psychiatric Association, "and experts in the field belonging to" WPATH. *Id.* at 2.

HRC stated that its "Corporate Equality Index" annually surveys the "LGBT [lesbian, gay, bisexual and transgender] workplace policies" of "the Fortune 1000 list of the largest publicly traded companies along with American Lawyer Magazine's top 200 revenue-grossing law firms" and considers "whether these organizations afford transgender-inclusive health care options through at least one firm-wide plan that covers surgical procedures." HRC Br. at 1, 11-12. HRC stated that in 2002, "zero percent of the rated companies had such plans" but "by 2008, nineteen percent met this criterion, and by 2013, forty-two percent of companies expressly covered" care related to gender reassignment. *Id.* citing HRC Ex. 30, at 28.[37]

Dr. Bowers, Dr. Hsiao and Dr. Ettner cited acceptance of the WPATH standards of care, which were first published in 1979 and last revised in 2011, as evidence that transsexual surgery is not experimental. Bowers Letter at 1; Hsiao Decl. at ¶ 22; Ettner Decl. at ¶¶ 38, 39; AP Ex. 7, at 165; *see also* AP Ex. 3 (AMA resolution stating that "[h]ealth experts in GID, including WPATH, have rejected the myth that such treatments are "cosmetic" or "experimental" and have recognized that these treatments can provide safe and effective treatment for a serious health condition"). The new evidence indicates that

[36] http://www.dmhc.ca.gov/library/reports/news/dl12k.pdf, accessed May 14, 2014.

[37] HRC Corporate Quality Index (2013), available at http://www.hrc.org/corporate-equality-index, accessed April 25, 2014.

the WPATH standards of care have attained widespread acceptance.[38] S*ee* Hsiao Decl. at ¶ 22 ("the WPATH established standards of care for patients with gender dysphoria … have been endorsed by the American Medical Association, the Endocrine Society, the American Psychological Association, and the American College of Obstetricians and Gynecologists"); AP Ex. 3 (AMA resolution stating that WPATH is "the leading international, interdisciplinary professional organization devoted to the understanding and treatment of gender identity disorders" and that its "internationally accepted Standards of Care for providing medical treatment for people with GID … are recognized within the medical community to be the standard of care for treating people with GID"). Federal courts have recognized the acceptance of the WPATH standards of care. *See, e.g.*, *De'lonta v. Johnson*, 708 F.3d 520, at 522-23 (4th Cir. 2013) (WPATH standards of care "are the generally accepted protocols for the treatment of GID"); *Glenn v. Brumby*, 724 F. Supp. 2d 1284, at 1289 n.4 (N.D. Ga. 2010) ("there is sufficient evidence that statements of WPATH are accepted in the medical community")."[39] The acceptance of the WPATH standards of care also suggests that transsexual surgery is no longer considered experimental.

In its amicus brief, WPATH cited a 2007 study that examined the results of 18 studies published between 1990 and 2006 as showing "that [sex reassignment surgery] can no longer be considered an experimental treatment" and that "it [has] bec[o]me the dominant treatment for transsexuality and the *only* treatment that has been evaluated empirically." WPATH Br. at 7-8, citing AP Ex. 10, at 214-15.[40]

We note that in addition to stating that transsexual surgery was experimental, the NCD and the 1981 report stated that transsexual surgery was "controversial." NCD Record at 18 (1981 report stating that "[o]ver and above the medical and scientific issues, it would also appear that transsexual surgery is controversial in our society"). The AP and the new evidence dispute the relevance of this statement. The AP objected that this point relies on two "polemics" that are "are either completely unscientific or fall far outside the scientific mainstream," and Dr. Ettner stated that the views expressed therein "fall far outside the mainstream psychological, psychiatric, and medical professional consensus,

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[38] WPATH was "formerly the Harry Benjamin International Gender Dysphoria Association." Ettner Decl. at ¶ 6. Harry Benjamin, M.D. "was an endocrinologist who in conjunction with mental health professionals in New York did pioneering work in the study of transsexualism." *O'Donnabhain v. Comm'r of Internal Revenue*, 134 T.C. 34, 37 n.8 (2010). The 1981 report cites a 1966 study by Dr. Benjamin finding a positive outcome from MF transsexual surgery as "perhaps the first report" on transsexual surgery "in the literature." NCD Record at 15, 21.

[39] The general acceptance of a set of standards of care for the treatment of transsexuals appears to render invalid one of the 1981 report criticisms of the studies it discussed, that "therapeutic techniques are not standardized." NCD Record at 18.

[40] Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges,* 18 Ann. Rev. Sex Res. 178-224 (2007).

and call into question the objective reasonableness of the NCD." AP Statement at 15-16; Ettner Supp. Decl. at ¶¶ 17-18. CMS has not asserted that the Board's decision may be based on factors "over and above the medical and scientific issues" involved. Considerations of social acceptability (or nonacceptability) of medical procedures appear on their face to be antithetical to Medicare's "medical necessity" inquiry, which is based in science, and such considerations do not enter into our decision that the NCD is not valid.

For the reasons stated above, we conclude that citing the alleged "experimental" nature of transsexual surgery as a basis for noncoverage of all transsexual surgery is not reasonable in light of the unchallenged new evidence and contributes to our conclusion that the NCD is not valid.

Conclusion

For the reasons explained above, we conclude that the AP has shown that NCD 140.3 is not valid under the reasonableness standard.

/s/
Leslie A. Sussan

/s/
Constance B. Tobias

/s/
Sheila Ann Hegy
Presiding Board Member

ATTACHMENT TO DECISION NO. 2576

Overview of the Scientific Literature in the New Evidence

We provide below brief summaries of key findings in some of the studies submitted and reviewed by the Board as new evidence. The key findings in the remaining studies reviewed by the Board (also as new evidence) do not differ in any way material to our decision.

Jan Eldh, et al., *Long Term Follow Up After Sex Reassignment Surgery*, 31 Scand. J. Plast. Reconstr. Surg. Hand Surg. 39-45 (1997), AP Ex. 9. This study was a "long-term follow up of 136 patients operated on for sex reassignment … to evaluate the surgical outcome" that divided MF and FM patients into "two groups according to the surgical technique: those operated on before 1986 and those operated on from 1986–1995." The study found that after 1985 "the outcome of surgery became much better not only because of changes in management but also because of improvements in surgical technique, preoperative planning, and postoperative treatment," that "[m]odern surgical techniques can give good aesthetic and functional results" and that "[p]ersonal and social instability before operation correlated with an unsatisfactory outcome of sex reassignment." *Id.* at 39, 44, 45.

Luk Gijs & Anne Brewaeys, *Surgical Treatment of Gender Dysphoria in Adults and Adolescents: Recent Developments, Effectiveness, and Challenges,* 18 Ann. Rev. Sex Res. 178-224 (2007), AP Ex. 10. This study examined results of 18 international studies published between 1990 and 2006 that reported follow-up data of at least one year from 807 persons who had undergone sex reassignment surgery (193 FM, 614 MF). The purpose of this study was to update and assess the current validity of a conclusion in a 1990 article (based itself on review of 11 studies following post-operation) that transsexual surgery is an effective treatment for the alleviation of gender disorder in adults. This study concluded that "[d]espite methodological shortcomings of many of the studies . . . SRS is an effective treatment for transsexualism and the only treatment that has been evaluated empirically with large clinical case series" and that the "conclusion that SR [sex reassignment] is the most appropriate treatment to alleviate the suffering of extremely gender dysphoric individuals still stands: 96% of the persons who underwent SRS were satisfied and regret was rare." The authors noted that the methodologies and designs of later studies were improved but that true randomized control studies are not feasible, and might be unethical for SRS. *Id.* at 178, 185, 215-16.

Ciro Imbimbo, M.D. Ph.D., et al., *A Report from a Single Institute's 14-Year Experience in Treatment of Male-to-Female Transsexuals*, 6 J. Sex. Med. 2736-45 (2009), AP Ex. 13. This study's aim was "to arrive at a clinical and psychosocial profile of male-to-female transsexuals in Italy through analysis of their personal and clinical experience and evaluation of their postsurgical satisfaction levels SRS." From January 1992 to September 2006, 163 MF patients who had undergone SRS were asked to complete

patient satisfaction questionnaires. The study concluded that the "relatively high satisfaction level" was the result of a combination of "competent surgical skills, a well-conducted preoperative preparation program, and adequate postoperative counseling . . . ." Although postoperative pain and required revision surgeries were reported, the study found that 94% were satisfied with their post-surgical status and did not report regret. *Id.* at 2736, 2740, 2743.

Ladislav Jarolim, et al., *Gender Reassignment Surgery in Male-to-Female Transsexualism: A Retrospective 3-Month Follow-up Study with Anatomical Remarks*, 6 J. Sex. Med. 1635-44 (2009), AP Ex. 14. This study aimed "[t]o evaluate the results of surgical reassignment of genitalia in male-to-female transsexuals" by measuring "[s]exual functions and complications 3 months after surgery." The study followed 134 patients who had undergone surgical procedures between 1992 and 2008 and described the evolution in surgical techniques since the 1950s. Although the study noted potential complications and risks specific to SRS ("such as impairment of urinary continence, fecal continence, intestinal fistula, urinary fistula, and necrosis of the skin graft"), it concluded that "[s]urgical conversion of the genitalia is a safe and important phase of the treatment of male-to-female transsexuals." It also concluded that "[a]n increasing number of patients undergo this treatment because of the extensive progress in surgery involving the genitals and urethra" and that "[f]or male transsexuals, surgery can provide a cosmetically acceptable imitation of female genitals that enables coitus with orgasm." *Id.* at 1635-36,1642-43.

Annika Johansson, et al., *A Five-Year Follow-Up Study of Swedish Adults with Gender Identity Disorder,* 39 Arch. Sex. Behav. 1429-37 (2010), AP Ex. 15. This study evaluated from the perspective of both clinicians and patients the outcome of sex reassignment of "42 [MF and FM] transsexuals [who] completed a follow-up assessment after 5 or more years in the process or 2 or more years after completed sex reassignment surgery." It found that "the outcome was very encouraging from both perspectives … with almost 90% enjoying a stable or improved life situation at follow-up and only six out of 42 (according to the clinician) with a less favorable outcome." *Id.* at 1429, 1436.

G. Kockott, M.D. & E. M. Fahrner, Ph.D., *Transsexuals Who Have Not Undergone Surgery: A Follow-Up Study,* 16 Archives of Sexual Behavior 511-22 (1987), AP Ex. 17. This single-clinic study compared 26 transsexuals who sought but did not undergo surgery with 32 who did; psychosocial adjustment of those who delayed surgery did not improve from the time of diagnosis to follow-up while statistically significant positive changes in gender role, sexual, and socioeconomic adjustment were seen in transsexuals who had had surgery. *Id.* at 511, 517-19, 521.

Anne A. Lawrence, *Patient-Reported Complications and Functional Outcomes of Male-to-Female Sex Reassignment Surgery*, 35 Arch. Sex. Behav. 717-27 (2006), AP Ex. 21. This study "examined preoperative preparations, complications, and physical and

functional outcomes of [MF SRS] based on reports by 232 patients, all of whom underwent penile-inversion vaginoplasty and sensate clitoroplasty, performed by one surgeon using a consistent technique," who were surveyed a mean of three years after surgery. The study found that "[r]eports of significant surgical complications were uncommon," although one third had urinary stream problems, and that "[o[n average, participants expressed high levels of satisfaction with nearly all of the specific physical and functional outcomes of SRS." *Id.* at 717, 719, 724.

Maria Inês Lobato, et al., *Follow-Up of Sex Reassignment Surgery in Transsexuals: A Brazilian Cohort,* 35 Arch. Sex. Behav. 711-15 (2006), AP Ex. 22. This small study examined the "impact of sex reassignment surgery on satisfaction with sexual experience, partnerships, and relationship with family members in … 19 patients who received sex reassignment between 2000 and 2004." The results "indicate[d] that SRS had a positive effect on different dimensions of the patients' lives in all three aspects analyzed: sexual relationships, partnerships, and family relationships." *Id.* at 711-12, 714.

Charles Mate-Kole, et al., *A Controlled Study of Psychological and Social Change after Surgical Gender Reassignment in Selected Male Transsexuals*, 157 Brit. J. Psychiatry 261-64 (1990), AP Ex. 23. This study reviewed 40 patients accepted for gender reassignment surgery, randomly assigned to have surgery early or later such that only half had had surgery by the time of a follow-up two years later. The study found that "[a]lthough the groups were similar initially, significant differences between them emerged at follow-up . . . ." Patients who received surgery were "seen to improve significantly as far as neurotic symptoms are concerned and to become more socially active" in comparison with the patients who had not yet received surgery. *Id.* at 261, 264.

Friedemann Pfafflin & Astrid Junge, *Sex Reassignment: Thirty Years of International Follow-Up Studies After Sex Reassignment Surgery: A Comprehensive Review 1961-1991* (Roberta B. Jacobson & Alf B. Meier trans., 1998) (1992), AP Ex. 25. This overview was completed in 1992 and published in English in 1998. It reviewed "30 years of international follow-up studies of approximately two thousand persons who had undergone sex reassignment surgery," including "more than 70 individual studies and eight published reviews from four continents." In general, more frequent and severe complications were found in the earlier years covered than in later reports. The overview concluded that "[s]ex reassignment, properly indicated and performed, has proven to be a valuable tool in the treatment of individuals with transgenderism," that "gender reassigning treatments are effective" and that "the treatment that includes the whole process of gender reassignment is effective." *Id.* at unnumbered pages 1, 45, 66-67.

Yolanda L.S. Smith, et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals,* 35 Psychol. Med. 89-99 (2005), AP Ex. 27. This study evaluated "outcomes of sex reassignment, potential differences between subgroups

of transsexuals, and predictors of treatment course and outcome" in 162 adults (104 MF, 58 FM). The study found that "[a]fter treatment the group was no longer gender dysphoric," had "improved in important areas of function, that 1-4 years after surgery, SR appeared therapeutic and beneficial . . . [and that] the vast majority expressed no regrets about their SR." The study further concluded "that sex reassignment is effective" but that "clinicians need to be alert for non-homosexual male-to-females with unfavourable psychological functioning and physical appearance and inconsistent gender dysphoria reports, as these are risk factors for dropping out and poor post-operative results." *Id.* at 89, 91, 96.

Svetlana Vujovic, M.D., Ph.D., et al., *Transsexualism in Serbia: A Twenty-Year Follow-Up Study*, 6 J. Sex. Med. 1018-23 (2009), AP Ex. 29. This study [a]imed to "describe a transsexual population seeking sex reassignment treatment in Serbia" by analyzing "data collated over a period of 20 years" from 147 transsexuals "applying for sex reassignment" of whom SRS was performed in 83% of MF and in 77% of MF patients. The study concluded that "in our population, there were no cases who regretted sex reassignment treatment," which was attributed to diagnostic procedures used and the "young [adult] age at which our subjects embarked on treatment." *Id.* at 1018-20, 1022.

Steven Weyers, M.D., et al., *Long-term Assessment of the Physical, Mental, and Sexual Health Among Transsexual Women*, J. Sex. Med. 752-60 (2009), AP Ex. 30. This study [a]imed "[t]o gather information on physical, mental, and sexual well-being, health-promoting behavior and satisfaction with gender-related body features of [49] transsexual women [MF] who had undergone SRS" with mean interval since vaginoplasty of 75.46 months. The study found that "sample … functions well after surgery on a physical, emotional, psychological and social level" and that "[o]nly with respect to sexuality do transsexual women appear to suffer from specific difficulties, especially concerning arousal, lubrication and pain." *Id.* at 752, 754, 759.

TAB 176-34

Pl. Trial Ex. 074

Moving Beyond Change Efforts:

Evidence and Action to Support and Affirm LGBTQI+ Youth

SAMHSA

Substance Abuse and Mental Health Services Administration

Acknowledgment

This report was prepared for the Substance Abuse and Mental Health Services Administration (SAMHSA) by Leed Management Consulting, Inc. under contract number HHSS283201700609I/HHSS28342001T with SAMHSA, U.S. Department of Health and Human Services (HHS).

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Navigating This Report

This report is written for multiple audiences, to include behavioral health providers, pediatric professionals and primary care providers, educators and school professionals, policymakers, and researchers. Families, parents, caregivers, and community leaders may also find it useful.

Two sections of this report are likely to be informative for all readers:

- **Executive Summary**, which synthesizes the key conclusions of the report
- **Statements of Professional Consensus on Beneficial and Harmful Practices with Youth of Diverse Sexual Orientation and Gender Identity**, which provides key scientific and treatment recommendations

Other sections of this report may be more accessible or useful to specific audiences and are noted below.

Behavioral health providers: All sections of this report are relevant to these professionals. Those primarily engaged in practice and treatment might focus on Section 2, which summarizes current research with lesbian, gay, bisexual, transgender, queer, questioning, and intersex youth and other sexual- and gender-diverse children and youth (LGBTQI+ youth). It describes evidence-based approaches to support and affirm LGBTQI+ children and youth. Section 3 includes an overview of laws that impact treatment and makes recommendations for targeted training and expanding treatment access.

Community leaders: Section 3 includes policy actions for those interested in supporting LGBTQI+ child and adolescent behavioral health. Appendix C provides selected resources for families and caregivers and those who work closely with them.

Educators and school professionals: Section 2 includes information on important school interventions this group can implement to improve the behavioral health of LGBTQI+ children and youth. Section 3 identifies vital steps that aim to improve behavioral health of LGBTQI+ children and youth.

Families and caregivers: Material in this report could help parents and caregivers understand and support a child's behavioral health. Some parents may find the information on schools and behavioral health in Section 2 useful when seeking support and treatment for their children. Appendix C provides selected resources for families, caregivers, and those who work closely with them.

Pediatric professionals and primary care providers: Providers may find Section 1 on the evidence regarding sexual orientation and gender identity (SOGI) change efforts useful, as well as the research summary and description of behavioral health treatment interventions (Section 2). Appendix C provides selected resources for families, caregivers, and those who work closely with them.

Policymakers: Section 3 targets policymakers interested in taking concrete steps to improve LGBTQI+ child and youth behavioral health. This section is relevant to federal, state, and local policymakers as well as advocates and behavioral health providers interested in public policy. Some policy professionals may find the entire report helpful as background information.

Researchers: The research summary in Section 2 and areas for future study provide an overview of recent evidence and scientific opportunities. Section 3 contains recommendations for future research initiatives.

A glossary of terms used throughout this report can be found in Appendix B.

Table of Contents

Executive Summary

Like all youth, lesbian, gay, bisexual, transgender, queer, questioning, and intersex youth and other sexual- and gender-diverse children and adolescents (LGBTQI+[] youth) deserve to grow up in supportive environments absent stigma and discrimination that allow them to thrive and achieve their human potential. When seeking behavioral health treatment (both mental health and substance use interventions), these children and adolescents, like their peers, and their families deserve the best evidence-based care from knowledgeable health providers without the risk of harm.

This report, *Moving Beyond Change Efforts: Evidence and Action to Support and Affirm LGBTQI+ Youth*, provides behavioral health providers, researchers, policymakers, and other audiences with current knowledge about LGBTQI+ youth, a comprehensive research overview, and important information on behavioral health concerns within this community. More specifically, the report provides details on helpful and harmful interventions for these populations in clinical, community, family, and school settings. In particular, the report documents that attempts to change an individual's sexual orientation and gender identity (SOGI; pronounced "SO-gee" change efforts) are harmful and should not be provided. Additionally, this report discusses evidence-informed policy options that could improve the overall health and well-being of LGBTQI+ youth.

As the abbreviation LGBTQI+ suggests, this population is not homogenous. It includes individuals with many distinct sexual orientations, gender identities, gender expressions, and variations in sex characteristics. Sexual and gender minorities are also diverse with respect to other identities, including age, race, ethnicity, language, national origin, religion, spirituality, ability, and socioeconomic status.[#]

This report is focused on the experiences and needs of LGBTQI+ children and adolescents up to age 17 years (referred to collectively as "youth"). In this report, the term "child" is used to refer to youth aged 3-11 years and "adolescent" is used to refer to youth aged 12-17 years.

Critically, LGBTQI+ youth experience significant physical and behavioral health inequities. Several factors contribute to these inequities and result in minority stress, which is harmful to behavioral health, including:[1,2,3,4]

- Stigma
- Negative social attitudes
- Systemic barriers in health care for LGBTQI+ people
- Rejection and lack of support from families, caregivers, and communities
- Bullying and harassment, and lack of recognition and support in schools

Lack of appropriately trained behavioral health providers and exposure to harmful efforts that attempt to change sexual orientation and/or

[] Even though the evidence is more limited regarding intersex persons, they are included in the acronym LGBTQI+ except when it would be inappropriate to do so, such as within journal article citations or a formal resource name. Additionally, LGBTQI+ is used interchangeably with "sexual and/or gender minority," and persons of "diverse sexual orientation and/or gender identity," (or similar language) throughout this report.

[#] For information regarding the terms used to describe sexual orientation and gender identity, see "Sexual Orientation and Gender Identity" within Youth.gov https://youth.gov/youth-topics/lgbt.

gender identity compound these challenges. Additionally, some transgender and gender-diverse youth require behavioral health support for their experience of gender dysphoria—that is, psychological distress arising from the incongruence between one's body and gender identity.[5]

The conclusions in this report are based on research and professional consensus statements from experts in behavioral health, research, education, and policy. They strengthen and build on the conclusions of a 2015 report published by the U.S. Substance Abuse and Mental Health Services Administration (SAMHSA), *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*, the precursor to this report.[6] An overarching and guiding conclusion of this new report is that SOGI change efforts in children and adolescents are harmful and should never be provided. Although the terms "conversion therapy" and "reparative therapy" are commonly used to describe efforts to repress or change someone's sexual orientation or gender identity, these efforts are not therapeutic, and using these terms reinforce disinformation that sexual- and gender-diverse people need repair or conversion. Efforts to change or suppress a person's sexual orientation or gender identity are grounded in the belief that being LGBTQI+ is abnormal. They are dangerous, discredited, and ineffective practices. Therefore, this report utilizes the term "SOGI Change Efforts" to describe so-called "conversion therapy." Recent studies have linked SOGI change efforts to significant harms, such as increased risk of suicidality and suicide attempts, as well as other negative outcomes including severe psychological distress and depression.[7,8,9,10,11,12,13]

An overarching and guiding conclusion of this report is that SOGI change efforts in children and adolescents are harmful and should never be provided.

Further, these practices are not supported by credible evidence and have been disavowed as harmful by behavioral health experts and scientific professional associations. SOGI change efforts do not align with current scientific

understanding of gender as well as the unfounded concept that being in a sexual or gender minority group or identifying as LGBTQI+ is an abnormal aspect of human development. Most importantly, they put young people at risk of serious harm.

The U.S. Department of Health and Human Services is committed to eliminating health inequities within communities, including the LGBTQI+ population. This report reflects that commitment by moving the focus away from SOGI change efforts and toward ensuring that behavioral health care for LGBTQI+ children and adolescents is safe and reflects the most current scientific evidence. This report also provides a roadmap for action centered on evidence-based care and helpful interventions for clinicians, all providers, educators, families, caregivers, and policymakers to improve the behavioral health of LGBTQI+ youth. Further, this report reflects priorities included in President Biden's June 15, 2022, Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals,[14] and the January 20, 2021, Executive Order on Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation.[15]

Key Findings

This report and its recommendations are based on scientific research distilled into consensus statements by a Subject Matter Expert Consensus Panel (the Panel; see Appendix D for members). After a thorough review of the scientific research; professional health and scientific association statements, guidelines, and reports; and state and national public policies, and in consultation with professionals across a wide range of expertise, the Panel revised and built on key statements from the 2015 report.

The term "evidence-based care" refers to care, practices, or policies that are based on current research evidence, clinical expertise, and expert consensus.

The Panel reaffirmed that:

- Variations in sexual orientation (including identity, behavior, and attraction) and variations in gender (including identity and expression) are part of the normal spectrum of human diversity and do not constitute mental disorders.

Based on recent studies on thousands of individuals who have undergone SOGI change efforts, the Panel concluded that:

- No available research supports the claim that SOGI change efforts are beneficial to children, adolescents, or families.
- Available research indicates that SOGI change efforts are not effective in altering sexual orientation. Further, no available research indicates that change efforts are effective in altering gender identity.
- Available research indicates that SOGI change efforts can cause significant harm.
- SOGI change efforts are inappropriate, ineffective, and harmful practices that should not be provided to children and adolescents.

In the past several years, the research on gender diversity, gender identity, and gender-affirming medical care for children and adolescents has expanded greatly. The Panel found that:

- Gender affirmation, including social transition, and gender-affirming medical care are appropriate and beneficial for many gender minority youth.

Research over the past 20 years has underscored the importance of family and community support to the health of LGBTQI+ youth. Family and community negativity toward sexual diverse sexual orientation and/or gender identity, especially family rejection and school bullying and harassment, can cause harm to the behavioral health of this population. The Panel confirmed that:

- Rejection and lack of social and emotional support from families and caregivers, schools, and communities negatively affects the health of sexual and gender minority youth. Such behaviors can cause harm, particularly family rejection of the youth's sexual and/or gender diversity.

After a comprehensive review of the substantial research assessing the impacts of public policies, the Panel determined that:

- Policies that stigmatize, restrict, or exclude sexual or gender minority youth are harmful to children and adolescents.
- Legal prohibitions on gender-affirming care (including medical treatment) are harmful to LGBTQ+ children and adolescents.

Understanding Sexual Orientation and Gender in Children and Adolescents

Behavioral health providers, parents, schools, policymakers, and communities can best provide support to children, adolescents, and their families and caregivers and improve their behavioral health when they have access to the most current information about sexual orientation, gender identity, and gender expression in youth. The following overview presents the most current understanding, based on scientific evidence of youth sexual orientation, gender identity, and gender expression.

Sexual orientation occurs across a continuum, and same-sex or same-gender attraction and relationships are normal and healthy variations of human sexuality.[16,17] Similarly, a gender identity that differs from assigned sex at birth, as well as a gender expression that is not aligned with usual or expected cultural norms for a particular gender, are normal and healthy variations of human gender identity.[18,19] It is a longstanding finding that being a person of diverse sexual orientation and/or gender identity, or identifying as LGBTQI+, is not pathological.[18,20,21,22,23,24,25]

While many youth have identified with having a diverse sexual orientation in the past, they have not always felt safe enough to share that diversity openly with others.[26,27,28] There is no single developmental trajectory for sexual orientation. Certainty about sexual orientation—e.g., gay/lesbian, bisexual, or straight—increases with age, suggesting "an unfolding of sexual identity during adolescence."[29] Some researchers have found that it has become more common in the 21st century compared to the 20th century for children to self-identify as having a diverse sexual orientation and/or gender identity.[30] What has changed from earlier periods is that youth appear to be publicly acknowledging their sexual orientation earlier as societal attitudes have increasingly become more accepting and open to diverse sexual orientations. Regardless of age, the increase in identifying as an individual of diverse sexual orientation may be tied to the increasing awareness and acceptance of diverse sexual orientations; the expansion of laws, policies, and practices that protect and support individuals regardless of sexual orientation; and an increased willingness and ability among people with diverse sexual orientations to self-identify.[31] Evidence suggests that acceptance of diverse sexual orientations does not make people more likely to identify with a diverse sexual orientation, but rather it increases the likelihood that people feel safer to identify this way publicly.[32,33,34]

Gender development begins in early childhood and continues throughout childhood and adolescence.[35,36] Gender diversity in youth can follow many possible paths. It may emerge as early as a child's preschool years, in late adolescence, or anytime in between.[37,38,39,40] Some gender-diverse children are actively exploring their gender, and there is variation regarding their identity development trajectories and ultimate identity outcomes.[38,39,40] Recent research has found that most gender-diverse children continue to identify as transgender or another gender identity that differs from their sex assigned at birth into adolescence and adulthood.[39,40,41] For those who exhibited diverse gender-typed behavior in childhood, but did not identify as transgender or nonbinary, the majority reported a diverse sexual orientation in adolescence.[42,43] For transgender children who have been supported in their gender identity and gender expression, the vast majority show consistency in their trans identity across time.[40,44]

Some people are born with differences in sex characteristics, such as reproductive anatomy,

chromosomes, or hormones that do not fit typical definitions of male and female. Intersex is an umbrella term used to describe people who can have different gender identities. Individuals with intersex traits may identify as male, female, nonbinary, or a different gender. Intersex individuals may consider themselves transgender if they do not identify with their sex assigned at birth. Like other LGBTQI+ youth, intersex youth experience pervasive stigma and discrimination. While research involving intersex individuals has been limited,[45] the Federal Government has taken steps to reduce this disparity, such as issuing a Request for Information on Promising Practices for Advancing Health Equity for Intersex Individuals in February 2023.[46]

Supportive families and caregivers, peers, and school and community environments are associated with improved psychosocial outcomes for all children and adolescents, and this is especially true for those children and adolescents with minority sexual orientations or gender identities that do not align with their sex assigned at birth.[47,48,49,50,51,52,53] Extensive research indicates that even just one supportive adult, such as a family member, teacher, or mental health provider, can have a positive impact on the mental health of youth of diverse sexual orientation and/or gender identity; such support can reduce adverse mental health impacts including suicide.[49] Additionally, family or caregiver, peer, school, and community support for youth of diverse sexual orientation and/or gender identity promotes better mental health and fewer negative outcomes, and can lead to positive development and emotional resilience.[47,48,49,53]

Behavioral Health: A broad term that includes mental health, resilience, and well-being; the treatment of mental and substance use disorders; and the support of those who experience and/or are in recovery from these conditions, along with their families and communities.

Behavioral Health Concerns Among LGBTQI+ Youth

LGBTQI+ adolescents face the same developmental milestones that accompany adolescence for all youth. However, unlike adolescents with a cisgender[1] and straight/heterosexual orientation, LGBTQI+ adolescents often must navigate an environment lacking awareness and acceptance of their sexual orientation and/or gender identity. Moreover, they might have to do so without family, community, or societal support, for example, through the child welfare system.

Limited research with sexual minority children indicates that mental health inequities may begin in childhood,[30,54] which may be connected to greater prevalence of discrimination and victimization among sexual minority children.[55,56] As a result of experiencing stigma and discrimination, some youth with diverse sexual orientation and/or gender identity are at increased risk for:

- Psychological distress (e.g., depressive symptoms, anxiety, and behavioral disorders)
- Substance use
- Suicidal ideation and attempts
- Victimization, violence, and homelessness

[1] "Cisgender" is a term that describes individuals whose gender identity is congruent with their sex assigned at birth. Please refer to Appendix B for a glossary of terms.

- Involvement with child welfare services, often stemming from family rejection
- Involvement in juvenile justice programs[57,58,59,60,61,62,63,64,65]

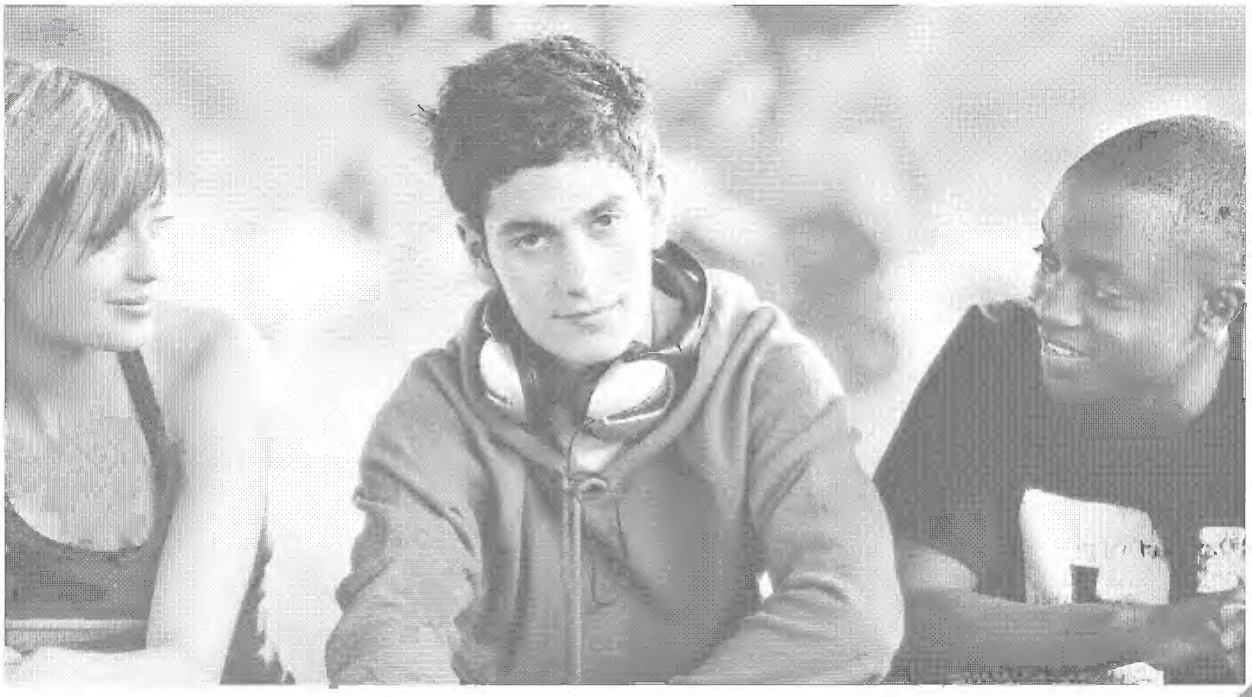
Psychosocial distress is often related to, if not caused by, negative social attitudes or rejection.[66] High levels of parental and caregiver support of youths' sexual orientation and gender identity can mitigate increased risk of behavioral health concerns. For example, transgender and gender-diverse youth with affirming parents and caregivers have similar levels of mental health challenges as their cisgender peers.[67] It is essential to note that youth with diverse sexual orientation and/or gender identity are resilient, and that with sufficient support and access to resources, they can thrive.[68,69]

Some children may experience gender dysphoria, meaning feelings of distress or incongruence between one's gender identity and sex assigned at birth. This distress, rather than the youth's gender diversity, is recognized as a behavioral health concern.[5] For some, the physical changes of adolescence may worsen feelings of gender dysphoria. For others, gender dysphoria or feelings of gender incongruence may begin post-puberty without any childhood history of gender dysphoria or gender diversity.[70]

Developmentally sensitive approaches consider appropriate development of emotional and cognitive capacities, achievement of developmental milestones, and possible emerging or existing behavioral health concerns.

Beneficial Therapeutic Approaches and Interventions With LGBTQI+ Youth

Given scientific findings that SOGI change efforts are harmful and medically inappropriate, the behavioral health approaches below are recommended instead. These approaches are consistent with the Panel's consensus



statements and current research. Several professional and scientific association guidelines recommend these approaches as well.[22,23,24,25,71,72,73,74]

When providing services to children, adolescents, families, and caregivers, appropriate therapeutic approaches include:

- Providing accurate information on sexual orientation, gender identity and expression, and variations in sex characteristics
- Identifying sources of distress, including internalized stigma and minority stress, and working with children, adolescents, families, and caregivers to reduce the distress LGBTQI+ youth experience
- Supporting adaptive coping to improve psychological well-being
- Supporting youth as they learn more about their sexual orientation and gender identity, and supporting families in accessing gender-affirming care for their transgender child when indicated
- Helping children and adolescents navigate their sexual orientation, gender identity, and gender expression within the context of their cultural, religious, and other identities

Interventions should be client-centered, culturally appropriate, and developmentally sensitive. The treatment goal should be to facilitate the best possible level of psychological functioning, rather than identifying with a specific gender or sexual orientation. Appropriate treatment approaches with youth of diverse sexual orientation and/or gender identity should focus on identity development and affirming exploration that allows the child or adolescent the freedom of self-discovery within a context of acceptance and support. It is important to identify the sources of any distress experienced by LGBTQI+ youth and their families and caregivers, and work to reduce this distress.

Working with parents and caregivers is important, as their behaviors and attitudes have significant effects on the mental health and well-being of youth with diverse sexual orientation and/or gender identity. Supportive family, caregivers, community, school, child welfare, and healthcare environments have been shown to positively impact both the short- and long-term health and well-being of LGBTQI+ youth. Families, caregivers, and those working with these youth can benefit from guidance and resources to increase support for sexual- and gender-diverse groups and to reduce stigma and discrimination.

In addition to the appropriate therapeutic approaches described above, social transition is appropriate and beneficial for many transgender and gender-diverse youth.[75,76,77,78] Although professional intervention is not required for youth to take steps in social transition, providers can support families and caregivers to protect youth's safety, ensure emotional, psychological, and social well-being, and help youth and families navigate the potential complexities of exploring and taking steps in social transition.[79] Based on the individual youth's needs, some forms of gender-affirming medical care may be medically necessary. Gender-affirming medical care that is provided in consultation with licensed healthcare providers is supported by extensive research and, based on the individual adolescent's needs, may be medically necessary.[80,81] Withholding timely gender-affirming medical care when indicated, withholding support for a gender-affirming exploratory process, and/or withholding support of social transition when desired, can be harmful because these actions may exacerbate and prolong gender dysphoria.[82,83]

Licensed healthcare providers play an important role in educating adolescents and their parents and caregivers about the various options for medical gender transition. They can also support youth, families, and caregivers in understanding this information and assess their understanding so that parents/caregivers and youth can provide fully informed consent and assent for the proposed care. The support of a behavioral health provider during these processes can aid an adolescent in identifying care needs, adjusting to their changing physical characteristics, and navigating responses from people in different aspects of their life.

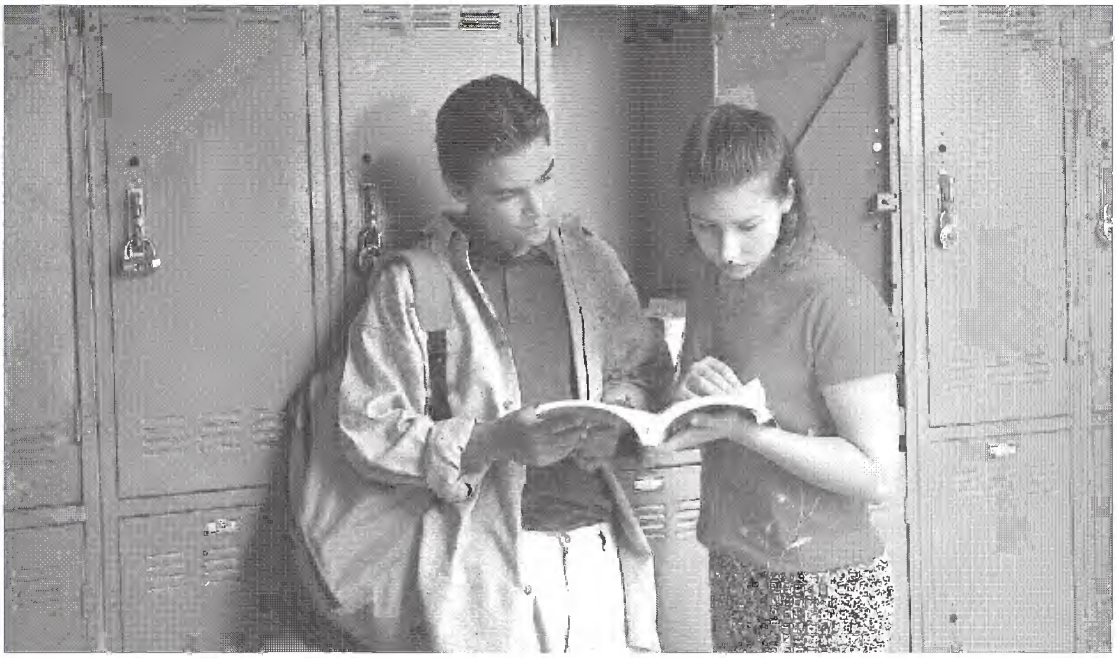
Policy Approaches to Support the Behavioral Health of LGBTQI+ Youth

LGBTQI+ youth and their families can benefit from policies that aim to:

- End harmful and ineffective efforts such as SOGI change efforts and ensure access to evidence-based care
- Promote behavioral health through protective and antidiscrimination policies
- Improve behavioral health through facilitating increased support from families, schools, and communities
- Conduct research that increases knowledge of health inequities with the goal to improve care

Given that SOGI change efforts are not appropriate therapeutic interventions, and are in fact harmful, immediate efforts are required to end their practice. Policy efforts to end SOGI change efforts have included:

- Passing state legislation to ban SOGI change efforts or provide supportive resources
- Introducing federal legislation to ban SOGI change efforts or provide supportive resources
- Banning licensed behavioral health providers from engaging in SOGI change efforts



- Restricting use of state funds and proposing the restriction of federal funds for these efforts
- Defining SOGI change efforts as consumer fraud

Efforts to improve understanding among behavioral health providers and other stakeholders of the harms of SOGI change efforts and the benefits of evidence-based care are essential. Other policy efforts can expand access to LGBTQI+ evidence-based care through reforming insurance and health services, ensuring nondiscrimination in health services programs, and increasing behavioral health and medical professional training in appropriate treatments. Bans on gender-supportive and gender-affirming care are harmful to individuals of diverse sexual orientation and/or gender identity.[84]

Policies can improve behavioral health and reduce health risks in this population by ensuring protection from discrimination, exclusion, and violence in schools and communities, and by expanding civil rights for LGBTQI+ individuals and families. Reducing stigma directed at LGBTQI+ individuals and families through affirmative public information that is respectful of families and youth from diverse religious, cultural, socioeconomic, and racial/ethnic backgrounds is important and consistent with professional ethical guidelines and standards of care. Supporting research to continue the development of evidence-based behavioral interventions for LGBTQI+ youth—especially those from diverse backgrounds—will contribute to the overall health and well-being of this community.

Introduction

This report, *Moving Beyond Change Efforts: Evidence and Action to Support and Affirm LGBTQI+ Youth*, revises and builds on the seminal 2015 SAMHSA publication, *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*.[6] Based on the usefulness of the 2015 report, SAMHSA determined that a revision was warranted to reflect advances in scientific research and practice. This report provides an overview of current scientific understanding on sexual orientation and gender identity development and research on the behavioral health of youth of diverse sexual orientation and/or gender identity. The report also includes professional consensus on best practices in behavioral health with lesbian, gay, bisexual, transgender, queer, questioning, and other sexual- and gender-diverse youth (LGBTQI+ youth) and describes actions and policy options based on scientific research to improve their health and well-being.

"Section 1. State of the Evidence on SOGI Change Efforts With Youth" addresses sexual orientation and gender identity (SOGI; pronounced "SO-gee") change efforts. SOGI change efforts include practices that are not supported by credible evidence, are harmful, and have been disavowed by behavioral health experts and professional and scientific associations. "Statements of Professional Consensus on Beneficial and Harmful Practices With Youth of Diverse Sexual Orientation and/or Gender Identity" describes updated statements from experts on best practices in behavioral health for sexual and gender minority youth. "Sexual Orientation and Gender Identity Change Efforts With Youth" is an update on current research regarding SOGI change efforts in youth, and formed the basis for the best practice statements.

"Section 2. Development, Behavioral Health, and Beneficial Therapeutic Approaches With Youth of Diverse Sexual Orientation and/or Gender Identity: A Research Overview" provides an updated and expanded overview of recent research with LGBTQI+ youth beyond change efforts. This section summarizes new developments in research with youth of diverse sexual orientation and/or gender identity, including sexual orientation and gender identity development and behavioral health. It also discusses positive and negative influences on the behavioral health and well-being of LGBTQI+ youth, including factors such as family, school, community, and policy. Importantly, this section also provides information about appropriate and beneficial therapeutic approaches to support the behavioral health and well-being of youth of diverse sexual orientation and/or gender identity and their families.

"Section 3. Policy Approaches to Support and Affirm the Behavioral Health and Well-Being of LGBTQI+ Youth" provides a comprehensive

outline of scientifically supported recommendations for policies to improve the behavioral health and well-being of youth of diverse sexual orientation and/or gender identity, including improving access to comprehensive, supportive care.

SAMHSA aims to reduce the impact of substance use and mental illness on America's communities. As such, SAMHSA endeavors to improve public health and eliminate health inequities, including those affecting LGBTQI+ communities. By addressing the issues included in this report that have a significant impact on the lives and well-being of LGBTQI+ youth, SAMHSA aims to enable families, caregivers, providers, educators, and policymakers to take actions that will reduce the behavioral health risks and inequities facing this vulnerable population.

Revision Process

Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth, a 2015 SAMHSA publication, was reportedly helpful to behavioral health providers, families, school professionals, policymakers, and other audiences.[6] SAMHSA determined that the report's utility could be enhanced and updated to reflect new advances in scientific research and practice. The revision—this report—includes:

- New research on SOGI change efforts
- Latest developments and research in the field of gender identity and sexual orientation development in youth
- Updated guidance for behavioral health providers, families, caregivers, and school-based professionals
- New section on public policy considerations

The 2015 report was based on a meeting of experts led by the American Psychological Association. Building on the successful 2015 process, a revision framework was developed by the contractor that culminated in a 2-day online meeting on September 9-10, 2021. During the meeting, experts in relevant fields considered a comprehensive array of research findings, professional guidelines, the current clinical knowledge base, behavioral health concerns of youth of diverse sexual orientation and/or gender identity, and policy opportunities. During this meeting, the Subject Matter Expert Consensus Panel (the Panel) and scientific writing team, under the direction of the contractor, helped develop and formulate this report.

The experts were identified based on their knowledge of a wide array of topics, including but not limited to:

- Gender identity and sexual orientation development in youth, including nonbinary and transgender individuals
- Youth clinical issues, including those related to gender dysphoria
- Concerns of ethnically, racially, and culturally diverse communities and under-resourced and underserved populations
- Family psychology
- Community and school mental health
- Professional ethics
- Research methods
- Intersection of behavioral health and spiritual diversity
- Legal issues and public policy
- SOGI change efforts

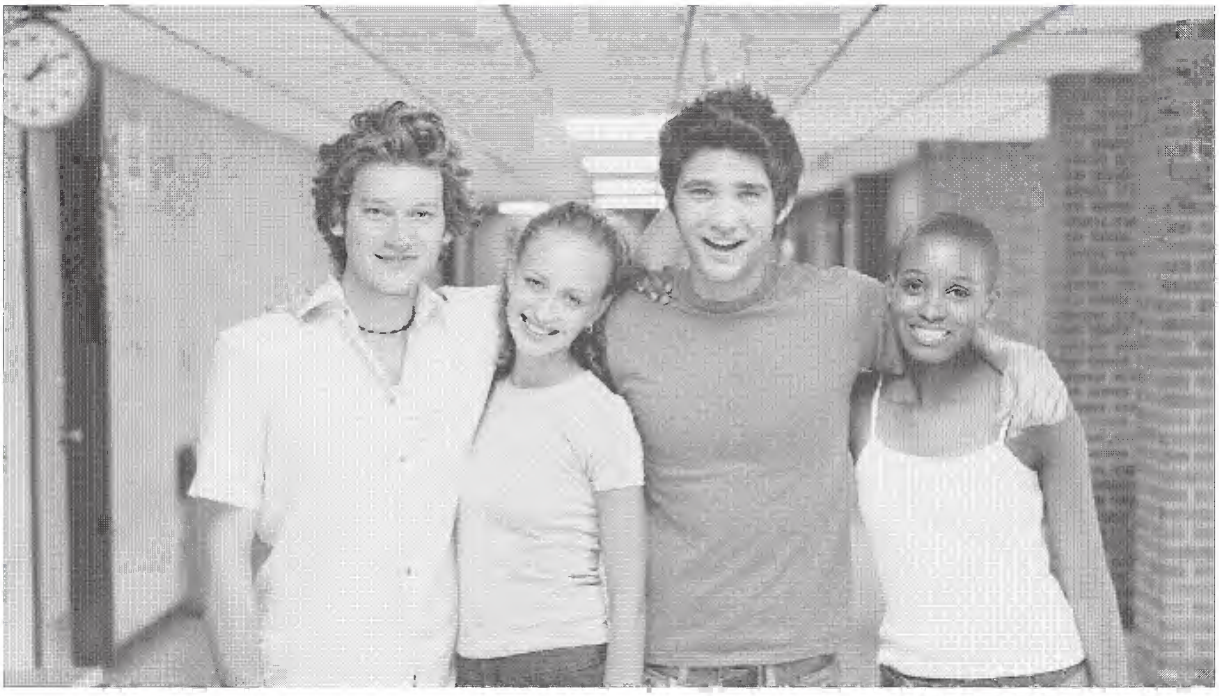
An extensive list of experts was generated from those with expertise in the above areas based on published research and innovation in the key knowledge areas; knowledge of, or participation in, the development of professional guidelines; expertise in clinical practice; referral by other

experts; and behavioral health specialty. SAMHSA also sought input from the experts who contributed to the 2015 report, including the American Psychological Association, and those who could assist in achieving the goals of this report.

Additional input was obtained from professionals in pediatrics, psychology, psychiatry, public health, social work, scientific research methodology, and legal issues and public policy. These individuals included researchers and practitioners in child and adolescent development and mental health, as well as researchers in gender development, gender identity, and sexual orientation in youth. The Panel, which helped develop and formulate this report, included experts with backgrounds in family therapy, ethnic, racial, and cultural diversity, needs of underrepresented populations, faith and psychology, and ethics. The Panel included those who practice in a variety of settings from different behavioral health specialties. (See Appendix D for members.)

As with the process developed for the 2015 consensus panel for the formulation of consensus statements, unanimous consensus was sought, but if it could not be reached, 80 percent support would constitute consensus. Versions of consensus statements were circulated after the September 2021 meeting with multiple opportunities provided for panelists to submit comments and revisions. Final versions were adopted by polling. Unanimous consensus was reached in nearly all instances. The statements of professional consensus are provided in "Section 1. State of the Evidence on SOGI Change Efforts With Youth."

Observers from SAMHSA's senior leadership team, internal experts, and cross-federal experts who had been involved in developing the 2015 report were present for the September 2021 meeting and offered the opportunity to submit written questions and input to the Panel throughout the meeting.



Section 1. State of the Evidence on SOGI Change Efforts With Youth

Statements of Professional Consensus on Beneficial and Harmful Practices With Youth of Diverse Sexual Orientation and/or Gender Identity

Guiding principles and statements of professional consensus regarding sexual orientation and gender identity and expression among youth were developed during the meeting of the Subject Matter Expert Consensus Panel (the Panel) meeting in September 2021 (see Revision Process in the previous section for a description of the Panel meeting and revision process). These statements revise and build on the professional consensus statements developed during a July 2015 American Psychological Association convening, as described in the 2015 report, *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*.[6] The 2021 convening and resulting statements reflect updates to current evidence and recommended clinical practice.

Guiding Principles for Behavioral Health Providers

The Panel updated a statement regarding the guiding human rights and scientific principles that provide a foundation for behavioral health providers working with this population. They are based on codes of professional ethics for the fields of psychology, psychiatry, counseling, social work, and pediatrics.[70,74,83,84,85,86,87]

- Behavioral health providers respect human dignity and human rights. Professional ethics necessitate that children and adolescents be supported in their right to explore and actualize their own identities.

Though the terms "conversion therapy" and "reparative therapy" are commonly used, these efforts are not therapeutic and reinforce harmful beliefs that sexual- and gender-diverse people need repair or conversion.

- All children and adolescents should have fair and equitable access to behavioral health services that will benefit their health and welfare without the risk of harm. Children and adolescents have the right to participate in decisions that affect their health care and future lives.
- Behavioral health providers assist children, adolescents, and their families in making informed healthcare decisions by providing developmentally appropriate information and assessing their decision-making capacities and family and community contexts.
- Behavioral health providers strive to provide care that is in the best interest of the child or adolescent.
- Behavioral health providers strive to incorporate cultural awareness, respect, and sensitivity into their work. They recognize that age, gender identity and expression, race, ethnicity, culture, language, national origin, religion, spirituality, sexual orientation, different abilities, and socioeconomic status are important factors to consider when working with children, adolescents, and families.

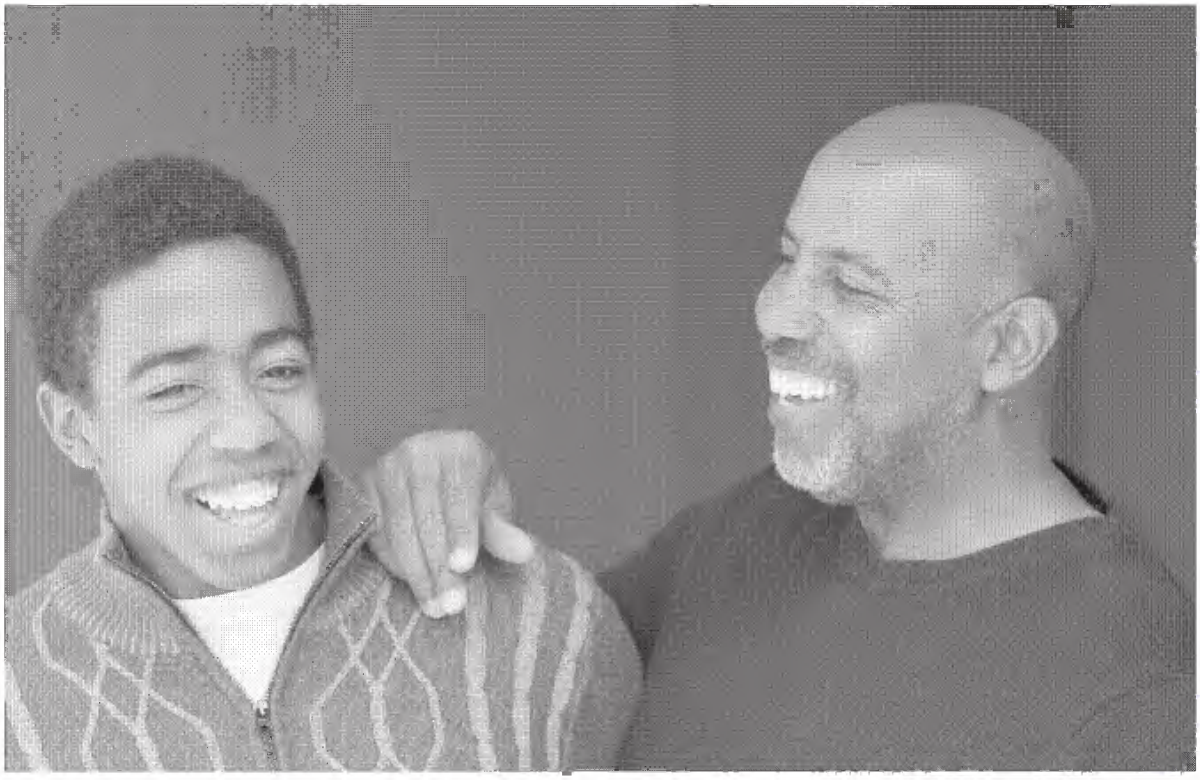
- Behavioral health providers strive to eliminate any impact of bias on their professional interactions and decisions.

Defining Sexual Orientation and Gender Identity Change Efforts

SOGI change efforts, commonly referred to as "conversion therapy" or "reparative therapy," are practices that aim to suppress or alter an individual's sexual orientation or gender to align with heterosexual orientation, cisgender identity, and/or stereotypical gender expression. SOGI change efforts are premised on or motivated by the belief that diversity in sexual orientation and/or gender identity and expression is a deficit, mental illness, or pathology.

SOGI change efforts do not include gender-affirming care. They do not include counseling that facilitates acceptance, social support, or open and affirming exploration and development of one's sexual or gender identity, including navigating sexual orientation and/or gender identity within the context of intersecting identities.

In the field of health care, the term "inappropriate" is used to designate care that is nonbeneficial, not medically indicated, and ineffective in achieving a patient's desired results. Medically inappropriate care is not needed or supported by clinical evidence and can result in negative health outcomes. The term "appropriate" is used to designate care when the expected health benefit exceeds the expected negative consequences by a sufficiently wide margin that the care is worthwhile.[88]



Professional Consensus on Sexual Orientation and Gender Identity Change Efforts With Youth

1. Variations in sexual orientation (including identity, behavior, and/or attraction) and gender (including identity and expression) are part of the normal spectrum of human development and do not constitute mental disorders.
2. Available research indicates that SOGI change efforts can cause significant harm. It also indicates that these efforts are not effective in altering sexual orientation. Further, no available research indicates that SOGI change efforts are effective in altering gender identity. No available research supports the claim that these efforts are beneficial to children, adolescents, or families.
3. SOGI change efforts are inappropriate practices that should not be provided to children and adolescents.
4. Rejection and lack of social and emotional support from families and communities negatively impact the health of sexual and gender minority youth. Such behaviors can cause harm, particularly family rejection of sexual orientation and/or gender diversity.

Professional Consensus on Appropriate Interventions With Youth of Diverse Sexual Orientation and/or Gender Identity and Their Families

1. Appropriate approaches to care for sexual and gender minority youth and their families:
    - Are evidence-based and person-centered
    - Reduce the rejection of sexual and gender minority youth
    - Increase family, school, and community support

    - Are responsive to children's, adolescents', and families' intersectional identities, including age, gender, race, ethnicity, culture, national origin, religion, spirituality, sexual orientation, different abilities, language, and socioeconomic status
2. Appropriate therapeutic approaches for sexual and gender minority youth do the following:
    - Provide accurate information on sexual orientation and gender identity and expression
    - Identify sources of distress for children, adolescents, and families and work with them to reduce it
    - Facilitate exploration and development of one's sexual and/or gender identity
    - Support adaptive coping to improve psychological well-being
    - Help youth navigate their sexual orientation, gender identity, and gender expression within the context of their cultural, religious, and other intersecting identities
3. Gender affirmation, including social transition (e.g., changing one's name, pronoun, and/or appearance), is appropriate and beneficial for gender minority children and adolescents.

Behavioral health providers may want to consult guidelines from major medical and mental health associations such as: American Academy of Child and Adolescent Psychiatry, American Academy of Pediatrics, American College of Physicians, American Counseling Association, American Medical Association, American Psychiatric Association, American Psychoanalytic Association, American Psychological Association, American School Counselor Association, Endocrine Society, National Association of School Psychologists, National Association of Social Workers, Pediatric Endocrine Society, Society for Adolescent Health and Medicine, World Medical Association, and World Professional Association for Transgender Health. (See Appendix C for some of these resources.)

Based on the youth's needs, gender-affirming medical care may be medically necessary. Such care is defined here as a care plan or service that is necessary to assess, maintain, or improve health and well-being and to avoid illness or reduce symptoms based on existing professional guidelines and scientific evidence. Withholding timely gender-affirming care when indicated, withholding support for a gender-affirming exploratory process, or withholding support of social transition when desired can be harmful because those actions may exacerbate and prolong gender dysphoria.

4. Legal prohibitions on gender-affirming care (including medical treatment) are harmful to children and adolescents. Further, policies that stigmatize, restrict, or exclude gender minority youth are harmful to children and adolescents.
5. When working with sexual and gender minority youth, behavioral health providers' ethical and professional responsibilities include delivering care that reflects respect, compassion, and cultural humility. It should be consistent with current professional, evidence-based, multidisciplinary resolutions and guidelines issued by leading health and scientific associations and professional ethical principles.

Person-centered, also known as client-centered, is a long-standing therapeutic approach that affirms and values all aspects of individuals.[89] It emphasizes unconditional positive regard and empathic understanding of all aspects of the person.

Professional Consensus on Education and Training

1. Like all youth, sexual and gender minority youth and their families have diverse cultural, ethnic, racial, religious, and other identities that shape their experiences, values, and behavioral health needs. These are important factors for behavioral health providers to understand and acknowledge. Providers should receive specific training in the development of diverse sexual orientations and gender identities, as well as training on culturally responsive approaches to working with sexual and gender minority youth and their families from diverse backgrounds.
2. While sexual and gender minority youth experience many of the same developmental milestones as other youth, they also encounter unique challenges and may need specific support and resources to thrive. All of those engaged in the care of youth, including parents and caregivers,

healthcare providers and staff, school and education professionals, community leaders, social service providers, legal professionals, and policymakers, can benefit from accurate, scientific, non-pathologizing information about sexual and gender diversity.

Sexual Orientation and Gender Identity Change Efforts With Youth

Over the past decade, additional high-quality research focused on documenting the practice and effects of SOGI change efforts has provided further evidence that these efforts should not be practiced with youth. This section includes a review of recent research on SOGI change efforts and information about their continued use across the United States. It also includes a detailed description of some of the methodological issues relevant to SOGI change efforts research that may be useful for researchers and policymakers. Finally, this section describes guidance from professional organizations disavowing SOGI change efforts.

Research on SOGI Change Efforts

There is now a significant body of research on SOGI change efforts. Overall, it has focused on sexual orientation change efforts more than gender identity change efforts. Although some study populations included both sexual and gender minorities, they often examined SOGI change efforts in ways that obscure whether transgender participants experienced change efforts related to their sexual orientation, gender identity, or both. This is both a methodological shortcoming of some SOGI change efforts research and a reflection of the realities of its practice, where it is not always possible to distinguish between sexual orientation and gender identity change efforts. For example, SOGI change efforts often include attempts to change children's and adolescents' gender expression to be more consistent with the stereotypical norms expected for their assigned sex at birth, with a goal to prevent both a transgender identity and a future diverse sexual orientation.[24,50,90]

In 2009, the American Psychological Association Task Force on Appropriate Therapeutic Responses to Sexual Orientation Change Efforts conducted an authoritative review of peer-reviewed literature published on sexual orientation change efforts.[24] Since its publication, a systematic review of research on sexual orientation change efforts has been published,[7] as well as quantitative and qualitative empirical studies examining sexual orientation change efforts among populations residing in the United States or Canada.[8,9,10,11,91,92,93,94,95,96,97,98,99,100,101,102,103,104]

A 2018 systematic review of research on gender identity change efforts published between 1990 and 2017 identified four studies reporting on its use, which consisted of three case reports and one case series.[105] Since then, three studies investigated gender identity change efforts among populations residing in the United States or Canada.[9,106,107,108] One study examined their use in New Zealand,[109] and several studies examined sexual orientation change efforts with transgender and gender-diverse populations in the United States and Canada.[10,11,103]

Lesbian, gay, bisexual, and other sexual orientations are normal variations of human sexuality and are not mental disorders. Transgender, nonbinary, and other gender identities are normal variations of human gender and are not mental disorders. Therefore, practices seeking to change an individual's sexual orientation, gender identity, and/or gender expression are not indicated and are inappropriate.

Several recent studies of SOGI change efforts reflect major methodological improvements over past work, such as larger sample sizes (e.g., 1,518[8]; 27,715[107]; 25,791[9]), a probability sample,[8] and controlling for other factors that may also cause harm (e.g., other adverse childhood experiences [ACEs]).[8] The majority of these studies were conducted with adults. One study included adolescents and young adults (ages 13-24),[9] and one study was limited to emerging adults ages 21-25 and asked about experiences of SOGI change efforts during adolescence.[10]

Research indicates that sexual orientation change efforts are not effective in altering sexual orientation. Research indicates that these efforts can cause significant harm, including suicide attempts and other negative behavioral health outcomes. No available research supports the claim that sexual orientation change efforts are beneficial to children, adolescents, or families.

Syntheses of research on sexual orientation change efforts have concluded that there is no evidence to support their effectiveness in altering sexual orientation or sexual attractions. A systematic review of peer-reviewed research on sexual orientation change efforts published from 1960 to 2007 concluded that they were not effective and may cause harm.[24]

Recent studies of sexual orientation change efforts corroborate those findings and provide stronger evidence of certain harms. Recent large, methodologically rigorous studies consistently find that exposure to sexual orientation change efforts places individuals at increased risk of suicidality and suicide attempts, as well as other negative outcomes including depression.[8,9,10,11] No studies have found evidence of any benefit of sexual orientation change efforts to children, adolescents, or their families. Other scholars and international organizations have independently conducted reviews of the sexual orientation change efforts literature, reaching the same conclusions.[7,12,13] It is now scientific consensus that sexual orientation change efforts are not effective and can cause significant harm.

No research indicates that gender identity change efforts are effective in altering gender identity. Research indicates that these efforts can cause significant harm, including suicide attempts and other negative behavioral health outcomes. No available research supports the claim that gender identity change efforts are beneficial to children, adolescents, or families.

SOGI change efforts have been used in an attempt to force children's behaviors, dress, and mannerisms to become more consistent with those stereotypically expected of their assigned sex at birth—that is, more stereotypically masculine expression for those assigned male at birth and more stereotypically feminine expression for those assigned female at birth. Historically, SOGI change efforts were the primary clinical approaches used with gender-diverse children, including those experiencing gender dysphoria.[39,50,90]

No research has demonstrated that gender identity change efforts are effective in altering

Despite evidence of harm, diverse populations across the United States, including children and adolescents, continue to be exposed to SOGI change efforts from a variety of licensed and unlicensed practitioners.

gender identity; there is also no evidence of any benefits of such practices to children, adolescents, or their families. Recent large, methodologically sound studies have investigated harms associated with gender identity change efforts.[9,107,108] These studies indicate that exposure to gender identity change efforts—in childhood, adolescence, and/or adulthood—is associated with harm, including suicidality, suicide attempt, and other negative mental health outcomes such as severe psychological distress.

Research that asked transgender participants about prior exposure to sexual orientation change efforts also reported that these efforts were associated with negative mental health outcomes including suicidal ideation and attempts.[10,11] Although this report focuses primarily on studies in the United States, a recent study in New Zealand corroborates findings of lasting harm associated with gender identity change efforts.[109] The findings of harm associated with SOGI change efforts—practices that exemplify anti-LGBTQI+ stigma and rejection—are bolstered by the extensive literature connecting minority stress, family/community rejection, and a lack of acceptance to negative health outcomes among youth of diverse sexual orientation and/or gender identity.[102,110,111]

Despite scientific consensus regarding the harms of SOGI change efforts and no evidence to support claims of its effectiveness or benefits, these efforts continue to be practiced across the United States by diverse health professionals and unlicensed community members.[8,9,106] It is estimated that anywhere from 3.5 to 18 percent of adults of diverse sexual orientation and/or gender identity have been exposed to SOGI change efforts; the single national probability sample reported a prevalence of 7 percent.[8] Its frequency of use among transgender and nonbinary populations is higher than that observed in cisgender LGB populations,[96,103,106,107] including in studies with adolescents and young adults.[9,10]

Though earlier reviews reported that most of the individuals who experienced sexual orientation change efforts were white men of higher socioeconomic status,[24] recent studies that rely on large national samples suggest greater diversity, indicating that women, people of color, and people from lower income levels are also affected by SOGI change efforts in the United States.[8,9,96,107]

Studies with individuals from religious traditions in which sexual orientation diversity and gender diversity are seen as contrary to faith teachings have often reported a greater prevalence of SOGI change efforts than studies that include individuals regardless of religious affiliation.[24,92,100,112] Based on these findings, it is likely that exposure to SOGI change efforts is greater among individuals from some religious backgrounds than those from more secular backgrounds.[24,91,100,112] However, current

Relative to young people who had not experienced SOGI change efforts, those who reported undergoing these efforts were more than twice as likely to report having attempted suicide and having multiple suicide attempts.[9]

research does not provide for estimates of prevalence.[91]

Of note, research indicates that younger generations may be at similar risk of exposure to SOGI change efforts as generations of youth before them.[8,103] As of 2018, adolescents and young adults from all regions of the United States reported exposure to these efforts.[9] A study of young adults of diverse sexual orientation and/or gender identity from community settings in the San Francisco area found that more than half had experienced SOGI change efforts from parents and caregivers, while just more than one-fifth had also experienced these efforts from an external source such as a religious leader or a behavioral health provider.[10]

Younger generations continue to be exposed to SOGI change efforts. Studies published recently show that adolescents and young adults across all regions of the United States continue to be exposed.[8,9,105]

Additionally, current research finds that SOGI change efforts result in negative consequences regardless of who attempts to effectuate the change. These change efforts are harmful whether undertaken by parents and caregivers, behavioral health providers, or other community members.[10,107] These findings indicate that efforts to reduce the harm caused by these practices would be most effective with a broad focus to include all forms of SOGI change efforts, as well as to reduce the stigma against LGBTQI+ people that drives their continued practice.

Methodological Considerations When Studying SOGI Change Efforts

Prospective, experimental research studies such as randomized controlled trials (RCTs) are considered a rigorous methodology for evaluating efficacy because these methods minimize selection bias and permit accurate estimates of causal effects. However, RCTs are not always an appropriate or ethical research design.[113] This is particularly true when multiple research studies indicate that a treatment or intervention is known to carry the risk to cause harm.[114]

To date, there have been no experimental research studies of SOGI change efforts with children or adolescents, nor would they be ethical to conduct. This is because there is sufficient evidence of harm associated with SOGI change efforts to conclude that they should not be provided to children and adolescents, and because previous studies have found no benefits. Coupled with the fact that professional consensus has established that diversity in sexual orientation and gender identity are normal variations for which treatment is unwarranted, an RCT is even more inappropriate to conduct. These ethical concerns are amplified in research with youth. Government regulations concerning research with children set strict limits and conditions on studies that could inappropriate to conduct. These ethical concerns are amplified in research with youth. Government regulations concerning research with children set strict limits and

conditions on studies that could pose harm to children and adolescents.[115]

There are valid ways to assess harm from SOGI change efforts without conducting an RCT or other rigorous quasi-experimental design (e.g., a nonrandomized design). Harm associated with an event or treatment can be evaluated through retrospective ("looking back") studies that examine the impact of those events and treatments by comparing outcomes for those who experienced them against people like them who did not. Mechanisms such as case studies, patient registries, and self-report surveys are also valid means to detect and report harms of a treatment.[114]

Most of the research using high-quality methodologies published since 2014 on sexual orientation or gender identity change efforts has been retrospective and employed cross-sectional designs, with adults asked to report their past experiences with change efforts at one point in time. This study design is appropriate for gathering evidence of harm. However, there are limitations to these study designs. Although they can identify harms, they cannot determine with certainty whether those harms are solely attributable to the SOGI change efforts. For example, research that relies on retrospective self-reports must address limits or differences in the accuracy of recollection of past events or experiences.

Sampling design—that is, how a research study recruits participants—can also limit the generalizability of the findings (i.e., the degree to which the results of a study can be applied to a broader group of people or situations). Much, though not all, of the research on SOGI change efforts uses what is called a "convenience sampling design," meaning it is unknown how representative the research participants are of all who have undergone these efforts. There is also natural bias in such samples because these are naturally occurring groups that share a common or similar social environment.

Current research on SOGI change efforts uses methodologies appropriate for the study of harm. Consistent findings across studies provide solid evidence that SOGI change efforts are harmful to the health of sexual and gender minority people, including children and adolescents.

Nonetheless, the public can have increased confidence in the research findings when many studies using a variety of research designs, conducted by independent research teams, consistently conclude that a "treatment" is associated with harm. This is the case with research on SOGI change efforts. Indeed, a strength of the existing research on these change efforts is the consistent finding that SOGI change efforts are associated with harms. This has been found across studies conducted by independent research teams using different methods and sampling strategies.

Despite methodological concerns that exist within specific studies, when taken together, the evidence is strong that SOGI change efforts are harmful to the health of people of diverse sexual orientation and/or gender identity, including children and adolescents. In recent decades, scholars and ethicists have proposed criteria for identifying potentially harmful behavioral health treatments when limited data exist. Potentially harmful treatments are defined as those that:

- Cause psychological or physical harm to the client or others
- Result in harmful effects that are long-lasting
- Have had independent research teams find and replicate the harmful effects[116]

This is the case with SOGI change efforts. Ineffective treatments—those that may not directly cause further harm but do not improve the health or well-being of the individual receiving treatment—may also be considered harmful in so far that they deprive an individual of needed care.[117,118]

Three sets of criteria have been proposed to identify potentially harmful treatments for children:

1. Criteria drawn from ACEs, revised to include experiences with therapists
2. Criteria drawn from studies of maltreatment and neglect
3. Criteria based on the plausibility of an intervention and its (in)congruence with what is known about child development.[119]

SOGI change efforts with children and adolescents meet all three criteria for identifying potentially harmful treatments for children.

Given the lack of evidence of efficacy and the potential risk of serious harm, every major medical, psychiatric, psychological, and professional mental health organization has taken measures to end sexual orientation change efforts and gender identity change efforts.

Consensus of Professional Organizations

Associations that have taken measures to end sexual orientation change efforts and/or gender identity change efforts include, among others:

- **Medical associations,** such as the American Academy of Child and Adolescent Psychiatry, American Academy of Family Physicians, American Academy of Pediatrics, American College of Physicians, American Medical Association, American Psychiatric Association, and the Society for Adolescent Health and Medicine
- **Psychological associations,** such as the American Psychoanalytic Association, American Psychological Association, and National Association of School Psychologists
- **Counselor associations,** such as the American School Counselor Association and American Counseling Association
- **Social worker associations,** such as the National Association of Social Workers
- **International health organizations,** such as the Pan American Health Organization (of the World Health Organization), World Professional Association for Transgender Health, and World Psychiatric Association

Conclusion

There is sufficient evidence to conclude that SOGI change efforts are inappropriate, harmful practices based on the knowledge that:

- These efforts are founded on a view of sexual and gender diversity that runs counter to scientific consensus.
- Research demonstrates that sexual orientation change efforts are ineffective, and no research demonstrates the effectiveness of gender identity change efforts.
- There is a growing body of evidence that exposure to SOGI change efforts can cause significant, lasting harm.

Other supportive behavioral health approaches are recommended for individual or family distress associated with sexual orientation and gender identity, as discussed in "Beneficial Therapeutic Approaches and Interventions in LGBTQI+ Youth and Their Families" in Section 2.

Section 2. Development, Behavioral Health, and Beneficial Therapeutic Approaches With Youth of Diverse Sexual Orientation and/or Gender Identity: A Research Overview

Sexual Orientation

Sexual orientation consists of sexual identity, sexual and romantic attraction, and sexual behavior. Great shifts in the understanding of sexual orientation have occurred over the past century.[120] Though a diverse sexual orientation was once considered abnormal or a medical problem, scientists now understand that sexuality occurs on a continuum and that variations in sexual orientation are part of the normal and healthy range of human sexuality.[16,17,23,24,121]

Although some people experience changes in sexual awareness, attractions, behaviors, and identities over time, this does not mean that sexual orientation can be willfully changed through their own or others' efforts, such as through sexual orientation and gender identity (SOGI; pronounced "SO-gee") change efforts.[23]

Today, many terms are used to describe sexual orientation. In addition to terms such as lesbian, gay, bisexual, and straight, many young people use a wider range of descriptive identity labels for their sexual orientation such as pansexual, asexual, queer, and questioning, among others.[122,123,124] Research with large, national samples of adolescents has found that approximately one-quarter of adolescents of diverse sexual orientation and/or gender identity use newer descriptive labels for their sexual orientation and/or gender identity.[124,125] Use of a wider range of descriptive sexual orientation labels appears to be more common among gender-diverse adolescents than among cisgender adolescents.[123]

The number of people in the United States who feel safe or comfortable to self-identify as a sexual minority is increasing, and most of this increase is occurring among women, people of color, and younger generations.[31] Nearly 5 percent of adults in the United States identify as lesbian, gay, or bisexual; this represents an increase of nearly 60 percent of individuals who were comfortable self-identifying as LGB than on surveys conducted 8 years earlier. Among U.S. high school students, nearly 15 percent identify as lesbian, gay, or bisexual or are unsure of their sexual orientation; this is nearly double the number of students who were comfortable self-identifying as non-heterosexual in surveys

Sexual orientation and gender are distinct yet related.

Everyone has a sexual orientation, including identity, attraction, and behavior, and a gender, including identity and expression. Individuals can belong to both a sexual minority population (i.e., lesbian, bisexual, gay, and other non-heterosexual orientations) and a gender minority population (i.e., transgender, nonbinary, and other diverse genders). Importantly, gender does not determine a person's sexual orientation. Gender-diverse populations include individuals with many different sexual orientations, including those who identify as straight/heterosexual and those who identify with a sexual minority identity.

Though they are distinct, gender and sexual orientation are related. Many adolescents and young adults who are gender diverse also identify with a sexual minority identity.

conducted 8 years prior.[59] The true size of sexual minority populations is likely higher than reported in these surveys. Stigmatizing societal attitudes and concerns about confidentiality may limit accurate reporting of sexual orientation identity and behavior.[126] Additionally, many surveys ask about only a limited number of sexual orientation options (e.g., lesbian, gay, bisexual, or heterosexual), which may miss individuals who use other terms (e.g., pansexual, asexual, or queer).[122,124] The increase in openly identifying as a sexual minority does not suggest that people are more likely to have the innate characteristics of being a sexual minority, but rather that individuals are increasingly able to publicly identify as LGBTQI+ because of increasing awareness and acceptance of diverse sexual orientations; the expansion of laws, policies, and practices that protect and support individuals regardless of sexual orientation; and an increased willingness and ability among LGBTQI+ people to self-identify due to decreased stigmatization and greater access to civil rights.[31]

How many people in the United States are sexual and gender minorities?

An estimated 11.4 to 12.2 million adults identify as LGBTQ+ in the United States, a number roughly equivalent to the population of Ohio.

An estimated 1.99 million adolescents ages 13 to 17 identify as LGBT in the United States, which is roughly equivalent to the combined populations of Dallas, Texas, and Detroit, Michigan.[31,127,128]

Sexual Orientation Development in Youth

Sexual orientation is usually conceptualized to begin at or near adolescence with the development of sexual feelings.[24] The average age at which sexual minority individuals reach important sexual orientation identity development milestones, such as becoming aware of same-sex attractions and coming out to others, commonly occurs during adolescence.[129,130] Various factors affect the trajectory of development related to sexual orientation, and there is no single or simple trajectory experienced by all individuals.[131,132,133,134,135] Recent generations of sexual minority individuals tend to reach milestones related to sexual orientation identity development and coming out (e.g., first becoming aware of their attractions, disclosing or sharing one's sexual orientation- or gender-diverse identity, first sexual minority relationship) at similar ages in adolescence.[129] In addition, it is becoming increasingly common for children to identify as lesbian, gay, or bisexual in childhood.[18] Youth's earlier public self-identification as having a minority sexual orientation is likely due to reduced stigma related to sexual orientation diversity. As more youth self-identify as sexual minorities, scholars have called for supporting the emotional and mental health needs that children express related to their sexual orientation.[136]

Sexual identity development is influenced by cultural factors that may differ across racial and ethnic groups. However, most research on sexual orientation identity development has included primarily white youth without examining differences related to race and ethnicity or cultural background.[124] As such, our cultural and scientific understandings of common experiences and developmental trajectories of sexual minority populations may better reflect the experiences of white sexual minority groups and be less relevant to the experiences of sexual minority people of color.[137] Limited research has examined the dual or multiple identity development processes among sexual minority youth of color.[138] Development related to racial/ethnic identity and sexual identity may occur concurrently among adolescents, though

involve different processes.[139,140,141] A variety of studies have identified cultural constructs and culturally specific expectations that have been identified as influencing sexual identity development among youth of color include familism (i.e., family needs take precedence over individual needs) and specific cultural understandings and expectations of masculinity among Black and Latino adolescent boys in particular.[138,142,143,144]

Significant physical, cognitive, and social development occurs during adolescence. Sexual minority adolescents face the same developmental tasks that accompany adolescence for all youth, including sexual identity development. However, sexual minority adolescents must also navigate an environment lacking awareness and acceptance of socially marginalized sexual identities, potentially without family, community, or societal support.[145,146]

Sexual identity development includes processes of identity formation (i.e., becoming aware of sexual attractions, exploring sexual feelings) and identity integration (i.e., integrating sexual identity within the larger view of self).[145] For sexual minority adolescents, difficulty with the identity development process, such as difficulty accepting one's sexual orientation and dissonance between one's self-image and cultural, religious, and societal beliefs about sexual minorities, can increase negative views of one's own and others' sexual minority identities and lead to adopting negative societal attitudes and beliefs about being a sexual minority.[147]

Sexual orientation conflict has been linked to negative psychosocial outcomes in adolescents and young adults.[146] Furthermore, a negative self-image as a sexual minority youth contributes to the relationship between sexuality-specific stressors (e.g., family

When discussing the concept of gender, scientists distinguish among a person's sex assigned at birth, gender identity, and gender expression.[24,25,125]

- **Sex assigned at birth is typically based on the appearance of external genital anatomy; male, female, or intersex are possible ways to identify sex.**
- **Gender identity refers to a person's deep internal sense of being female, male, a combination of both, somewhere in between, or neither.**
- **Gender expression refers to the external way a person communicates their gender, such as with clothing, hair, mannerisms, activities, or social roles. A person's gender expression may or may not be consistent with culturally prescribed gender roles or their sex assigned at birth and may or may not reflect their gender identity.**

rejection, victimization) and poorer mental health outcomes.[146,147]

Positive identity development, however, is associated with better mental health among sexual minority adolescents.[145,148] For example, one study found that for sexual minority college students, those who reported strong religious beliefs also reported lower psychological distress, but only among those students who had high levels of self-acceptance of their sexual orientation.[149] Strong religious beliefs on their own were not protective in terms of psychological distress for students who reported lower levels of self-acceptance of their sexual orientation.

Important areas of focus for behavioral health providers who work with adolescents include helping them address negative views about aspects of their identity and supporting positive identity development. For behavioral health providers who work with sexual minority adolescents, this includes reducing the client's negative views of their own sexual orientation identity and supporting positive identity development. This encompasses the integration of sexual orientation identity into the adolescent's larger sense of self, alongside intersecting identities (e.g., cultural, racial/ethnic, and other identities).

Gender

Transgender is a term that refers to individuals whose gender identities are incongruent with their sex assigned at birth.[75] The term gender diverse is a broader term that includes transgender individuals, as well as others whose gender behaviors, appearances, or identities are incongruent with those culturally expected based on sex assigned at birth.[75]

Significant advances have occurred over time in the scientific understanding of gender. It is now understood that gender diversity—identifying with a gender that does not align with sex assigned at birth, and/or having a gender expression that varies from that which is culturally expected for one's gender or sex assigned at birth—is part of the normal and healthy spectrum of human diversity, is not pathological, and does not require clinical attention on its own.[19,22,25,150]

Gender diversity was depathologized with changes made to the 5th revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and the 11th revision of the International Classification of Diseases (ICD-11).[151,152] These changes make it clear that gender diversity is not a disorder. Instead,

current guidelines focus on treating and supporting individuals who may experience feelings of distress (i.e., gender dysphoria) or incongruence between their gender identity and body or sex assigned at birth, as well as any distress associated with stigma and discrimination.[25] Note that throughout this report, "gender dysphoria" (not capitalized) refers to the general concept of distress associated with incongruence between one's gender identity and body or sex assigned at birth, while "Gender Dysphoria" (capitalized) refers to the DSM diagnosis.

Access to gender affirmation can alleviate or improve distress due to feelings of gender incongruence. Gender affirmation refers to processes by which an individual is recognized and affirmed in the gender with which they identify.

Gender affirmation can include psychological, social, medical, and legal aspects. Access to gender affirmation can reduce gender dysphoria and improve mental and physical health outcomes among transgender and gender-diverse people and is protective against the negative effects of gender-related stigma and discrimination.[153,154] There is substantial evidence of the behavioral health benefits of access to gender affirmation for transgender and gender-diverse children, adolescents, and adults.[51,52,53,80,81,155,156]

The belief that people can only belong to one gender category—male or female—has been prevalent in many contemporary Western societies. However, over the past several decades there has been a growing scientific understanding that sex and gender are more complex. Some people are born with sex characteristics that fall outside of male and female categories, and gender identity occurs on a spectrum.[157,158,159,160,161]

Scientists now recognize that many gender identities and gender expressions exist, and have always existed in a wide range of cultures across history.[157,162,163,164]

Terms such as nonbinary, gender queer, gender fluid, agender, bi-gender, and others are used by many individuals to express their gender identity.[162,164]

Identifying with more than one identity is also common.[165] There are also many culturally specific terms that have long been used for third gender or nonbinary identities and gender roles, including two-spirit among some Indigenous North American cultures, fa'afafine in Samoan culture, and māhū in Native Hawaiian culture.[165,166,167,168]

What about intersex youth?

Intersex is an umbrella term used to describe people born with differences in sex characteristics, such as reproductive anatomy, chromosomes, or hormones that do not fit typical definitions of male and female. Intersex people can have many different gender identities.

Individuals with intersex traits may identify as male, female, nonbinary, or a different gender. Intersex individuals may consider themselves transgender if they do not identify with their sex assigned at birth.

Like other LGBTQI+ youth, intersex youth experience pervasive stigma and discrimination. The Federal Government has taken steps to reduce disparities facing people who are intersex, such as issuing a Request for Information on Promising Practices for Advancing Health Equity for Intersex Individuals in February 2023.[46]

Identifying as nonbinary appears to be more common among younger generations.[165] This may be related to greater visibility and social acceptance of gender diversity.[122] One study with a large national sample found that nearly one-quarter of adolescents of diverse sexual orientation and/or gender identity self-identified as nonbinary.[124] Of note, some people who describe themselves as nonbinary or another gender consider themselves transgender, while others do not.[158]

In this report, "transgender and gender diverse" is used as a broad term that refers to people whose gender identity and/or gender expression are incongruent with their sex assigned at birth, including binary transgender people, nonbinary people, and cisgender people with a diverse gender expression.

Estimates of the size of the transgender and gender-diverse population in the United States vary. It is only in recent years that some national, population-based surveys have started to include questions to assess gender identity, and the practice remains far from widespread. It is estimated that between 0.1 and 2.0 percent of adults in the United States identify as transgender.[124,169] These figures likely underestimate the size of the transgender and gender-diverse populations, because much of this research has not used current best practices for asking separately about current gender identity and sex assigned at birth and did not consistently include gender-diverse individuals who do not identify with the term transgender.[170,171] Recent population-based research with adults of diverse sexual orientation and/or gender identity has found that 1.2 million adults in the United States identify as nonbinary, including people who both do and do not consider themselves transgender.[158]

Research with high school students has found that between 1.1 and 9.2 percent identify as transgender, nonbinary, or another gender identity that differed from their sex assigned at birth.[122,171,172,173] Studies that specifically asked about identifying as nonbinary and other gender identities in addition to identifying as transgender reported larger proportions of transgender and gender-diverse youth, emphasizing the importance of asking about nonbinary and other diverse gender identities.[169,171,174]

Gender Development in Youth

Gender-related development begins in early childhood and progresses through adolescence.[21] Processes of gender-related identity development among transgender and other gender-diverse populations are varied, non-linear, and not necessarily anchored to specific ages or developmental periods.[37,38] For some individuals, gender identity appears stable across development, while others experience changes in their gender identity over time.

Youth who start to think of themselves as transgender or gender diverse may share this identity with others, and take steps in social transition across a wide range of ages.[29,30,177,178] There is no single developmental trajectory for transgender and gender-diverse youth—that is, there is healthy and normal variation in the age that youth recognize themselves as gender diverse.[25]

Individuals who exhibit gender diversity in childhood include those who:

- Consistently identify with a gender that differs from their sex assigned at birth
- Identify with the gender that aligns with their sex assigned at birth and have a diverse gender expression
- Are exploring their gender identity and/or gender expression[179,180]

While earlier research from clinics specializing in childhood gender identity suggested that many individuals who exhibited gender diversity in childhood did not later identify as transgender in adolescence, significant methodological weaknesses preclude use of these findings to identify trajectories of gender identity development and their associated frequencies.[180] However, more recent research and clinical expertise suggests that children who consistently identify with a gender different from their sex assigned at birth typically express a similar clarity in adolescence.[50,77,150,179,181,182] Research also indicates that children whose gender expression differs from social norms, but who do not identify as transgender or nonbinary, are more likely to have a diverse sexual orientation in adulthood.[24,183,184]

A significant body of research demonstrates that affirming a child's current gender identity and gender expression, as well as supporting their process of understanding more about their identity, is beneficial for all children. The benefits of providing affirming mental health care include reducing the risk of suicide in transgender and gender-diverse youth. Given the significant mental health risks that gender minority youth face when affirming mental health care is not available, affirming mental health care is appropriate and necessary even for youth who may later identify differently in adulthood.[78,179,185,186,187]

Younger generations understand, experience, and communicate their gender-related experiences in different ways than previous generations. These understandings of gender include an increased recognition of the complexity of gender, sexuality, and identity and fewer stereotypes or expectations of what it means to be a certain gender.[157,175,176]

Children who identify as transgender early in their development are increasingly supported and affirmed in their identities by many families at young ages. Research with transgender youth who have socially transitioned—that is, who present as their gender identity in everyday life—provides evidence that early in childhood, gender-related development is similar among transgender and cisgender children with the same gender identity, regardless of sex assigned at birth.[188,189,190] These similar areas of gender-related development between transgender and cisgender children include consistency and strength of identification with their gender and expression of gender preferences, stereotypes, behaviors, and beliefs.[40]

Other youth identify as transgender or gender diverse for the first time in adolescence.[35,177,191,192,193] Puberty can be a pivotal time when youth become more aware of their gender and experience physical changes that can trigger or exacerbate dysphoria.[194] Some individuals who initially identify as transgender or gender diverse in adolescence do not have a history of gender diversity or gender "non-conforming" behaviors or preferences in childhood.[178] This can make disclosure of a gender identity that differs from sex assigned at birth in adolescence surprising to parents, guardians, and others.

Some adolescents who identify as transgender or gender diverse report that they felt different at a young age but expressed or engaged in behaviors that were stereotypical for their sex assigned at birth earlier in life, while others do not feel differently about their gender until adolescence.[35,177] Given the advances in scientific understanding of the normal and healthy diversity of gender identities, understanding the current experiences of youth whose gender incongruence presents in adolescence is an important area of study. No singular narrative can describe the totality of transgender and gender-diverse youth experiences.

Identity development is among the key tasks of adolescence for all adolescents, including those who are transgender and gender diverse. Self-acceptance of one's gender identity, identity pride, and valuing self are factors that promote resilience among transgender and gender-diverse adolescents.[146,195,196,197] However, transgender and gender-diverse adolescents may experience identity conflict when reconciling a gender identity that may diverge from the expectations of their family, peers, and community. This can be particularly pertinent for transgender and gender-diverse adolescents of color, who often experience multiple forms of discrimination (e.g., racial discrimination when seeking out supportive services, or anti-transgender stigma in one's racial/ethnic or cultural community) and may perceive incompatibility between their gender identity and racial/ethnic identities.[141,199]

Conversely, racial/ethnic identity development processes may beneficially impact how youth navigate gender identity development, such as experience coping with adversity and developing a sense of pride in one's identity.[196] While self-acceptance and identity pride are associated with well-being, adopting negative societal attitudes and beliefs about being transgender or gender diverse and having a negative gender-related self-concept have been connected to mental health challenges and greater substance use among transgender and gender-diverse adolescents.[200,201]

Minority stressors experienced due to anti-LGBTQ+ stigma include major life events, such as assault because of one's sexual orientation, gender identity, or gender expression, as well as everyday forms of discrimination and non-affirmation, such as receiving poor services, being assumed to be straight, or being misgendered. Minority stress is also caused by policies that limit the opportunities, resources, and well-being of LGBTQI+ populations.[111,198]

Important areas of focus for behavioral health providers who work with adolescents includes helping them address negative views about aspects of their identity and supporting positive identity development. Therefore, important areas of focus for behavioral health providers who work with transgender and gender-diverse adolescents are reducing negative views of their own gender identity and supporting positive identity development.[199,200,201] As with adolescents of diverse sexual orientations, this includes integration of gender identity and gender self-concept into their larger sense of self, alongside cultural, racial/ethnic, and other identities.

Research on how gender identity development varies by gender, race and ethnicity, and other cultural, social, and environmental factors remains in its early stages. Some studies have identified potential differences in developmental trajectory by gender.[35] Many studies have disproportionately low representation of transgender girls and other gender-diverse youth assigned male at birth, suggesting that transgender girls and women are coming out at later ages.[202,203,204]

One study investigating age upon accessing gender-affirming medical care found that it was influenced by contextual factors, such as family religion, having a helpful caregiver, as well as developmental milestones reached upon recognition of gender incongruence and age at coming out or disclosing gender identity.[205] Another study of young transgender women found differences by racial/ethnic group, suggesting that youth of color may achieve some social milestones (e.g., disclosure of gender identity) at younger ages than white youth.[206]

Most research with transgender and gender-diverse youth has been conducted with mostly white, higher income families living in urban areas who have access to specialized pediatric gender clinics. In recent years, more research has been conducted with nonclinical populations of children.[36] Given the tremendous variation in attitudes and expectations related to gender by cultural group and family background, more research is needed with racially and ethnically diverse children and families, lower income families, and families from different cultural and religious backgrounds to better understand the experiences and needs of diverse gender minority children and adolescents and to ensure access to evidence-based care.

Health and Well-Being of LGBTQI+ Youth

In the United States and worldwide, sexual- and gender-diverse populations experience inequities in many behavioral health outcomes.[207,208] This report uses the phrase "health inequities" as opposed to "health disparities" to refer to unnecessary and avoidable health differences.[209] These health inequities are not caused by one's sexual orientation, gender identity, or gender expression, but rather by anti-LGBTQI+ stigma that is embedded in proposed and enacted laws, policies, and societal attitudes.

The Minority Stress Model provides an empirically validated conceptual model for understanding how stress due to anti-LGBTQI+ stigma, coupled with general life stressors, puts individuals of diverse sexual orientation and/or gender identity at increased risk for negative behavioral health outcomes.[111,210,211] These external experiences of minority stress cause cognitive, affective, and behavioral reactions, such as internalized stigma, identity concealment, and social isolation, all of which are associated with poorer mental health.[154,210,212,213,214]

Despite the impact of anti-LGBTQI+ stigma, which individuals can experience in tandem with other forms of discrimination, many youth and adults of diverse sexual orientation and/or gender identity can adapt, thrive, and demonstrate resilience despite risk exposure, high levels of stress, and other forms of adversity.[215] Resilience refers to a dynamic process of adapting positively within the context of significant adversity.[216] Resilience among sexual- and gender-diverse populations is promoted through:

- Self-acceptance of sexual orientation and gender identity, self-esteem, and identity pride
- Social support and sexuality- and gender-specific support from family, peers, schools, and community organizations
- School and community connectedness
- Inclusive and supportive federal and state policies[60,66,148,217]

It is important to recognize that sexual and gender minorities are not a single, homogeneous population. In addition to including individuals with many distinct sexual orientations, gender identities, and gender expressions, LGBTQI+ populations are also diverse with respect to other identities, including age, race, ethnicity, immigration status, language, national origin, religion, spirituality, ability, and socioeconomic status. Individuals with multiple minority identities experience unique stigma and stressors, as well as unique opportunities for resilience.[197,218,219,220]

To support individual LGBTQI+ youth in achieving their optimal health and well-being, and to take action to address health inequities among LGBTQI+ populations, behavioral and other healthcare providers, families, school administrators, boards, and educators, community leaders, and policymakers must understand the health concerns that may affect LGBTQI+ youth and be knowledgeable about the factors that lead to risk and resilience among LGBTQI+ youth. The following sections provide an overview of behavioral health concerns among LGBTQI+ youth, as well as what is known about the influence of families, school, religion and spirituality, community climate and policies, and gender affirmation on the behavioral health of LGBTQI+ youth.

Behavioral Health Concerns Among LGBTQI+ Youth

Variations in sexual orientation (identity, behavior, and/or attraction) and gender (identity and expression) are part of the normal spectrum of human development and do not constitute mental disorders. However, youth of diverse sexual orientation and/or gender identity are at elevated risk for mental illness and substance use due to experiences of discrimination related to sexual orientation, gender identity, rejection, trauma, violence, and a lack of support from families, school systems, and communities.[111] Transgender and gender-diverse children and adolescents may also experience psychological distress related to gender dysphoria.[25] It is important to emphasize that youth of diverse sexual orientation and/or gender identity are

resilient, and that with sufficient support and access to resources, they can thrive.[68,69] Behavioral health concerns that behavioral health providers can be aware of and attend to among sexual- and gender-diverse youth are summarized below.

Behavioral Health Concerns Among LGBTQI+ Children

Recent research has begun to investigate behavioral health among sexual- and gender-diverse children and has found that inequities in behavioral health may begin in childhood. While some sexual- and gender-diverse children are distressed, others are not. Among those who are distressed, the source of distress varies.

Several studies found that more children who self-identify as gay, bisexual, or questioning reported distress, including mood disorders, non-suicidal self-injury, suicide ideation, and suicide attempts than did children who do not identify as gay, bisexual, or questioning.[30,54] Additionally, two longitudinal studies found that children who later identified as a sexual minority began experiencing mental health challenges as early as age 11.[55,56] Other studies indicate that mental health concerns among sexual minority children may be linked to experiences of victimization, such as bullying behaviors perpetrated by peers.[221,222]

Gender-diverse children appear to have elevated rates of mental health concerns, including symptoms of anxiety and depression, history of self-harm, and suicidality, compared to cisgender children.[223,224,225] When gender-diverse children have behavioral health concerns, these may be related to invalidation or rejection of their gender diversity, or distress related to current anatomical dysphoria and/or anticipation of future pubertal development incongruent with their current gender. Alternatively, their mental health concerns may be entirely unrelated to their gender.[25,50]

At the same time, research also suggests that gender-diverse children who receive meaningful gender identity support do not necessarily experience elevated rates of depression and anxiety.[51,226] Research with a national sample of socially transitioned prepubescent transgender children found this group to have developmentally normative levels of depression, only minimal elevations in anxiety, and comparable levels of self-worth, suggesting that behavioral health concerns are not inevitable among this group.[51,226]

Behavioral Health Concerns Among LGBTQI+ Adolescents

As LGBTQI+ adolescents navigate the challenges of adolescence, some experience a variety of behavioral health concerns and psychosocial challenges. Compared to their heterosexual and cisgender counterparts, some adolescents of diverse sexual orientation and/or gender identity are at disproportionate risk of behavioral health symptoms, driven by increased exposure to stigma, rejection, and victimization.[48,227,228,229,230] It is also important to note that behavioral health concerns may be unrelated to sexual and gender diversity. Exposure to SOGI change efforts is a key risk factor that has been shown to increase risk of

suicide attempt among adolescents and young adults of diverse sexual orientation and/or gender identity.[9,10,49,229]

Compared to heterosexual and cisgender peers, adolescents of diverse sexual orientation and/or gender identity are more likely to experience psychological distress, symptoms of depression, and symptoms of anxiety.[57,65] Studies indicate large differences in rates of suicidal ideation and attempts among adolescents in the United States by sexual orientation and gender identity. The Youth Risk Behavior Surveillance System (YRBSS) documented increased odds of suicide risk among both sexual minority and gender minority high school students compared to heterosexual and cisgender students, including suicide attempt requiring medical treatment.[227,228,230,231]A recent public health study with data from six states found that while suicide rates are dropping, sexual minority adolescents in this study were three times as likely to attempt suicide relative to heterosexual adolescents.[58] Research with gender minority adolescents has documented that between 25 percent and 51 percent of transgender and gender-diverse adolescents have attempted suicide, with the highest rates among transgender boys and nonbinary youth.[192,232,233,234]

Research using YRBSS data indicates that some adolescents of diverse sexual orientation and/or gender identity are more likely than heterosexual and cisgender adolescents to engage in substance use.[228,229,231,235,236] Research found that adolescents of diverse sexual orientation and/or gender identity also experience greater incidence of eating disorders and disordered eating behaviors than their heterosexual and cisgender counterparts.[237]

Adverse mental health outcomes tend to be more prevalent among gender minority youth compared to sexual minority youth due to specific stigma and discrimination against transgender individuals.[61] The higher rates of substance use and suicidality are partly explained by experiences of discrimination, victimization, and higher rates of depressive symptoms reported by transgender and gender-diverse adolescents as compared to cisgender adolescents.[60,233,238,239,240]

Among transgender and gender-diverse adolescents, some research suggests that mental health outcomes may be worse among nonbinary adolescents and transgender boys.[61,232,241,242] Gender dysphoria, which can initiate or intensify in adolescence, can cause psychological distress among transgender and gender-diverse adolescents.[25] Increased experiences of victimization, rejection, and exposure to discriminatory policies may also drive the higher rates of adverse mental health seen among transgender and gender-diverse adolescents compared to sexual minority adolescents.[228,242,243]

Trauma is also a common behavioral health concern among adolescents of diverse sexual orientation and/or gender identity, who have an increased likelihood of experiencing child maltreatment, school-based victimization, violence, and homelessness, and who are overrepresented in both the child welfare system and the juvenile correctional system.[63,64,227,228,231,243,244,245,246,247]

A number of studies suggest that some neurodiverse youth are gender diverse.[224,248,249,250,251] The most recent clinical guidelines suggest that such youth benefit from an individualized approach to treatment.

The fact that research consistently demonstrates large inequities in behavioral health among LGBTQI+ adolescents indicates that this is a vulnerable population that needs psychosocial support, equitable social conditions, and access to affirming mental health care. At the same

time, it is important to emphasize that many LGBTQI+ adolescents are resilient and although experiencing discrimination and behavioral health challenges can thrive.[68,69,252,253]

Influences on Health and Well-Being

The increased risks of behavioral health distress that LGBTQI+ youth face are not a function of their identities. Rather, these risks stem from the stresses of stigma, discrimination, rejection, and violence.[240] The presence of sexual orientation- and gender-related stressors—and opportunities for emotional support and connection—encompasses multiple social systems, including, for instance, family, culture, values, school, and community networks.[254,255,256] Therefore, when LGBTQI+ youth are evaluated by a behavioral health provider, assessment should routinely include family, school, and community systems in which they live to identify both sources of distress and sources of support and connection as protective factors.[256] By increasing LGBTQI+ youth's access to support and resilience-promoting resources across their daily environments, and decreasing exposure to stigma and discrimination in communities and healthcare systems, more LGBTQI+ youth can achieve optimal health and well-being.

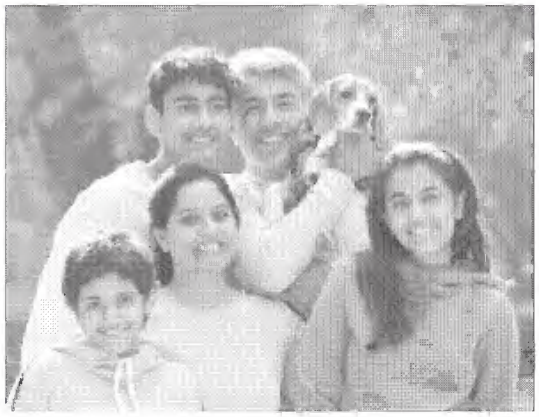
Family

Family response to youth's sexual orientation, gender identity, or gender expression has a significant impact on the youth's well-being, with effects that appear to extend into young adulthood.

Parents, caregivers, and families can serve as both a source of stress and a source of support for youth of diverse sexual orientation and/or gender identity.[40,53,257] Negative parental responses to sexual orientation, gender identity, and/or gender expression are associated with mental health concerns including psychological distress, depression, suicidality, and substance use.[10,253] Alternatively, parent-child relationships characterized by closeness and support are an important correlate of mental well-being.

Strong parental support for a child's gender identity may offset the mental health challenges commonly documented among gender-diverse children.[51,226] The use of a transgender or gender-diverse adolescent's chosen—rather than given—name has been linked to decreased depressive symptoms, suicidal ideation, and suicidal behavior.[49,52] Among adolescents of diverse sexual orientation and/or gender identity, high levels of sexual orientation and gender identity acceptance from parents and other relatives has been associated with reduced suicidality.[49,258,259] Further, the behavioral health benefits from high levels of family acceptance of youth's diverse sexual orientation and/or gender identity appear to last through young adulthood.[103] The limited research that has focused on family members outside of parents and primary caregivers suggests that siblings and extended family members can be key sources of support for youth of diverse sexual orientation and/or gender identity.[260,261]

Studies have found that some adolescents of diverse sexual orientation and/or gender identity report strikingly high rates of adverse childhood experiences (ACEs). High ACE scores and parental rejection have been associated with



suicidality in youth of diverse sexual orientation and/or gender identity[262] and may put these adolescents at greater risk for being victimized in other settings.[263] Notably, though some scholars and practitioners consider SOGI change efforts from family members potentially traumatic events, ACE measures do not capture youth's experiences of SOGI change efforts.[120]

It is important to note that some LGBTQI+ youth who lack family and/or parental support find resilient ways to access needed support and guidance. Many people of diverse sexual orientation and/or gender identity, including those with and without supportive families of origin, form "chosen families" with sexual- and gender-diverse friends who provide social support and resources.[266] In urban areas across the United States, LGBTQI+ adolescents and young adults of color—particularly Black and Latino youth—may join informal communities and LGBTQI+ family structures.

Religion & Spirituality

When considering family and community influences, a child's or adolescent's religious background is an important factor. Religious beliefs and background are far-reaching influences that encompass multiple arenas of one's life, including personal and family religious identity, beliefs, and coping; family attitudes, beliefs, and relationships; and community character and support. Religious views of sexual and gender diversity in the United States vary widely[269,270] and can have a large influence on sexual- and gender-diverse adolescents' mental health and well-being.[147,269,270] When working with youth of diverse sexual orientation and/or gender identity, it is important to consider the intersection of religion with youth's racial and ethnic identity and cultural background.[271,272]

Religion and spirituality are complex, nuanced aspects of human diversity. Parents from all backgrounds have a full range of reactions to their child's sexual orientation and gender identity and expression regardless of religious or spiritual traditions (e.g., confusion, desire for information, questions about social implications, love and loyalty, coming to terms with differences, growth and expansion of spiritual understanding, and for some a sense of loss).[273,274] Rather than focus on faith beliefs, where they might lack expertise, behavioral health providers can focus on encouraging key measurable behaviors among families and caregivers that have been found to be supportive and protective for children, as well as informing families how some of their behaviors and interactions might lead to negative behavioral health outcomes.[102,258,273]

Youth of diverse sexual orientation and gender—and particularly those youth of color—are overrepresented among youth experiencing homelessness, as well as across multiple state-based systems[214,264,265]

- **Up to 40% of all youth experiencing homelessness and housing instability are youth of diverse sexual orientation and gender.**
- **Up to one-third of youth in foster care systems are youth of diverse sexual orientation and gender.**
- **Up to one-fifth of youth in the juvenile justice system are youth of diverse sexual orientation and gender.**

Parent or caregiver rejection due to sexual orientation and gender diversity is just one of many reasons for these inequities; other factors such as parental mental health and substance use, poverty, and racism are common drivers of housing instability and system involvement among youth of diverse sexual orientation and gender.

School

LGBTQI+ adolescents may experience a myriad of sexual orientation- and gender-related stressors in the school environment, where they spend a large portion of their time. Despite increasing cultural visibility and acceptance of people of diverse sexual orientation and/or gender identity, the climates of U.S. secondary schools remain generally unsupportive and unsafe for many sexual- and gender-diverse youth, who experience high levels of verbal and physical harassment and assault, sexual harassment, social exclusion and isolation, and other interpersonal problems with peers.[48]

School bullying and victimization is often linked to nonconformity to gender norms.[275] Across racial/ethnic groups, approximately half of all sexual- and gender-diverse students of color were bullied or harassed based on their racial/ethnic identity.[48] Further, sexual- and gender-diverse students of color were at greater risk of experiencing multiple forms of victimization and were more likely to feel unsafe at school than their white sexual- and gender-diverse peers.[48]

This mistreatment has a significant effect on sexual- and gender-diverse adolescents' mental health and well-being. Victimization due to sexual orientation or gender expression is associated with depressive symptoms, low self-esteem, and suicidality,[111,275,276] as is not having access to appropriate bathrooms and feeling unsafe in bathrooms and other school facilities.[277,278,279]

Experiences of victimization and discrimination are also linked to negative academic outcomes among sexual- and gender-diverse youth.[184] Victimization from peers and school staff, combined with discriminatory policies, likely contributes to the over-representation of sexual and gender minorities in the juvenile justice system.[48,279] Sexual- and gender-diverse youth of color, particularly girls, are extremely overrepresented among incarcerated youth.[214,279, 280] Research shows that youth of diverse sexual orientation and/or gender identity are not only more likely to experience exclusionary discipline at school, but also appear to be sanctioned more harshly than heterosexual, cisgender teens for the same behavior and are at an increased risk for juvenile justice involvement.[248,281]

School and peer networks can also be a place where youth of diverse sexual orientation and/or gender identity find support. High levels of support from friends, classmates, and school professionals is associated with better mental health and lower suicidality among youth of

School resources that support the health and well-being of youth of diverse sexual orientation and/or gender identity include:

- **The presence of Gender and Sexuality Alliances (GSAs) or other similar supportive peer networks**
- **Antidiscrimination and antibullying policies that explicitly include sexual orientation, gender identity, and gender expression**
- **Policies that allow youth to use their chosen name, pronouns, and facilities that align with their gender identity**
- **Educators who are trained and accept and support students of diverse sexual orientation and/or gender identity**
- **Inclusive curricula resources, such as including the history of people and families with diverse sexual orientation and/or gender identity, and age-appropriate health curricula that discuss sexual orientation and gender identity.[39,43]**

diverse sexual orientation and/or gender identity.[49] Additionally, when youth have access to high levels of peer or school support, this may reduce the negative impact that experiencing victimization has on their mental health.[276] Friends of diverse sexual orientation and/or gender identity may be of particular importance, because they are more likely to provide support for sexuality- and gender-related stress.[282,283] Many youth of diverse sexual orientation and/or gender identity connect with peers and access social support online that may be unavailable to them in person.[284,285] Online sources of support have become increasingly important for youth of diverse sexual orientation and/or gender identity during the COVID-19 pandemic.[286]

School policies and resources that create an inclusive, safe environment positively influence student behavioral health and well-being.[287,288] Specifically, these school policies reduce substance use and planned suicide and suicide attempts.[287] GSA is a student-led, school-based club that aims to provide a safe space for LGBTQI+ students. "GSA" originally referred to "Gay-Straight Alliance," but many GSAs now use the acronym to refer to "Gender and Sexuality Alliance" to acknowledge the full spectrum of sexual orientation and gender diversity.[289]

Both the presence of and participation in a GSA has beneficial outcomes for sexual- and gender-diverse students and others, including increased feelings of safety, lower truancy, and decreased threats of violence in school.[48,287] School policies associated with improved health and well-being of students of diverse sexual orientation and/or gender identity include:

- Antidiscrimination and antibullying policies that enumerate sexual orientation, gender identity, and gender expression
- Policies that allow youth to use facilities that align with their gender identity and/or that provide gender-neutral facilities
- Policies that allow students to use their chosen name and pronouns[278,279]

Training school staff and educators about how to support youth of diverse sexual orientation and/or gender identity is related to lower suicide attempts among these students when provided.[287] Finally, curricula that are inclusive of students and families of diverse sexual orientation and/or gender identity are associated with beneficial outcomes such as fewer

In the most recent National School Climate Survey of LGBTQ+ youth, the Gay, Lesbian & Straight Education Network (GLSEN) found that:

- **60% felt unsafe**
- **69% were verbally harassed**
- **58% were sexually harassed**
- **26% were physically harassed**
- **11% were physically assaulted**
- **45% were cyberbullied**

60% of students of diverse sexual orientation and gender surveyed experienced policies that are discriminatory based on sexual orientation, gender identity, or gender expression at school. Transgender and gender-diverse students were most likely to report incidences with discriminatory policies and practices, including being prevented from using their chosen name and pronouns, and bathrooms and locker rooms aligned with their gender identity.[48]

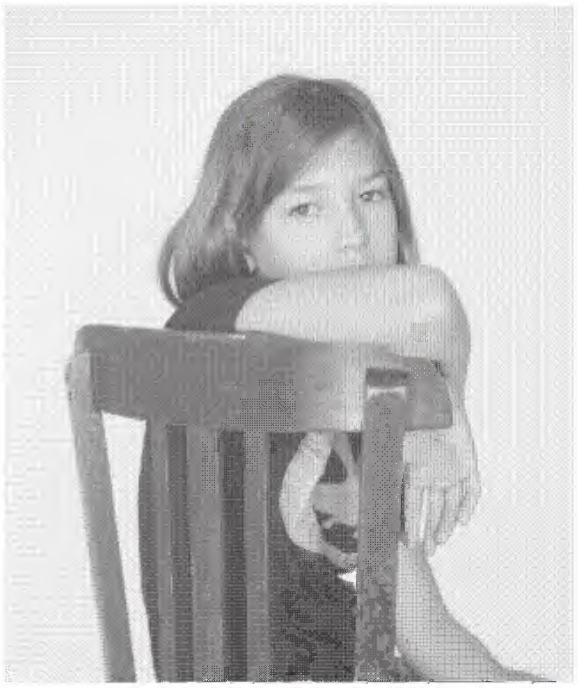
instances of biased language against students of diverse sexual orientation and/or gender identity, students feeling safer, fewer reported instances of victimization, increased peer acceptance, and lower levels of depression; these benefits may be related to the curricula helping to reduce negative stereotypes against LGBTQI+ students.[48] These policies and practices not only are associated with benefits for students of diverse sexual orientation and/or gender identity but also have school-wide beneficial effects across behavioral health and psychosocial outcomes among heterosexual youth.[287]

Community Climate & Policies

Community climate and policies also have an impact on the health and well-being of youth of diverse sexual orientation and/or gender identity. Community climate—defined by the presence or absence of supportive policies, places of worship that are open and inclusive, other LGBTQI+ people, and anti-LGBTQI+ rhetoric—is associated with behavioral health outcomes among LGBTQI+ adolescents. Studies have found that adolescents of diverse sexual orientation and/or gender identity living in areas with a more supportive community climate have better mental health and are less likely to use substances.[290,291]

State and federal laws and policies also affect the health and well-being of sexual- and gender-diverse populations, including youth.[292] More research has been conducted with adults, where supportive and protective policies—such as protection from discrimination in schools and ability to change name and gender on identity documents—have consistently been linked with

better mental health, reduced substance use, and increased access to health care.[205,293,294] Meanwhile, policies that permit discrimination against people of diverse sexual orientation and/or gender identity are linked with poorer behavioral health outcomes.[85] It appears that state and federal laws and policies have a similar effect on youth of diverse sexual orientation and/or gender identity, with the presence of supportive laws and policies associated with reduced suicidality among high school students.[295,296]



Gender Affirmation

In addition to benefiting from gender-affirming support from families, communities, peers, and school professionals as described above, taking desired steps in social transition and access to medical gender transition for those for whom it is medically necessary is associated with better mental health among transgender and gender-diverse youth.[51,67,80,81,155,226,297,298,299,300,301,302,303]

Social transition and medical gender transition are discussed in greater detail in the next section. Improving access to gender affirmation for gender-diverse youth across the various domains of their lives may reduce the mental health inequities seen in this population.

Beneficial Therapeutic Approaches and Interventions in LGBTQI+ Youth and Their Families

Behavioral health professionals provide youth and their families with developmentally sensitive, culturally appropriate, and client-centered interventions that emphasize acceptance, support, and understanding and that match the child and adolescent's cognitive and emotional development.

Appropriate therapeutic approaches with LGBTQI+ youth do the following:

- Provide accurate information on sexual orientation and gender identity and expression.
- Identify sources of distress, including internalized stigma and minority stress, and work with children, adolescents and families to reduce distress experienced by children and adolescents.
- Support adaptive coping to improve psychological well-being.
- Support youth as they learn more about their sexual orientation and gender identity, and supporting families in accessing gender-affirming care for their transgender child when indicated.
- Help children and adolescents navigate their sexual orientation, gender identity, and gender expression within the context of their intersecting identities.

Client-Centered Individual Approaches

Behavioral health providers offer developmentally sensitive, affirmative interventions to youth. Developmentally sensitive approaches account for appropriate developmental emotional and cognitive

capacities, developmental milestones, and emerging or existing behavioral health concerns.

Affirmative approaches recognize and communicate that being of diverse sexual orientation and/or gender identity does not constitute a mental disorder, and that variations in sexual orientation, gender identity, gender expression, and sex characteristics are normal aspects of human diversity, including nonbinary gender identities.[75,304,305,306] Affirmative approaches recognize that when behavioral health issues exist, they often stem from stigma and negative experiences rather than being intrinsic to the child or adolescent.[76] When working with children and adolescents, providers examine not only risk factors but also sources of resilience across the multiple environments that influence the health and well-being of young people.[306]

Effective approaches support youth in identity exploration and development without seeking predetermined outcomes related to sexual orientation, gender identity, or gender expression.[189,305] Key aims are to dispel negative stereotypes and provide accurate information in developmentally appropriate terms for children and adolescents.

Scientists and researchers are constantly discovering more about sexual orientation, gender identity, and expression. For some youth, a focus on identity development and

exploration that allows them the freedom of self-discovery within a context of acceptance and support is vital to improving behavioral health and well-being.[307] It is important to note, however, that identity exploration is not relevant or needed by all youth or a required focus of therapy for youth of diverse sexual orientation and/or gender identity. Additionally, it is important for behavioral health providers to respect what the identity exploration process looks like to each individual. Taking steps in social transition is one way for gender-diverse youth to explore their gender (see "Social Transition" section below).

Practices that attempt to change or prevent youth from identifying as sexual- and gender-diverse or from expressing their sexual orientation and gender identity are harmful and are never appropriate.[10,307] This includes approaches that discourage youth from identifying as transgender or gender-diverse and/or from expressing their gender identity. Sometimes these are misleadingly referred to as "exploratory therapy." Additionally, providers support youth in age-appropriate tasks, such as integrating sexual orientation and gender identities with other identities, safely navigating coming out or sharing their identities with others, and fostering positive relationships with caregivers, families, and peers.[79,307]

Exposure to laws and policies that do not support youth of diverse sexual orientation and/or gender identity, and other negative experiences, including bullying and family rejection, drive risk for certain behavioral health concerns among these youth.[55,308,309] Behavioral health providers should assess for ACEs, other family rejecting behaviors, additional experiences of victimization, trauma-related disorders, and suicidality, and be prepared to address these concerns with LGBTQI+ youth in treatment. Appropriate interventions may aim to reduce or remove stressors a child or adolescent is experiencing that are associated with poor behavioral health. Alternatively, interventions may aim to change the cognitive, affective, and behavioral ways that youth of diverse sexual orientation and/or gender identity react to these stressors.[214]

Several cognitive behavioral therapy (CBT) interventions for youth of diverse sexual orientation and/or gender identity have been developed, including EQuIP,[310] AFFIRM,[311] and Rainbow SPARX.[312] LGBTQ-affirmative CBT appears to be particularly efficacious for Black, Latino, and Asian American and Pacific Islander young people of diverse sexual orientation and/or gender identity, potentially because the focus on stressors may also help young people of color navigate stressors related to being a racial/ethnic minority.[214,313] There is also evidence supporting the use of mindfulness-based coping for sexual orientation-related school-based victimization.[314] Evidence-based trauma-focused interventions designed for youth of diverse sexual orientation and/or gender identity and their families can reduce symptoms of past trauma and enhance coping and well-being.[315]

Behavioral health providers should be aware of and share crisis services specific to LGBTQI+ youth, local resources for LGBTQI+ youth, and online platforms where LGBTQI+ youth can find affirming social connections and support. Given the increased rates of suicidality seen among youth of diverse sexual orientation and/or gender identity, LGBTQI+ crisis services, such as those provided by The Trevor Project are vital. The Trevor Project offers direct suicide and crisis intervention services for LGBTQI+ youth by phone, text, or online chat.[214,316]

Behavioral health providers should be aware of available community resources that support LGBTQI+ youth and their families, such as local

LGBTQI+ community centers, GSAs in schools, and support groups for youth and/or their caregivers, as well as online platforms. In addition to crisis services, The Trevor Project provides a safe social-networking community for LGBTQI+ youth and their friends and allies. This online platform became even more critical during the pandemic because it allowed youth to find affirming connections even when physically isolated. PFLAG, which is the largest organization in the United States focused on providing support, education, and advocacy for LGBTQI+ people and their loved ones and has more than 325,000 members with hundreds of local chapters. PFLAG can serve as another resource of support for LGBTQI+ youth and their families.[317]

Behavioral health providers should describe their treatment plan and interventions to children, adolescents, and their parents and families to ensure they understand the goals, potential benefits, and any risks of treatment. Behavioral health providers should obtain informed consent with all parties—including minors—for treatment, and should always involve parents and caregivers in decisions about a minor's care if the minor is not old enough to legally give consent.[318] When obtaining informed consent/assent, it is important to be aware of and attend to power dynamics between parents/caregivers and youth, as well as between the provider and youth. Interventions that attempt to change sexual orientation, gender identity, or gender expression, or any other form of SOGI change efforts are inappropriate and can cause significant harm. Informed consent/assent for clinical care would include ensuring understanding of various components, including associated risks, expected benefits, and alternative treatment options; therefore, by definition, informed consent/assent cannot be provided for an intervention known to cause

significant harm and does not have any known benefit to the client.[319]

Family Approaches

Wherever it is safe to do so for the child, parental and caregiver involvement is an important part of supporting LGBTQI+ youth. Parental and caregiver attitudes and behaviors play a significant role in the adjustment of children and adolescents. Parent and caregiver distress may be the cause of a referral for treatment.[24,102,258] Reducing family rejection, hostility, and violence (verbal or physical), and increasing family acceptance and support, contributes to the mental health and safety of the child and adolescent.[53,102,258,320]

Interventions that increase family and community support and understanding while decreasing rejection directed at LGBTQI+ youth are recommended for families. Behavioral health providers supply family members with accurate, developmentally appropriate information regarding diversity in sexual orientation and gender, and strive to dispel myths regarding the lives, health, and psychological well-being of individuals of diverse sexual orientation and/or

gender identity.[304,307] Family therapy that provides anticipatory guidance to parents and caregivers about the significant mental health risks caused by rejection of their child's sexual orientation and gender identity is vital.[102,258] Understanding and addressing parent and caregiver concerns regarding current or future sexual orientation and gender identity is important. Further, behavioral health providers can attempt to help families and caregivers modify rejecting behaviors by explaining the link between family rejection and negative health problems, identifying rejecting and accepting behaviors, and providing recommendations for increasing supportive behaviors on the part of the family.

Some affirming approaches to family therapy that include youth of diverse sexual orientation and/or gender identity aim to demonstrate how family members' identities—such as their race and ethnicity, immigration, socioeconomic status, and more—affect their ability to understand and support their youth.[321,322] Attachment-based approaches to family therapy have been used with suicidal sexual minority adolescents.[323] Trauma-focused CBT is an evidence-based treatment for trauma-impacted youth aged 3 to 17 and their parents or primary caregivers. This intervention has been adapted for use specifically with youth of diverse sexual orientation and/or gender identity by integrating the treatment framework with the Family Acceptance Project.[315]

Family therapists and researchers often focus on reframing family concerns—even their disapproval and rejection of sexual orientation and gender diversity—as a manifestation of care and love and focus on teaching non-rejecting ways to communicate those positive emotions. For example, providers can help the family create an atmosphere of mutual respect as a natural extension of seeing each person as having intrinsic worth.[324] This can help ensure the safety of each person from being hurt or bullied in the home. This communicates an important message to a young person that their safety is important to the provider and to the family. Eventually, this mutual respect and

support can be extended to other settings, such as neighborhoods, community institutions, and schools. Safety in this context is not only physical safety, but also emotional safety.[324]

Behavioral health providers may wish to increase their own competence in working with communities with diverse values and beliefs, and focus on viewing these values and beliefs with humility and mutual respect.[325] This includes understanding how to translate between psychology and deeply held values rather than judging those beliefs. Certain language, such as acceptance and/or affirmation, might not resonate with some communities, whereas the concept of unconditional love might.[324]

Many parents and caregivers must also navigate their own process of "coming out" and resolve fears of discrimination or negative social reactions if they disclose their child's sexual- and gender-diverse identity within their communities, at work, and to other family members.[326] Parents and caregivers often have fears for their child's emotional and physical safety, among other worries for their future.[37,327] Behavioral health providers can help parents plan in an affirmative way for the unique life challenges that they may face as parents of an LGBTQI+ child.

Further, behavioral health providers can address other stresses, such as managing life celebrations and transitions and coping with feelings of loss, and aid parents in advocating for their children in school situations—for example, when they face bullying or harassment. Groups for multiple families led by behavioral health providers, as well as online groups or forums for parents and caregivers of LGBTQI+ children and adolescents, may be helpful to build connections and share resources.[328]

Additional Approaches With Gender-Diverse Youth

Social Transition

Social gender transition refers to living daily life in line with one's gender identity, and the processes by which a child or adolescent is acknowledged by others as this gender.[39,40] Social transition can include a range of gender-related changes that individuals may make, and often includes adopting a name, pronouns, and clothing consistent with one's gender identity.[35,39,40] There is no one way or right way to socially transition. Transgender and gender-diverse youth may seek out social transition at different ages and stages of development.[34] Social gender transition does not require assessment or intervention from health professionals. However, providers can help families protect children's safety, ensure emotional, psychological, and social well-being, and help children and families navigate possible complexities of exploring and taking steps in social transition.[80]

Taking steps in social transition allows youth the ability to explore and make meaning of how they experience their gender, which is an important

Gender affirmation, including social transition (e.g., changing one's name, pronoun, and/or appearance) and gender-affirming medical care, is appropriate and beneficial for many gender minority children and adolescents. Based on the individual child's or adolescent's needs, gender-affirming medical care may be medically necessary. Withholding timely gender-affirming care when indicated, withholding support for a gender-affirming exploratory process, and/or withholding support of social transition when desired, can be harmful. These actions may exacerbate and prolong gender dysphoria.

part of developing a positive identity and sense of self. For some youth, desires for their name, pronouns, and appearance continue to change and evolve over time; for others, these remain stable over time.[35,39,40] For gender-diverse children who want to socially transition, social transition appears to serve a protective function and contribute to positive mental health and well-being.[51,67,78,229]

Given this, experts increasingly agree that children should not be denied the opportunity to explore and/or express their gender through social transition steps when desired by the child.[75,185,186,329] The possibility that a children's gender identity can be dynamic and may change over time should not be used as a justification to restrict a child from taking social transition steps. Children should be affirmed in how they currently identify and express their gender and be supported throughout their development and exploratory process, including the potential for future changes in how they identify and express their gender.[180,185,186] Behavioral health specialists in pediatric gender care can offer psychosocial support, insights, and guidance regarding the appropriateness of gender-related needs of gender-diverse children at different developmental stages.[25]

Withholding support for a gender-affirming exploratory process and/or for social transition when desired, can be harmful because those actions may exacerbate and prolong gender dysphoria.[78,299,329] At the same time, parents and caregivers may have valid concerns about reactions from others, including bullying and safety. When weighing factors related to social gender transition, concerns related to social transition should be weighed against the risks of not affirming a child's experienced gender, including increased distress or feelings of dysphoria, social isolation, depression, or suicide due to lack of social support.[29] Whether or not a child socially transitions or desires to, behavioral health providers can help explain to parents and caregivers how gender development is dynamic for some but not all children and highlight the importance of being open to and accepting of the possibility that their youth may remain stable in their feelings or may desire to make changes again in the future.[305]

Medical Gender Transition

Gender-affirming medical care is often medically necessary for individuals with a diagnosis of gender dysphoria, and can refer to a range of evidence-based interventions provided in consultation with licensed medical providers. Such care is defined here as a care plan or service that is necessary to assess, maintain, or improve health and well-being and to avoid illness or reduce symptoms based on existing professional guidelines and scientific evidence. The appropriateness of medical interventions varies by the individual's age, developmental stage, and experience of dysphoria, and decisions about providing gender-affirming care are reached with the involvement of an adolescent's parent or legal guardian.[332] No medical interventions are currently undertaken

Gender-Affirming Care: A specialized model of care used in the treatment of gender dysphoria that uses evidence-informed treatment options to promote patient health and prevent the risk of poor mental and physical health outcomes.[330,331] Not all youth need to undergo medical intervention; indeed, this is often not the case. Gender-affirming care is highly individualized and focuses on the needs of each individual by including psychoeducation about gender and sexuality (appropriate to the age and developmental level).

or recommended for gender-diverse children before the initial onset of puberty.[74,75] Gender-affirming medical care, including both pubertal suppression and hormone therapy, has proven effective in improving the well-being of young transgender and gender-diverse adolescents both during and well after initiation of treatment.[81,82,156,296,297,298,299,300,302,303,333]

Recent research indicates that gender-affirming care has a positive impact on mental health. Current professional guidelines provide information on the appropriate application of gender-affirming care interventions.[25] It is widely held that withholding gender-affirming care for an adolescent who needs this care is detrimental to their mental health.[77,186] Withholding timely gender-affirming care when indicated may cause harm by exacerbating and prolonging gender dysphoria.[83,84]

Behavioral health providers play an important role in educating adolescents and their parents, caregivers, and supporting families on this information as well as in assessing their understanding so that they can give full informed consent and assent.[187,334] This education includes information on:

- Various options for medical gender transition
- Up-to-date information about the effects of treatment
- Benefits on well-being
- Potential side effects

The support of a behavioral health provider during these processes can aid adolescents in identifying care needs, adjusting to their changing physical characteristics, and navigating responses from people in different aspects of their lives. Continued mental health care should be offered when an adolescent's gender care needs require continued affirming exploration and/or when other psychological, psychiatric or family problems exist. Given that pubertal suppression or administration of hormone therapy occurs over many years during important developmental periods, the need for behavioral health care, and type of behavioral health intervention needed, may change with time as new questions arise.[335] Transgender and gender-diverse youth, like all youth, should have the option to access psychological treatment if they choose. However, if there are no concerns, this may not be necessary.

For additional information and guidance related to youth and medical gender transition, see "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents" from the American Academy of Pediatrics[76] and the most recent guidelines from the World Professional Association on Transgender Health (WPATH; www.wpath.org).[25]

Future Directions for Research

As recommended by the U.S. Surgeon General in the 2021 report *Protecting Youth Mental Health*, future research must prioritize data and research with youth populations who are at-risk for adverse mental health outcomes.[336] This includes LGBTQI+ youth broadly, as well as LGBTQI+ youth who are also racial/ethnic minorities, have experienced poverty during childhood, have disabilities/different abilities, and are involved in child welfare or juvenile justice systems. Areas of opportunity for future research, as well as the validity and quality of existing research, are discussed in several sections of this report. Methodologically rigorous peer-reviewed research is vital to improving our understanding of the complexities of sexual orientation and gender among children and adolescents. Several potential areas for future research are identified below.

Documenting Sexual Orientation and Gender Diversity in Youth

To better understand the experiences and needs of LGBTQI+ youth, research focused on youth in the general population should regularly assess sexual orientation, gender identity, and gender expression as demographic indicators. Given the expansive range of descriptive identity terms that people today use to describe their sexual orientation and gender (e.g., pansexual, asexual, nonbinary, gender queer), asking about sexual orientation and gender in ways that include these identities and provide an option for open-ended responses will ensure that LGBTQI+ youth are appropriately included and represented in research.

Development of Sexual Orientation and Gender Identity

There remains much to learn about the development of sexual orientation and gender identity in youth. Basic research on the developmental pathways of these identities is necessary. How these identities are embedded in cognitive and emotional development and other developmental processes would aid in the understanding of human development as well as developing and refining appropriate interventions to support behavioral health. Such research must be inclusive of nonbinary identities. To better understand the various developmental trajectories of gender-diverse youth, prospective, longitudinal studies that follow gender-related development of youth over time are needed.

Culturally Specific Mitigation of Distress Relating to Sexual Orientation, Gender Identity, and Gender Expression

SOGI change efforts are harmful practices that are never appropriate with LGBTQI+ youth, and efforts are needed to end these practices. Families experiencing conflict related to their youth's sexual orientation, gender identity, and gender expression need access to alternative interventions to mitigate this distress that are appropriate and beneficial for youth and families. More targeted research that acknowledges the intersections of identity, including race, ethnicity, culture, faith, and socioeconomic status could shed light on positive, appropriate, whole-family therapeutic approaches to addressing these issues.

Researchers should evaluate these practices and integrate them into behavioral health care. Researchers should also work collaboratively with young people and families from faith communities to better understand the interplay between values and traditions and the safety and well-being of LGBTQI+ youth. The work of the Family Acceptance Project, cited in this report, speaks to the necessity of an increased focus on approaches specific to various communities, including those that are culturally and religiously diverse. These include conversations about sexual orientation, gender identity, and gender expression and how to support LGBTQI+ youth in culturally congruent ways.

Addressing Health Inequities Within LGBTQI+ Youth Populations

LGBTQI+ youth experiencing homelessness, in juvenile justice facilities, or otherwise in out-of-home care may lack permanent and stable family connections in part because of family distress or rejection relating to their LGBTQI+ identity. These vulnerable populations, as well as low-income and racial and ethnic minority LGBTQI+ youth, are often neglected in research studies that most often recruit youth who are already connected to clinics or providers. Future researchers interested in research with sexual- and gender-diverse youth should address this need for more representative sampling and better recruitment efforts.

Building Resilience and Promoting Health and Well-Being

Beyond ending harmful practices with LGBTQI+ youth and addressing health inequities, more research is needed that focuses on the ways LGBTQI+ youth are thriving. Greater understanding is needed of the factors that contribute to resilience and positive behavioral and physical health outcomes among LGBTQI+ youth, as is an increased focus on the development, evaluation, and dissemination of health-promoting interventions. Research using participatory methodologies to collaborate with LGBTQI+ youth to identify their needs, priorities, and ideas for intervention strategies is vital to increase the relevance, quality, and impact of research and interventions with this population.

Long-Term Outcomes

More research would be beneficial to further explore the developmental trajectories of sexual orientation, gender identity, and gender expression. Additionally, future research could focus on better understanding the long-term medical and behavioral health outcomes associated with early experiences of family and community distress due to sexual orientation and gender identity and expression. Other recommended areas of opportunity for longitudinal research include:

- Long-term outcomes from early social transition and pubertal suppression
- Rigorous evaluation of current practices and protocols, including affirmative models, structural interventions, and culturally specific models
- Harms associated with laws and policies that bar youth from participating at school or in extracurricular activities in a way that is consistent with their gender identity
- Prospective research focusing on younger children, in partnership with pediatric clinics, schools, and other community-based institutions
- Methods of supporting positive behavioral health for LGBTQI+ youth, including building resiliency against suicidality, self-harm, risky behaviors, depression, anxiety, substance use, and other behavioral health issues

Integration, Collaboration, and Dissemination

Researchers and clinicians should examine and evaluate the best methods for integrating and disseminating best and promising practices for addressing sexual orientation and gender identity and expression among youth, and how to successfully collaborate with parents, guardians, caregivers, providers, and community leaders. This could include conducting research with these populations focused on knowledge, attitudes, and beliefs relating to efforts to change sexual orientation, gender identity, or gender expression.

Finally, the behavioral health community can work to support community-based organizations to develop common ground and consensus on these topics to promote health and well-being within youth populations. This might include:

- Support for LGBTQI+ youth programming and services across the country
- Outreach to parents, caregivers, and families with accurate information about supporting LGBTQI+ youth's behavioral health
- Inclusion of LGBTQI+-specific questions in national behavioral and mental health surveys

Section 3: Policy Approaches to Support the Behavioral Health and Well-Being of LGBTQI+ Youth

Introduction and Foundational Principles[1]

Moving from evidence to action necessitates scientifically grounded public policies. This section focuses on selected policy levers that aim to improve the behavioral health of LGBTQI+ youth.

U.S. Department of Health and Human Services (HHS) policy priorities for improving the mental health of and reducing substance use by LGBTQI+ youth are based on efforts to ensure LGBTQI+ civil rights and to increase access to, affordability of, and equity in health care. Such policies include implementation of the June 15, 2022, Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals,[14] the January 20, 2021, Executive Order on Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation,[15] and the January 20, 2021, Executive Order on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government.[337]

HHS policies include protection against discrimination based on sexual orientation and gender identity as found in the Affordable Care Act (ACA).[338] HHS also has other policies and programs specific to nondiscrimination on the basis of sexual orientation and gender identity.[339,340] For example, HHS issued a Notice of Proposed Rulemaking related to Section 1557 of the ACA, to further prevent discrimination on the basis of sexual orientation and gender identity.[341]

To further strengthen protections for LGBTQI+ youth, their parents, and caregivers, on March 2, 2022, HHS Secretary Xavier Becerra issued a statement reaffirming HHS efforts to support and protect LGBTQI+ youth and assist their parents, caretakers, and families in accessing gender affirming care.[342]

SOGI change efforts are inappropriate practices that should not be provided to children or adolescents.

A Memorandum issued by the Children's Bureau at the Administration for Children and Families for child welfare professionals and healthcare providers aims to protect LGBTQI+ youth.[343] HHS has also issued guidance stating that denying health care based on gender identity or restricting doctors and healthcare providers from providing care because of a patient's gender identity may constitute prohibited discrimination.[344]

The following key policy areas have been identified by the federal government, researchers, and advocates:

- End harmful and ineffective efforts such as sexual orientation and gender identity (SOGI) change efforts.
- Ensure access to evidence-based care.
- Promote behavioral health by strengthening nondiscrimination policies.

[1] All statements in text boxes are Consensus Statements provided in Section 1 of this document.

- Improve behavioral health through support from families, schools, and communities.
- Advance research that improves care.

Ending Sexual Orientation and Gender Identity Change Efforts

SOGI change efforts are ineffective and harmful to children and adolescents (see Sections 1 and 2). The continued practice of these efforts puts LGBTQI+ youth at risk of significant harm and prevents them and their families from receiving appropriate evidenced-based behavioral health care that is consistent with existing professional guidelines.

Based on scientific evidence and broad professional and scientific consensus, many federal, state, and local governments have taken steps to regulate and eliminate the practice of SOGI change efforts directed at children and adolescents. These efforts include legislative bans, executive orders, and pathways to civil court claims alleging consumer fraud, among others.

Several bills and resolutions have been introduced in Congress in the past decade to discourage SOGI change efforts or to require nondiscrimination in the provision of behavioral health services to sexual- and gender-diverse youth. This legislation would ban federal funding, encourage state bans, or define SOGI change efforts as consumer fraud.

On June 15, 2022, the Biden Administration issued the Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals.[14] It includes a charge to HHS to take steps to end SOGI change efforts in the United States, by exploring guidance for federally funded programs, supporting provider training and technical assistance, and providing public information about harms and alternatives.

At the state level, as of January 2023, 20 states and the District of Columbia have passed laws to protect minors from the practice of SOGI change efforts. An additional six states and one territory have partial bans.[345] These laws bar behavioral health providers from practicing SOGI change efforts with minors. Some states provide protections for vulnerable adults, impose restrictions on the use of state and federal funds, and offer consumer protection provisions. At the local level, about 90 municipal and county governments prohibit SOGI change efforts.[346]

Advocates have suggested federal, state, and local policy efforts to end SOGI change efforts that include the following:

- Legislative restrictions on the use of federal or state funding for SOGI change efforts by state health programs (including Medicaid funds), by recipients

of such funding, or through health insurance reimbursements (see for example, H.R. 2328, "Prohibition of Medicaid Funding for Conversion Therapy Act" from the 117th Congress).[347]

- Policies that prohibit SOGI change efforts with minors receiving care in programs that receive federal funds to serve youth, such as community mental health centers, and juvenile justice, child welfare, and foster care programs.
- Clarification that existing nondiscrimination policies prohibit the practice of SOGI change efforts with minors. These legal claims of discrimination have been based on the theory that providing this ineffective and harmful therapy is due solely to an individual's sexual orientation or gender identity.

In addition to federal and state legislative and regulatory action, consumer protection laws have been suggested as a mechanism for ending the use of SOGI change efforts. This strategy extends beyond prohibiting change efforts by behavioral health professionals to affect any commercial act (for a fee), including those by unlicensed practitioners and groups.

These efforts derive from a civil action in which a New Jersey court ruled in 2015 that an organization's sexual orientation change efforts program violated the state's consumer fraud law through multiple misrepresentations.[348] The Court ruled as a matter of law that scientific evidence demonstrated that being gay, lesbian, or bisexual was not a mental disease or disorder and could not be changed. Thus, the Court found that a fraudulent misrepresentation was made every time an individual accepts payment for sexual orientation change efforts because being gay, lesbian, or bisexual is not a disease and cannot be "cured." The Court awarded the plaintiffs financial compensation and prohibited the organization from providing sexual orientation change efforts.[348]

Available research indicates SOGI change efforts can cause significant harm. Available research indicates that these efforts are not effective in altering sexual orientation; no available research indicates that they are effective in altering gender identity. No available research supports the claim that SOGI change efforts are beneficial to children, adolescents, or families.

Efforts to protect consumers through consumer protection laws have been taken at the federal and state levels. At the federal level, the Biden Administration is encouraging the Federal Trade Commission (FTC) to consider whether SOGI change efforts are an unfair and deceptive practice and whether to issue consumer warnings or notices. Additionally, in the 117th Congress, bills were introduced that define SOGI change efforts as unfair or deceptive acts or practices under the jurisdiction of the FTC Act (Therapeutic Fraud Prevention Act of 2021; HR.4146 and S.2242). Some advocates believe that the FTC can act even without new legislation. In 2016, a complaint was filed with the FTC alleging fraudulent misrepresentation by a group that advertises change efforts.[349,350]

At the state level, Illinois passed a ban on SOGI change efforts with minors (Illinois Public Act 099-0411).[351] The law specifies that advertisements for sexual orientation change efforts that represent being gay, lesbian, or bisexual as a disease or disorder for minors and adults is a violation of the state's consumer fraud and deceptive business act. As of January 1,

2023, jurisdictions banning SOGI change efforts with minors included California, Colorado, Connecticut, Delaware, District of Columbia, Hawaii, Illinois, Maine, Maryland, Massachusetts, Nevada, New Hampshire, New Jersey, New Mexico, New York, Oregon, Rhode Island, Utah, Vermont, Virginia, and Washington. Additionally, jurisdictions with partial bans on SOGI change efforts included Michigan, Minnesota, North Carolina, North Dakota, Pennsylvania, Puerto Rico, and Wisconsin.[345]

Ensuring Access to Evidence-based Care

Beyond ending harmful practices such as SOGI change efforts, it is vital that LGBTQI+ youth have access to evidence-based care. Removing limits to appropriate care is multifaceted and may vary based on multiple factors, including other health inequities such as those based on income and race/ethnicity, among others. Policy levers to improve access include:

- Preventing bans on gender-affirming care
- Improving access to gender-affirming care in health plan benefits across all payors
- Ensuring LGBTQI+ youth can access appropriate care and support in child welfare programs
- Increasing professional training and education to improve access to and quality of behavioral health care especially for gender-diverse and transgender youth

Preventing Bans on Gender-Affirming Care

Gender-affirming care is supported by extensive research, and based on the individual child's or adolescent's needs, may be medically necessary. Evidence has demonstrated mental health benefits associated with receipt of gender-affirming care, such as reduced depression and decreased risk for suicide. Withholding timely gender-affirming care when indicated, withholding support for a gender-affirming exploratory process, and/or withholding support for social transition when desired can be harmful.[25,352,353,354] However, some states have introduced or passed laws that ban access to this medically necessary care.[107,355]

Policies that seek to categorically ban gender-affirming medical care or penalize providers, parents, and caregivers who provide or seek gender-affirming medical care pose serious risks.[353,354] Prohibitions on or penalties for providing or seeking out medically necessary and therapeutically indicated best practices place behavioral health and medical providers and parents and caregivers in situations that conflict with evidence-based professional guidelines, ethics, and standards.[354] Lack of access to such care poses serious behavioral health risks to youth of diverse sexual

Groups that have stated opposition to policies that limit access to or ban appropriate gender-affirming care include American Academy of Child and Adolescent Psychiatry, American Academy of Family Physicians, American Academy of Pediatrics, American College of Obstetricians and Gynecologists, American College of Physicians, American Medical Association, American Osteopathic Association, American Psychiatric Association, American Psychological Association, Endocrine Society and Pediatric Endocrine Society, U.S. Professional Association for Transgender Health, and World Professional Association for Transgender Health.[106,356,361]

orientation and/or gender identity and their families, parents, and caregivers, such as an increased risk of suicidal ideation, depression, and trauma.[107,343,353,354,356]

As noted above, the Biden Administration has taken multiple steps to improve behavioral health care by ensuring access to medically necessary and evidence-based care for LGBTQI+ youth. This includes policies to address state restrictions in such care. For example, the June 15, 2022, Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals includes a charge to HHS to ensure that LGBTQI+ youth and their families have access to medically necessary care including mental health care, consistent with applicable law.[14]

HHS has taken steps to maintain access to evidence-based care, especially for transgender youth. HHS has provided child welfare professionals, healthcare providers, and states and localities with information on the federal protections that exist to ensure that civil rights are protected and LGBTQI+ youth receive medically necessary and evidence-based care.[343,344]

As an example of efforts to maintain access to evidence-based care, the U.S. Department of Justice (DOJ) intervened in a federal lawsuit challenging a recently enacted Alabama law, Senate Bill (S.B.) 184, that makes it a felony to cause or provide gender-affirming care to transgender youth under the age of 19.[357,358] In May 2022, the court issued a preliminary injunction preventing the law from being enforced Additionally, the DOJ filed a statement of interest and amicus brief in a case challenging an Arkansas law banning gender-affirming care.[357,359]

State bans on gender-affirming care are unlike laws banning SOGI change efforts. Legal bans on SOGI change efforts are consistent with existing professional guidelines and resolutions and prohibit potentially harmful efforts while permitting behavioral health providers to deliver evidence-based care to LGBTQI+ youth. Numerous professional associations and experts have spoken out against laws or other government actions that limit access to, penalize, or ban appropriate gender-affirming care (see text box).

Improving Access to Behavioral Health and Gender-Affirming Care

LGBTQI+ youth and adults face serious barriers to accessing behavioral health care as well as gender-affirming care. Access to care is especially limited for gender-diverse youth and their families who seek gender-affirming care.[360] The Federal Government and many states have taken steps to reduce barriers to gender-affirming care, improve behavioral health equity, and reduce healthcare discrimination. Several federal and state laws have been interpreted to or expressly prohibit insurance discrimination based on SOGI.

The Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals makes family counseling and support of LGBTQI+ youth a public health priority.[14] This Executive Order charges HHS to seek ways to increase the availability of such family counseling and support programs in federally funded, human services, and child welfare programs among other actions.

Aligned with the Executive Order on Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation,[15] HHS issued a Notice of Proposed Rulemaking in July 2022 related to Section 1557 of the ACA, which prohibits discrimination on the basis of race, color, national origin, sex, disability, or age in

certain health programs and activities. The Proposed Rulemaking would codify protections against discrimination on the basis of sex as including discrimination on the basis of sexual orientation and gender identity, which is consistent with the Supreme Court's decision in *Bostock*.[341] This type of federal policy addressing sex, sexual orientation, and gender identity nondiscrimination can help mitigate gaps in state protections.

Almost half of all states prohibit the exclusion of gender-affirming care by private health insurance plans subject to state oversight.[362] Other state laws include protections against discrimination in private health insurance by expressly prohibiting discrimination based on sexual orientation and gender identity.[362,363,364] Experts have also suggested that states and localities provide such benefits to their own employees and dependents and, while almost half have such protections, many do not.[365]

Research on health coverage in private insurance and federal and state health financed programs indicates that youth and adults might not have access to comprehensive gender-affirming care or in-network providers with LGBTQI+ expertise.[247,360,362,363,364,366,367,368,369,370] Consequently, experts have suggested that legislative and regulatory steps be taken to ensure that all such plans reimburse medically necessary treatment for LGBTQI+ individuals of all ages, including gender-affirming care.[365,370]

One way to improve treatment options is through state initiatives, such as explicitly including gender-affirming care as a covered service in the state's benchmark plan in individual and small group market plans. In 2021, the Centers for Medicare & Medicaid Services (CMS) approved Colorado's expansion of the Essential Health Benefit (EHB) benchmark plan that aims to improve access for client-centered gender-affirming care.[368] This change to the EHB benchmark plan aims to expand access to a wider range of services for transgender individuals in addition to benefits already covered. The state is also expanding covered services in the state benchmark plan to include mental wellness exams, which will help all individuals not only those who are LGBTQI+.[369]

Training and Education to Improve Care

A key priority is to expand the number of behavioral health providers who have the expertise to work with LGBTQI+ children, youth, and their families. Research indicates that only a small percentage of gender-diverse youth seeking transition medical services receive them as minors.[366] One aspect of this problem is the lack of behavioral health providers with training and expertise in this area.

Federal Government initiatives have expanded education and training opportunities and the June 15, 2022, Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals charges HHS with providing training and technical assistance in promising evidenced-based care, including mental health care.[14] The SAMHSA Center of Excellence on LGBTQ+ Behavioral Health Equity provides training and consultation for a variety of behavioral health providers.[371] Scientific associations have developed resources and practice guidelines on treatment of LGBTQI+ children, adolescents, and adults that are useful for professional education and practice (see Appendix C).

Several training programs offer education to a wide variety of providers working with LGBTQI+ youth and their families.[371] These trainings can continue to be expanded to improve professional competence in providing services to this population. For example, APA Division 17 (Counseling Psychology) Special Task Group Making Room at the Table: Trans/Nonbinary Pipeline to Counseling Psychology developed "*A Resource for Incorporating Trans and Gender-Diverse Issues in Counseling Psychology Curricula*."[372]

National and state professional associations, including HHS grantees, also maintain webpages with training information on LGBTQI+ issues, including postgraduate and peer education resources.[372,373] Such programs could also expand specialty workforce training opportunities in pediatric and LGBTQI+ concerns across the professional lifecycle from graduate student to seasoned practitioner.

Given the diversity within children, adolescents, and their families, trainings that recognize differences in culture, ethnicity, geography, race, and other factors are critical for effective behavioral health treatment. Increasing cultural responsiveness is especially important to address unique stressors and behavioral health inequities within the sexual- and gender-diverse community, especially in communities of color.[199,374]

Behavioral health providers with competence in the related aspects of religion, spirituality, and sexual- and gender-diverse issues could assist families and individuals in reducing identity and family conflicts that can arise.[374,375,376,377,378,379,380,381] Linkages among community institutions, professional and scientific groups, behavioral health providers, and LGBTQI+ groups that are respectful and open can improve therapeutic services for LGBTQI+ youth and families. One possibility includes collaborations among behavioral health and community leaders and professionals in gender-affirming care to increase understanding about clients from a variety of cultural traditions.[382] Providing education in universities and educational facilities attuned to diverse communities may be a start to initiating dialogue and improving care. Some success has been achieved with dialogues seeking common ground between scientists and such groups rooted in common goals such as child health and optimal child development.[382,383]

Improving Behavioral Health through Antidiscrimination Policies

Youth of diverse sexual orientation and/or gender identity are negatively affected by policies that sanction or sustain discrimination based on sexual orientation and gender identity,[2] even increasing the risk of suicide,[59,292] Although stigma and discrimination can lead to behavioral health concerns, poor behavioral health is not inherent to sexual and gender minorities. Additionally, exposure to school-based bullying and exclusion based on sexual- and gender-diverse prejudice has an adverse impact on the behavioral health of school-aged

Policies that stigmatize, restrict, or exclude gender minority youth are harmful to children and adolescents.

youth.[48,384,385] Transgender and gender-diverse youth face additional discrimination and disadvantage due to the longstanding stigma toward gender-diverse individuals.[356] However, appropriate protections from discrimination allow individuals of diverse sexual orientation and/or gender identity of all ages to thrive.[194,213,355]

Important scientific research indicates that policies that reduce discrimination and advance equal rights have positive effects on behavioral health. Research studies indicate that enacting protective policies that safeguard individuals from discrimination and violence lead to improved physical and mental health for sexual- and gender-diverse youth and adults.[211,386,387,388] Federal and state laws that equalize civil rights and the status of LGBTQI+ individuals are linked to the improved behavioral health noted above. Some states require health insurance plans to cover gender-affirming care and include protections against discrimination in private health insurance by expressly prohibiting discrimination based on sexual orientation and gender identity.[362]

Steps have been taken at the federal, state, and local levels to expand equalizing policies. At the federal level, the Biden Administration has issued important Executive Orders, memoranda, and public statements to reduce discrimination toward individuals with diverse sexual orientations and/or gender identities and support LGBTQI+ civil rights.[14,338,342,343,389,390,391] In the 117th Congress, The Equality Act (H.R. 5) was introduced and would have explicitly prohibited discrimination toward LGBTQI+ individuals.[392] Some states have adopted antidiscrimination and antibullying policies and expanded benefits for LGBTQI+ state employees.[393] State efforts have also included:

- Bans on discrimination by state-licensed healthcare providers
- Bans on SOGI change efforts
- Nondiscrimination laws based on sexual orientation and gender identity
- Supports for same-sex families
- Antibullying laws
- Inclusive curriculum in schools

Local governments have also taken steps to reduce bias and discrimination based on sexual orientation and gender identity and expand protective policies at the local level.[365]

Improving Behavioral Health Through Support for Families, Caregivers, Schools, and Communities

Research summarized earlier in this report indicates that families, schools, and communities contribute to the behavioral health of LGBTQI+ youth. Efforts can facilitate positive behavioral health by providing a climate of support and acceptance. Families, schools, and communities can undermine behavioral health through rejection or discrimination, which have adverse health effects. Policies that increase the dissemination of resources to families, communities, and schools to encourage support and acceptance of LGBTQI+ youth is a high priority. For example, the June 15, 2022, Executive Order on Advancing Equality for Lesbian, Gay, Bisexual, Transgender, Queer, and Intersex Individuals includes initiatives that aim to increase such family counseling and information.[14]

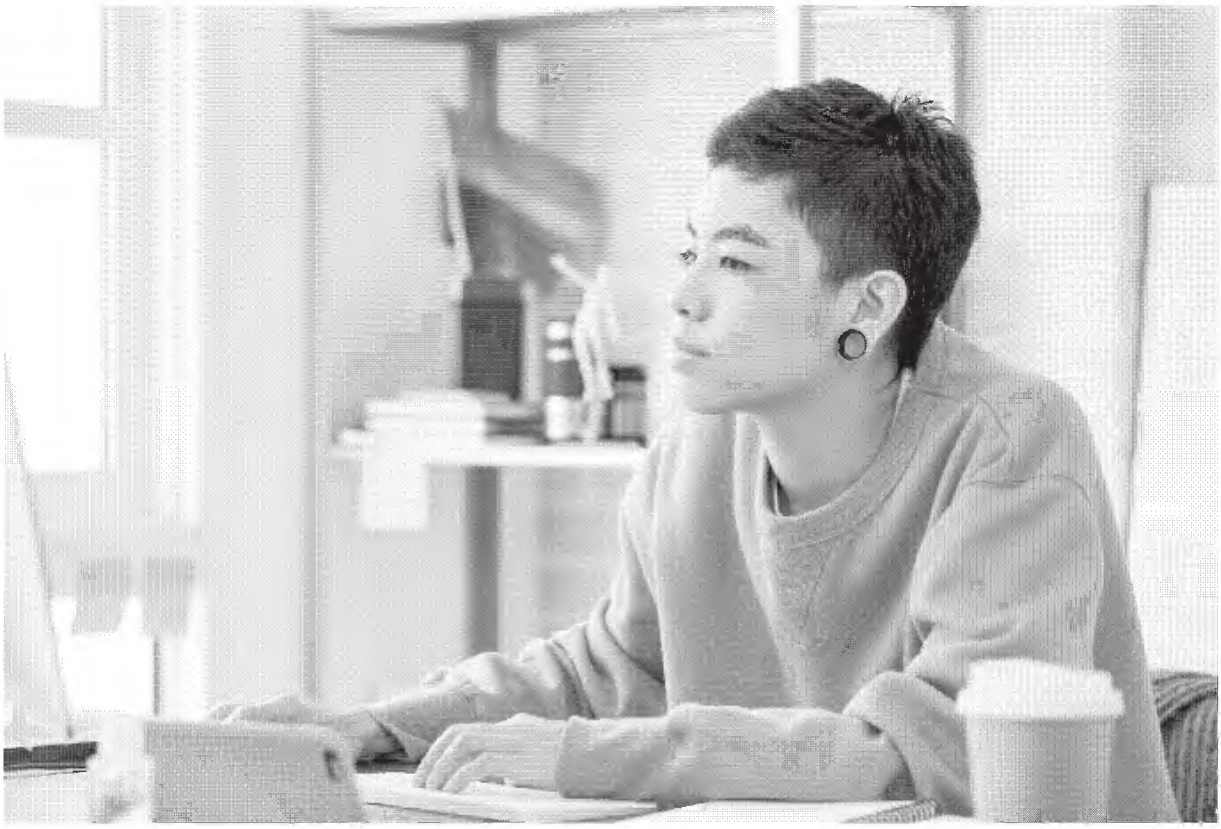
Interventions to Support Children and Families

Families play an important protective role in child development and benefit from information

about how to appropriately help their children. The Family Acceptance Project provides such resources through publications for diverse families, which are available in multiple languages.[394] Other resources include Lead with Love, PATHS and AFFIRM Caregiver (see Appendix C), and information offered by SAMHSA[395] and the Centers for Disease Control and Prevention.[396] The American Psychological Association provides a guide for parents in choosing an appropriate therapist with gender expertise.[397]

Education for families, caregivers, child welfare professionals, and individuals can be tailored to the specific needs of diverse communities.[397,398,399] One option is a public health campaign to educate parents and caregivers on appropriate treatment options that are safe and effective for youth. Such a program can alert families, caregivers, child welfare professionals, schools, and communities on the risks of family rejection and SOGI change efforts and the benefits of recognizing sexual orientation and gender development and access to affirming care.

Healthcare providers can offer age-specific guidance to parents and guardians to help them understand growth- and development-related expectations associated with healthy behaviors and disease prevention; this is known as anticipatory guidance.[400] Pediatricians and behavioral health providers have urged for more anticipatory guidance[401] that pediatricians and early childhood and educational providers can provide to inform parents about sexual orientation and gender identity, as well as their LGBTQI+ child's needs. This would aim to enhance family support and reduce rejection.[402]



The American Academy of Pediatrics urges pediatricians to assess risk factors related to child maltreatment in their general assessments of children and adolescents.[403] Seeking gender-affirming assessment, consultation, and care is not maltreatment.[352,353] The Information Memorandum issued March 2, 2022, by HHS makes clear that state child welfare systems should support LGBTQI+ youth and ensure their safety.[354]

Interventions to Support Youth in Schools

Education and behavioral health associations, professionals, and researchers across the country have urged proactive steps to support and protect LGBTQI+ youth and other students through the inclusion of policies, resources, and training that provide information, safety, and support.[356,361,404,405] These policies have been evaluated over the past decade in nationwide samples and are found to reduce victimization and behavioral health problems and improve mental health.[198,287,288,406,407]

The Society for Research in Child Development,[356] the American Psychological Association,[361] the American Counseling Association,[406] the National Association of School Psychologists, and medical professionals recommend crucial educational policies to create a positive and healthy environment for all youth, especially those who are LGBTQI+ or have emerging sexual orientation or gender identities. These include the following:

1. Establish and implement supportive policies that provide guidelines for respectful interactions (in-person and online), promote acceptance of all sexual orientations and gender identities and expressions, promote the use of identified pronouns, and respect confidentiality and privacy.
2. Enable full participation and access to school activities including athletics and resources for all students and school personnel consistent with their gender identity, including use of school facilities (e.g., bathrooms, locker rooms) that align with their gender identity.
3. Establish protective policies, such as antibullying and antidiscrimination policies, that explicitly include protections for sexual orientation, gender identity, and gender expression.
4. Provide high-quality, evidence-informed LGBTQI+ professional development for school staff.
5. Develop school resources for LGBTQI+ youth and connect to supportive resources and information, such as GSAs, school clubs that are inclusive of LGBTQI+ people, and age-appropriate curriculum that is inclusive of LGBTQI+ people.

   Title IX prohibits sex-based discrimination in any school or any other education program that receives funding from the Federal Government. HHS and the Department of Education have clarified legal requirements with their interpretation of Title IX prohibiting discrimination on the basis of sexual orientation and gender identity. Strong antidiscrimination policies can protect LGBTQI+ youth and their families from discrimination in federal programs.

The Federal government has created a website with information on bullying prevention, including information on bullying of LGBTQI+ youth, ways to create safe school environments, and applicable federal civil rights laws: stopbullying.gov. Such nondiscrimination efforts to ensure the safety and well-being of LGBTQI+ youth and their families in schools and other federal programs are consistent with existing

behavioral health research and professional association recommendations.[355,356,407]

Some states and localities have established such education policies, but they are far from universal. More states have added protective policies over the past 7 years, but a majority of states do not have policies to protect LGBTQI+ students from bullying or discrimination. Inclusive policies are still rare at the state level. Some states are considering and enacting laws and policies that are inconsistent with the above empirically based recommendations, such as those that prevent discussion of LGBTQI+ issues or exclude LGBTQI+ youth from activities or athletics. Given the strength of the evidence of the benefits of the protective policies, policies that stigmatize youth of diverse sexual orientation and/or gender identity pose risks to their health.[354,355,356]

Future Directions: Research to Improve Care

Scientific research can advance our understanding of LGBTQI+ youth and improve their behavioral health through prevention and new interventions.

Increasing Research Insights Through Inclusive Demographic Questions

Health policy experts have called for data collection and priorities that are inclusive of LGBTQI+ people to ensure research accuracy and health equity.[408,409,410,411] Inclusive data collection and research policies support consistent collection of demographic information, including information about respondent sexual orientation and gender identity, regardless of whether the survey is focused on LGBTQI+ populations. Having accurate data and information about sexual orientation and gender identity improves public policies by identifying specific behavioral health needs, preventing adverse health conditions, and addressing health inequities. This is especially true when addressing the diversity within children, adolescents, and their families based on cultural background, ethnicity, race, geography, and other aspects of identity.

Progress has been made in federal, state, and municipal data collection and research as demographic information on sexual orientation and gender identity has been added to some research tools and health records.[412] In 2023, the Federal Government released the first-ever Federal Evidence Agenda for LGBTQI+ Equity, a roadmap that federal agencies will use to ensure they are collecting the data and evidence they need to improve the lives of LGBTQI+ Americans.[413] Other existing efforts include the Centers for Disease Control and Prevention's Youth Risk Behavior Survey (YRBS), which includes national, state, and local surveys, assesses key behavioral and other health risks in youth and includes questions on sexual orientation and sex of sex partners in the national survey.[414] However, although the state and local surveys are currently conducted in 47 states and 28 large urban school districts, not all states and local jurisdictions include sexual orientation and sex of sex partner questions. Questions on gender identity and self-identification as transgender are available for states and local jurisdictions to include in their YRBS surveys, consistent with the Protection of Pupil Rights Amendment, and utilization of those questions has been increasing during each administration of the survey.

There are resources for addressing this gap in data collection on sexual orientation and gender identity. The National Academies report, *Measuring Sex, Gender Identity, and Sexual Orientation,* commissioned by the National Institutes of Health (NIH), provides recommendations on how to formulate appropriate questions regarding sexual

orientation and gender identity to address the complexity of diversity within these communities.[31] For example, an important recommendation is ensuring that approaches to SOGI measurement and data collection are tested and validated in youth populations. Given the diversity of the LGBTQI+ population, it is important to use an intersectional approach that considers multiple aspects of diversity and demography (e.g., cultural background, values, ethnicity, geography, and race).

Selected LGBTQI+ Research Topics

Studies of LGBTQI+ youth have begun to examine important developmental and clinical needs in these populations. Focused research can expand our understanding of these youth and guide clinical interventions. For example, studies of development of transgender children provide new windows into our understanding of gender development and well-being in childhood.[189] Research to elucidate how intersecting sociocultural factors and experiences (e.g., race, ethnicity, socioeconomic status, cultural background and values) influence sexual orientation and gender development is in its early stages. To better understand the needs of sexual and gender minority children and adolescents, new lines of research can include sexual- and gender-diverse children and adolescents from diverse family backgrounds, especially from general populations rather than those limited to samples of people receiving clinical care.

Intersex individuals face known health disparities although research that specifically focuses on intersex individuals is limited and needs to be expanded both broadly and across time within longitudinal studies.[45,415] The Administration's Federal Evidence Agenda on LGBTQI+ Equity identified a lack of national surveys that collect data about "variations in sex characteristics or intersex people" and underscored the need to collect those data.[413]

Limited research has considered economic impact of SOGI change efforts, which could be expanded. A recent study found negative economic consequences for those adolescents and young adults who experience SOGI change efforts when compared to those with no intervention or affirming interventions. These negative economic impacts include the costs associated with adverse events as well as the expense of the efforts.[416] Further, despite its lack of efficacy and its serious harms to clients, SOGI change efforts appear to be lucrative, which may serve as an inducement to some providers.[416]

Evaluations of clinical approaches and development of best practices can be fostered by funding research collaborations; this type of research can lead to improved care.[214,417] Key research areas should also include suicide prevention, evidence-based trauma-focused interventions, and approaches to counter minority stress. Studies of community-based populations provide an emerging understanding of the key developmental concerns. A resource for those conducting LGBTQI+ research is the NIH Sexual and Gender Minority Research Office. NIH has also developed tools to study social determinants of health.[418] A National Academies report includes recommendations on key areas of LGBTQI+ research.[31]

Summary and Conclusions

SAMHSA is committed to eliminating health inequities experienced by marginalized communities, including LGBTQI+ youth. To build a healthy and supportive environment for all youth, families, caregivers, providers, and educators need resources and accurate information to inform healthy decision making. Two key strategies that can help prevent adverse outcomes and support healthy development for LGBTQI+ youth are:

1. Strong and positive family, school, and community engagement
2. Appropriate and supportive therapeutic interventions by physical and behavioral health providers

Policies at the local, state, and federal levels are needed to foster supportive, affirming environments and ensure access to appropriate care.

These strategies must and can be grounded in research. Being a sexual or gender minority, or identifying as LGBTQI+, is not a mental disorder. Variations in sexual orientation, gender identity, and gender expression are normal and healthy. Sexual- and gender-diverse youth have unique health and behavioral health needs and may experience distress due to discrimination and barriers to support that remain widespread for LGBTQI+ youth. In addition, transgender and gender-diverse youth may experience distress caused by the incongruence between their gender identity and physical body.

Current research, evolving clinical expertise, and expert consensus underscore that efforts to attempt to change a youth's sexual orientation, gender identity, or gender expression are never appropriate. No evidence supports the efficacy of such interventions, and evidence shows that they can cause severe harm. Appropriate therapeutic approaches to working with LGBTQI+ youth include:

- Providing accurate information on sexual orientation and gender identity and expression
- Identifying sources of and working to reduce distress
- Supporting adaptive coping
- Supporting youth as they learn more about their sexual orientation and gender identity, and supporting families in accessing gender-affirming care for their transgender child when indicated
- Helping youth navigate sexual orientation, gender identity and expression within the context of other intersecting identities

Additionally, providers can help increase family and school support, and reduce family, community, and social rejection of LGBTQI+ youth. Social transition and medical interventions, including pubertal suppression and hormone therapy, are additional therapeutic approaches that may be medically necessary, appropriate, and beneficial for gender minority youth based on the individual youth's needs. Withholding timely gender-affirming medical care when indicated, withholding support for a gender-affirming exploratory process, and/or withholding support of social transition when desired, can be harmful. These actions may exacerbate gender dysphoria.

Beyond ending harmful change efforts, it is important to build greater social acceptance of LGBTQI+ youth across all environments where they live, learn, and play; adopt appropriate and

supportive interventions; and provide targeted resources and accurate developmentally informed information for children, adolescents, their families, and providers. Building better supportive environments and working to eliminate negative social attitudes will reduce health inequities and improve the health and well-being of LGBTQI+ youth.

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Appendix B: Glossary of Terms

Agender: Describes individuals who do not identify as any gender.

Asexual: Describes individuals who do not experience sexual attraction. An individual can also be aromantic, meaning that they do not experience romantic attraction.

Behavioral health: A broad term that includes mental health, resilience, and well-being; the treatment of mental and substance use disorders; and the support of those who experience and/or are in recovery from these conditions, along with their families and communities.

Behavioral health provider: A broad term used here to describe individuals across settings and disciplines who are engaged in the provision of care and/or support related to behavioral health. Behavioral health providers include both licensed and non-licensed professionals, including mental health counselors, marriage and family therapists, pastoral counselors, psychiatrists, psychologists, psychiatric nurses, school counselors and health providers, peer support professionals, social workers, substance use counselors, addiction medicine specialists, and all staff of mental health and substance use treatment facilities.

Bisexual: Describes an individual who has the capacity to form enduring physical, romantic, and/or emotional attractions to those of the same gender or to those of another gender.

Cisgender: Describes individuals whose gender identity is congruent with their sex assigned at birth.

Developmentally sensitive approaches: Clinical and educational approaches that account for the appropriate developing emotional and cognitive capacities, developmental milestones, and emerging or existing behavioral health concerns.

Diverse sexual orientation and/or gender identity: A term to describe persons who are lesbian, gay, bisexual, transgender, queer, intersex, those who are questioning their sexual orientation or gender identity, and others who are not cisgender or straight/heterosexual. Diverse sexual orientation and/or gender identity is used interchangeably with "LGBTQI+" and "sexual and/or gender minority" (or similar language) throughout this report.

Fa'afafine: Describes individuals assigned male sex at birth who identify themselves as having a third gender or nonbinary in Samoan culture.

Gay: Describes individuals whose enduring physical, romantic, and/or emotional attractions are to people of the same gender.

Gender-affirming care: A specialized model of care used in the treatment of gender dysphoria that uses evidence-informed treatment options to promote patient health and prevent the risk of poor mental and physical health outcomes. Not all youth need to undergo medical intervention; indeed, this is often not the case. Gender-affirming care is highly individualized and focuses on the needs of each individual. Gender-affirming care may include psychoeducation about gender and sexuality (appropriate to the age and developmental level), parental and family support, social interventions, and gender-affirming medical interventions.

Gender diverse: A broad term that includes individuals whose gender identities and/or gender expressions are incongruent with those culturally expected based on sex assigned at birth. This includes those who are exploring their gender and is used interchangeably with "gender minority."

Gender expression: The external ways a person communicates their gender, such as clothing, hair, mannerisms, activities, or social roles.

Gender fluid: A term used to describe individuals whose gender changes over time.

Gender identity: A person's deep internal sense of being female, male, or another identity.

Genderqueer: Describes individuals who experience their gender identity and/or gender expression as falling outside the categories of man and woman.

Intersex: An umbrella term used to describe people with variations in sex characteristics, including chromosomes or hormones that do not fit typical definitions of male and female.

Lesbian: A woman who has romantic and/or sexual orientation toward women.

LGBTQI+: Lesbian, gay, bisexual, transgender, queer, intersex, those who are questioning their sexual orientation or gender identity, and others who are not cisgender or straight/heterosexual. LGBTQI+ is used interchangeably with "sexual and/or gender minority" and persons of "diverse sexual orientation and/or gender identity" (or similar language) throughout this report.

Māhū: Describes individuals who identify as a third gender or nonbinary in Native Hawaiian culture.

Nonbinary: Describes individuals whose gender identity is not exclusively male or female. Individuals may identify as nonbinary or other identities, including, but not limited to, genderqueer, two-spirit, agender, bigender, and genderfluid.

Pansexual: Describes individuals who experience sexual, romantic, physical, and/or spiritual attraction for members of all gender identities/expressions.

Queer: Historically, this has been a pejorative term used to describe LGBTQI+ people, but is now used by some people, particularly younger people, whose sexual orientation is not exclusively straight/heterosexual. Some people may use queer, or more commonly genderqueer, to describe their gender identity and/or gender expression.

Questioning: A term used to describe individuals who are unsure about their sexual orientation and/or gender identity.

Sex assigned at birth: The assignment of male, female, or intersex when an individual is born, typically made based on the appearance of external genital anatomy.

Sexual and/or gender minority: Sexual and gender minority populations include, but are not limited to, individuals who identify as lesbian, gay, bisexual, asexual, transgender, Two-Spirit, queer, and/or intersex. Individuals with same-sex or -gender attractions or behaviors and those with a difference in sex development are also included. Sexual and gender minority is used interchangeably with "LGBTQI+" and persons of "diverse sexual orientation and/or gender identity" (or similar) throughout this report.

Sexual orientation and gender identity change efforts (SOGI change efforts): Practices that aim to suppress or alter an individual's sexual orientation or gender to align with heterosexual orientation, cisgender identity, and/or stereotypical gender expression. Though not therapeutic, these practices are often referred to as "conversion therapy" or "reparative therapy."

Sexual orientation: A person's emotional, sexual, and/or relational attraction to others.

Transgender: Describes individuals whose gender identity is incongruent with their sex assigned at birth.

Two-Spirit: Two Spirit refers to someone who is Native and expresses their gender identity or spiritual identity in indigenous, non-Western ways. This term can only be applied to a person who is Native. A Two Spirit person has specific traditional roles and responsibilities within their tribe. Not all Native LGBTQ people identify as Two Spirit.

Victimization: The act or process of singling someone out for cruel or unfair treatment, typically through physical or emotional abuse.

This glossary is not an exhaustive list of terminology relevant for LGBTQI+ youth. Additional key terms and concepts are defined at Youth.gov.

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Appendix C: Selected Resources

This appendix highlights selected materials that are accessible to a variety of providers, community professionals, parents, caregivers, and youth. It also includes resources that, after reviewing, professionals may share with families, youth, and community-based collaborators. The appendix does not cover every important aspect of all issues addressed in this report, and the list of resources is illustrative, not exhaustive.

The Department of Health and Human Services maintains information online at: https://www.hhs.gov/programs/topic-sites/lgbtq/index.html

If you or someone you know is in crisis or emotional distress, or experiencing suicidal thoughts, please contact:

988 Suicide and Crisis Lifeline

If you're thinking about suicide, are worried about a friend or loved one, or would like emotional support, the Lifeline network is available 24/7.

- **Dial: 988**
- **Text: 988**
- **Chat: https://988Lifeline.org/chat**

The Trevor Project

***Connect to a crisis counselor*:**
866-488-7386 |
www.thetrevorproject.org/get-help

LGBT National Help Center

Peer support: www.lgbthotline.org

Resources for Behavioral Health and Medical Providers

Resources for Understanding Sexual Orientation and Gender Identity

These resources include information on sexual orientation and gender identity and development for behavioral health providers and other professionals.

Online Resources for Providers

- American Counseling Association. (n.d.). https://www.counseling.org/knowledge-center/mental-health-resources/lgbtq
- American Psychological Association. (n.d.). https://www.apa.org/topics/lgbtq
- National LGBTQIA+ Health Education Center. (n.d.). https://www.lgbtqiahealtheducation.org/resources/in/transgender-health/
- National Association of School Psychologists. (n.d.). https://www.nasponline.org/lgbtqi2-s
- World Professional Association for Transgender Health. (2022). Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People. https://www.wpath.org/publications/soc
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- National Child Traumatic Stress Network. (2022). Gender-Affirming Care Is Trauma-Informed Care. https://www.nctsn.org/sites/default/files/resources/fact-sheet/gender-affirming-care-is-trauma-informed-care.pdf

Books for Providers

- Irwin Krieger. (2018). *Counseling Transgender and Non-Binary Youth: The Essential Guide*. London: Jessica Kingsley Publishers, Ltd.
- Colt Keo-Meier and Diane Ehrensaft. (2018). *The Gender Affirmative Model: An Interdisciplinary Approach to Supporting Transgender and Gender Expansive Children*. Washington, DC: American Psychological Association.

Resources for Pediatric and Primary Care Providers

In addition to the resources above, these selected resources assist pediatric and primary care health professionals who may be the first point of contact for families and youth.

- Rafferty J; Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*. 2018;142(4):e20182162. doi:10.1542/peds.2018-2162. https://pubmed.ncbi.nlm.nih.gov/30224363/
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- National LGBT Health Education Center. (n.d.). https://www.lgbtqiahealtheducation.org/resources/in/transgender-health/

Resources for Providers to Discuss with Families, Caregivers, and Others

These resources are designed for professionals to discuss with families, caregivers, and others.

- HHS. (n.d.). LGBTQI+ Health & Well-being. https://www.hhs.gov/programs/topic-sites/lgbtqi/index.html
- The Family Acceptance Project http://familyproject.sfsu.edu/ works with parents and caregivers to help them support their LGBTQI+ youth to reduce health risks and promote well-being. This information is offered within the context of diverse cultures and faith communities by identifying and understanding the impacts of rejecting and supportive behaviors. Films, posters and trainings are available for behavioral health providers and others and information is provided for families in many languages. http://familyproject.sfsu.edu/
- OASH. Office of Population Affairs. (2022). *Gender-Affirming Care and Young People*. https://opa.hhs.gov/sites/default/files/2022-03/gender-affirming-care-young-people-march-2022.pdf
- AFFIRM Caregiver is a seven-session intervention that helps caregivers clarify what supportive behaviors are and how to move away from rejecting behaviors. https://www.affirmativeresearch.org/affirm-care.html

Resources for Providers on Cultural Responsiveness

These resources highlight the scientific consensus for assisting professionals who work with diverse families and youth.

- Asian American Psychological Association. (n.d.). https://aapaonline.org/resources/lgbtq-aapi-resources/
- 2019 Black and African American LGBTQ Youth Report. (2019). https://www.hrc.org/resources/black-and-african-american-lgbtq-youth-report
- The Trevor Project. (July 14, 2021). Black & LGBTQ: Approaching Intersectional Conversations. https://www.thetrevorproject.org/resources/guide/black-lgbtq-approaching-intersectional-conversations/
- The Trevor Project. (June 1, 2020). Supporting Black LGBTQ Mental Health. https://www.thetrevorproject.org/resources/guide/supporting-black-lgbtq-youth-mental-health/
- 2018 LGBTQ Latinx Youth Report. (2018). https://www.hrc.org/resources/latinx-lgbtq-youth-report
- National Queer Asian Pacific Islander Alliance (NQAPIA). (n.d.). http://www.nqapia.org

Resources for Educators and School and Community Leaders

Resources for School Professionals

These resources highlight approaches that build educator support and student resilience.

- Advocates for Youth. (2020). *Creating Safer Spaces for LGBTQ Youth: A Toolkit for Education, Healthcare and Community-Based Organizations.* http://www.advocatesforyouth.org/wp-content/uploads/2020/11/Creating-Safer-Spaces-Toolkit-Nov-13.pdf
- American Psychological Association. (2014). Safe & Supportive Schools Project. http://www.apa.org/pi/lgbt/programs/safe-supportive/default.aspx
- GLSEN Research Institute. (2021). *LGBTQ Students and School Sports Participation: Research Brief.* https://www.glsen.org/sites/default/files/2022-02/LGBTQ-Students-and-School-Sports-Participation-Research-Brief.pdf
- Additional GLSEN Resources. (n.d.). https://www.glsen.org/
- CDC DASH Supporting LGBTQ Youth. (n.d.). https://www.cdc.gov/healthyyouth/safe-supportive-environments/lgbtq_youth.htm
- Human Rights Campaign, Welcoming Schools Initiative. (n.d.). Creating Safe and Welcoming Schools. www.welcomingschools.org
- National Center for Lesbian Rights, Youth Project. (n.d.). www.nclrights.org/our-work/youth
- National Association of School Psychologists, Committee on LGBTQI2-S Issues: Safe & Supportive Schools. (n.d.). https://www.nasponline.org/lgbtqi2-s

Resources for Families and Caregivers

Parent/Caregiver Support-Focused Resources

These resources highlight ways for parents and caregivers to connect with other parents and caregivers of LGBTQI+ youth, and to learn more about their responses to LGBTQI+ youth.

- PFLAG. (n.d.) Families connecting with other families. www.pflag.org

- National Queer Asian Pacific Islander Alliance (NQAPIA). (n.d.). Videos and resources for parents. https://www.youtube.com/user/nqapia/videos
- Lead with Love (n.d.). Film-based intervention to improve parental responses to their sexual minority children. www.leadwithlovefilm.com

Resources for Families and Caregivers of Transgender and Gender-Diverse Youth

These resources highlight specific considerations for parents and caregivers of gender minority youth.

Online Resources for Families and Caregivers

- American Psychological Association. (December 2020). *A Consumer's Guide for Parents and Guardians of Gender Diverse Children and Adolescents: 10 Considerations for Finding a Gender Competent Therapist for Your Child*. https://www.apa.org/pi/lgbt/resources/gender-diverse-children.pdf
- PFLAG Transgender Network. (n.d.). https://pflag.org/transgender
- Gender Spectrum offers resources for multiple audiences. (n.d.). www.genderspectrum.org

Books for Families and Caregivers

- Janna Barkin. (2017). *He's Always Been My Son: A Mother's Story About Raising her Transgender Son*. London: Jessica Kingsley Publishers, Ltd.
- Stephanie Brill and Lisa Kenney. (2016). *The Transgender Teen: A Handbook for Parents and Professionals Supporting Transgender and Non-Binary Teens*. Jersey City, NJ: Cleis Press.
- Diane Ehrensaft. (2011). *Gender Born, Gender Made: Raising Healthy Gender-Nonconforming Children* (1st ed.). New York: The Experiment.
- Irwin Krieger. (2019). *Helping Your Transgender Teen* (2nd ed.). New Haven, CT: Genderwise Press.
- Jodie Patterson. (2019). *The Bold World: A Memoir of Family and Transformation*. New York: Penguin Random House.
- Rachel Pepper. (2012). *Transitions of the Heart: Stories of Love, Struggle and Acceptance by Mothers of Transgender and Gender Variant Children*. Jersey City, NJ: Cleis Press.

Resources for Youth

Online Resources for Youth

These resources are places where LGBTQI+ youth can access information and online support.

- It Gets Better Project. (n.d.). www.itgetsbetter.org
- The Trevor Project. (n.d.). www.thetrevorproject.org
- Gender Spectrum. www.genderspectrum.org

Appendix D: Contributions

This report was prepared for SAMHSA by Leed Management Consulting, Inc. (LMCi) under contract number HHSS283201700609I/HHSS28342001T with SAMHSA, U.S. Department of Health and Human Services (HHS). Arlin Hatch, CAPT, USPHS, PhD, served as the Task Lead, Aida Balsano, PhD, served as the Deputy Task Lead, and Brian Altman, JD, served as Senior Advisor. David Lamont Wilson, BFA, served as the Contracting Officer Representative, and Marion Pierce, BA, served as the Alternate Contracting Officer Representative.

Laura Jadwin-Cakmak, MPH, was the lead scientific writer for this report, with substantial contributions from Judith Glassgold, PsyD; assistance from the subject matter expert panelists; technical, bibliographic, and editorial assistance from Kathi E. Hanna, PhD; and support from Karen Braxton, MA, as task lead from LMCi.

The Subject Matter Expert Consensus Panel was convened by Judith Glassgold, PsyD, the lead subject matter expert, remotely from September 9 to 10, 2021, with technical support from LMCi. The Panel included researchers and practitioners in child and adolescent development and mental health, as well as researchers in gender development, gender identity, and sexual orientation in children and adolescents. The Panel also included experts with a background in family therapy, ethnic and racial diversity, the needs of underrepresented populations, the intersection of behavioral health and spiritual diversity, and ethics. Panel members were Renata Arrington-Sanders, MD, MPH, ScM; Laura Edwards-Leeper, PhD; Gary Harper, PhD, MPH; Laura Kuper, PhD; Scott Leibowitz, MD; Christy Mallory, JD; Robin Lin Miller, PhD; Kristina Olson, PhD; Thomas Plante, PhD; Clifford Rosky, JD; Caitlin Ryan, PhD, ACSW; Russell Toomey, PhD; and Mark Yarhouse, PsyD.

SAMHSA subject matter experts provided input on the report: Brian Altman, JD; Amy Andre, MA, MBA; Mitchell Berger, MPH; Victoria Chau, PhD, MPH; Jeff Coady, CAPT, USPHS, PsyD, ABPP; Ed Craft, DrPh, Med, LCPC; Trina Dutta, MPP, MPH; and Michelle Kim Leff, CAPT, USPHS, MD, MBA. Elliot Kennedy, JD, from the Administration for Community Living, provided consultation and served as the SAMHSA Task Lead for the 2015 report, *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*, on which this revision is based.

SAMHSA
Substance Abuse and Mental Health Services Administration

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Any person depicted in a photo is a model.

Publication No. No. PEP22-03-12-001
Released 2023

TAB 176-36

Presidential Documents

Pl. Trial Ex. 076

Proclamation 10355 of March 30, 2022

Transgender Day of Visibility, 2022

By the President of the United States of America

A Proclamation

To everyone celebrating Transgender Day of Visibility, I want you to know that your President sees you. The First Lady, the Vice President, the Second Gentleman, and my entire Administration see you for who you are—made in the image of God and deserving of dignity, respect, and support. On this day and every day, we recognize the resilience, strength, and joy of transgender, nonbinary, and gender nonconforming people. We celebrate the activism and determination that have fueled the fight for transgender equality. We acknowledge the adversity and discrimination that the transgender community continues to face across our Nation and around the world.

Visibility matters, and so many transgender, nonbinary, and gender nonconforming Americans are thriving. Like never before, they are sharing their stories in books and magazines; breaking glass ceilings of representation on television and movie screens; enlisting—once again—to serve proudly and openly in our military; getting elected and making policy at every level of government; and running businesses, curing diseases, and serving our communities in countless other ways.

Despite this progress, transgender Americans continue to face discrimination, harassment, and barriers to opportunity. Transgender women and girls—especially transgender women and girls of color—continue to face epidemic levels of violence, and 2021 marked the deadliest year on record for transgender Americans. Each of these lives lost was precious. Each of them deserved freedom, justice, and joy. We must honor their lives with action by advancing equity and civil rights for all transgender people.

In the past year, hundreds of anti-transgender bills in States were proposed across America, most of them targeting transgender kids. The onslaught has continued this year. These bills are wrong. Efforts to criminalize supportive medical care for transgender kids, to ban transgender children from playing sports, and to outlaw discussing LGBTQI+ people in schools undermine their humanity and corrode our Nation's values. Studies have shown that these political attacks are damaging to the mental health and well-being of transgender youth, putting children and their families at greater risk of bullying and discrimination.

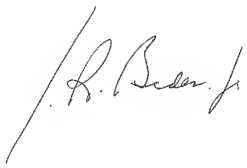
My entire Administration is committed to ensuring that transgender people enjoy the freedom and equality that are promised to everyone in America. That is why I signed an Executive Order Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation. We are expanding Federal non-discrimination protections; promoting strategies to address violence against the transgender community and advance gender equity and equality; and disseminating new resources to enhance inclusion, opportunity, and safety for transgender people. Additionally, Americans will soon be able to select more inclusive gender markers on their passports. I continue to call on the Congress to swiftly pass the bipartisan Equality Act, which will ensure that LGBTQI+ individuals and families cannot be denied housing, employment, education, credit, and more because of who they are or who

they love. We will continue to work to help transgender people around the world live free from discrimination and violence.

On this Transgender Day of Visibility, we honor transgender people who are fighting for freedom, equality, dignity, and respect. We also celebrate the parents, teachers, coaches, doctors, and other allies who affirm the identities of their transgender children and help these young people reach their potential. Transgender people are some of the bravest Americans I know, and our Nation and the world are stronger, more vibrant, and more prosperous because of them. To transgender Americans of all ages, I want you to know that you are so brave. You belong. I have your back.

NOW, THEREFORE, I, JOSEPH R. BIDEN JR., President of the United States of America, by virtue of the authority vested in me by the Constitution and the laws of the United States, do hereby proclaim March 31, 2022, as Transgender Day of Visibility. I call upon all Americans to join us in lifting up the lives and voices of transgender people throughout our Nation and to work toward eliminating discrimination against all transgender, gender nonconforming, and nonbinary people—and all people.

IN WITNESS WHEREOF, I have hereunto set my hand this thirtieth day of March, in the year of our Lord two thousand twenty-two, and of the Independence of the United States of America the two hundred and forty-sixth.



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TAB 176-37

Presidential Documents

Pl. Trial Ex. 077

Proclamation 10538 of March 30, 2023

Transgender Day of Visibility, 2023

By the President of the United States of America

A Proclamation

Transgender Day of Visibility celebrates the joy, strength, and absolute courage of some of the bravest people I know—people who have too often had to put their jobs, relationships, and lives on the line just to be their true selves. Today, we show millions of transgender and nonbinary Americans that we see them, they belong, and they should be treated with dignity and respect. Their courage has given countless others strength, but no one should have to be brave just to be themselves. Every American deserves that freedom.

Transgender Americans shape our Nation's soul—proudly serving in the military, curing deadly diseases, holding elected office, running thriving businesses, fighting for justice, raising families, and much more. As kids, they deserve what every child deserves: the chance to learn in safe and supportive schools, to develop meaningful friendships, and to live openly and honestly. As adults, they deserve the same rights enjoyed by every American, including equal access to health care, housing, and jobs and the chance to age with grace as senior citizens. But today, too many transgender Americans are still denied those rights and freedoms. A wave of discriminatory State laws is targeting transgender youth, terrifying families and hurting kids who are not hurting anyone. An epidemic of violence against transgender women and girls, in particular women and girls of color, has taken lives far too soon. Last year's Club Q shooting in Colorado was another painful example of this kind of violence—a stain on the conscience of our Nation.

My Administration has fought to end these injustices from day one, working to ensure that transgender people and the entire LGBTQI+ community can live openly and safely. On my first day as President, I issued an Executive Order directing the Federal Government to root out discrimination against LGBTQI+ people and their families. We have appointed a record number of openly LGBTQI+ leaders, and I was proud to rescind the ban on openly transgender people serving in the military. We are also working to make public spaces and travel more accessible, including with more inclusive gender markers on United States passports. We are improving access to public services and entitlements like Social Security. We are cracking down on discrimination in housing and education. And last December, I signed the Respect for Marriage Act into law, ensuring that every American can marry the person they love and have that marriage accepted, period.

Meanwhile, we are also working to ease the tremendous strain that discrimination, bullying, and harassment can put on transgender children—more than half of whom seriously considered suicide in the last year. The Department of Education is, for example, helping ensure that transgender students have equal opportunities to learn and thrive at school, and the Department of Justice is pushing back against extreme laws that seek to ban evidence-based gender-affirming health care.

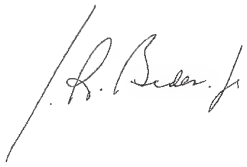
There is much more to do. I continue to call on the Congress to finally pass the Equality Act and extend long-overdue civil rights protections to all LGBTQI+ Americans to ensure they can live with safety and dignity.

Together, we also have to keep challenging the hundreds of hateful State laws that have been introduced across the country, making sure every child knows that they are made in the image of God, that they are loved, and that we are standing up for them.

America is founded on the idea that all people are created equal and deserve to be treated equally throughout their lives. We have never fully lived up to that, but we have never walked away from it either. Today, as we celebrate transgender people, we also celebrate every American's fundamental right to be themselves, bringing us closer to realizing America's full promise.

NOW, THEREFORE, I, JOSEPH R. BIDEN JR., President of the United States of America, by virtue of the authority vested in me by the Constitution and the laws of the United States, do hereby proclaim March 31, 2023, as Transgender Day of Visibility. I call upon all Americans to join us in lifting up the lives and voices of transgender people throughout our Nation and to work toward eliminating violence and discrimination against all transgender, gender nonconforming, and nonbinary people.

IN WITNESS WHEREOF, I have hereunto set my hand this thirtieth day of March, in the year of our Lord two thousand twenty-three, and of the Independence of the United States of America the two hundred and forty-seventh.



[FR Doc. 2023–07089
Filed 4–3–23; 8:45 am]
Billing code 3395–F3–P

TAB 176-38

Presidential Documents

Pl. Trial Ex. 078

Executive Order 13988 of January 20, 2021

Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation

By the authority vested in me as President by the Constitution and the laws of the United States of America, it is hereby ordered as follows:

Section 1. *Policy*. Every person should be treated with respect and dignity and should be able to live without fear, no matter who they are or whom they love. Children should be able to learn without worrying about whether they will be denied access to the restroom, the locker room, or school sports. Adults should be able to earn a living and pursue a vocation knowing that they will not be fired, demoted, or mistreated because of whom they go home to or because how they dress does not conform to sex-based stereotypes. People should be able to access healthcare and secure a roof over their heads without being subjected to sex discrimination. All persons should receive equal treatment under the law, no matter their gender identity or sexual orientation.

These principles are reflected in the Constitution, which promises equal protection of the laws. These principles are also enshrined in our Nation's anti-discrimination laws, among them Title VII of the Civil Rights Act of 1964, as amended (42 U.S.C. 2000e *et seq.*). In *Bostock* v. *Clayton County*, 590 U.S.__(2020), the Supreme Court held that Title VII's prohibition on discrimination "because of . . . sex" covers discrimination on the basis of gender identity and sexual orientation. Under *Bostock's* reasoning, laws that prohibit sex discrimination—including Title IX of the Education Amendments of 1972, as amended (20 U.S.C. 1681 *et seq.*), the Fair Housing Act, as amended (42 U.S.C. 3601 *et seq.*), and section 412 of the Immigration and Nationality Act, as amended (8 U.S.C. 1522), along with their respective implementing regulations—prohibit discrimination on the basis of gender identity or sexual orientation, so long as the laws do not contain sufficient indications to the contrary.

Discrimination on the basis of gender identity or sexual orientation manifests differently for different individuals, and it often overlaps with other forms of prohibited discrimination, including discrimination on the basis of race or disability. For example, transgender Black Americans face unconscionably high levels of workplace discrimination, homelessness, and violence, including fatal violence.

It is the policy of my Administration to prevent and combat discrimination on the basis of gender identity or sexual orientation, and to fully enforce Title VII and other laws that prohibit discrimination on the basis of gender identity or sexual orientation. It is also the policy of my Administration to address overlapping forms of discrimination.

Sec. 2. *Enforcing Prohibitions on Sex Discrimination on the Basis of Gender Identity or Sexual Orientation*. (a) The head of each agency shall, as soon as practicable and in consultation with the Attorney General, as appropriate, review all existing orders, regulations, guidance documents, policies, programs, or other agency actions ("agency actions") that:

(i) were promulgated or are administered by the agency under Title VII or any other statute or regulation that prohibits sex discrimination, including any that relate to the agency's own compliance with such statutes or regulations; and

(ii) are or may be inconsistent with the policy set forth in section 1 of this order.

(b) The head of each agency shall, as soon as practicable and as appropriate and consistent with applicable law, including the Administrative Procedure Act (5 U.S.C. 551 *et seq.*), consider whether to revise, suspend, or rescind such agency actions, or promulgate new agency actions, as necessary to fully implement statutes that prohibit sex discrimination and the policy set forth in section 1 of this order.

(c) The head of each agency shall, as soon as practicable, also consider whether there are additional actions that the agency should take to ensure that it is fully implementing the policy set forth in section 1 of this order. If an agency takes an action described in this subsection or subsection (b) of this section, it shall seek to ensure that it is accounting for, and taking appropriate steps to combat, overlapping forms of discrimination, such as discrimination on the basis of race or disability.

(d) Within 100 days of the date of this order, the head of each agency shall develop, in consultation with the Attorney General, as appropriate, a plan to carry out actions that the agency has identified pursuant to subsections (b) and (c) of this section, as appropriate and consistent with applicable law.

Sec. 3. *Definition.* "Agency" means any authority of the United States that is an "agency" under 44 U.S.C. 3502(1), other than those considered to be independent regulatory agencies, as defined in 44 U.S.C. 3502(5).

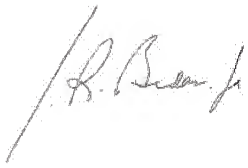
Sec. 4. *General Provisions.* (a) Nothing in this order shall be construed to impair or otherwise affect:

(i) the authority granted by law to an executive department or agency, or the head thereof; or

(ii) the functions of the Director of the Office of Management and Budget relating to budgetary, administrative, or legislative proposals.

(b) This order shall be implemented consistent with applicable law and subject to the availability of appropriations.

(c) This order is not intended to, and does not, create any right or benefit, substantive or procedural, enforceable at law or in equity by any party against the United States, its departments, agencies, or entities, its officers, employees, or agents, or any other person.



THE WHITE HOUSE,
January 20, 2021.

[FR Doc. 2021–01761
Filed 1–22–21; 11:15 am]
Billing code 3295–F1–P

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
VOLUME 6 OF 10 (Tabs 178-11 – 183-20)

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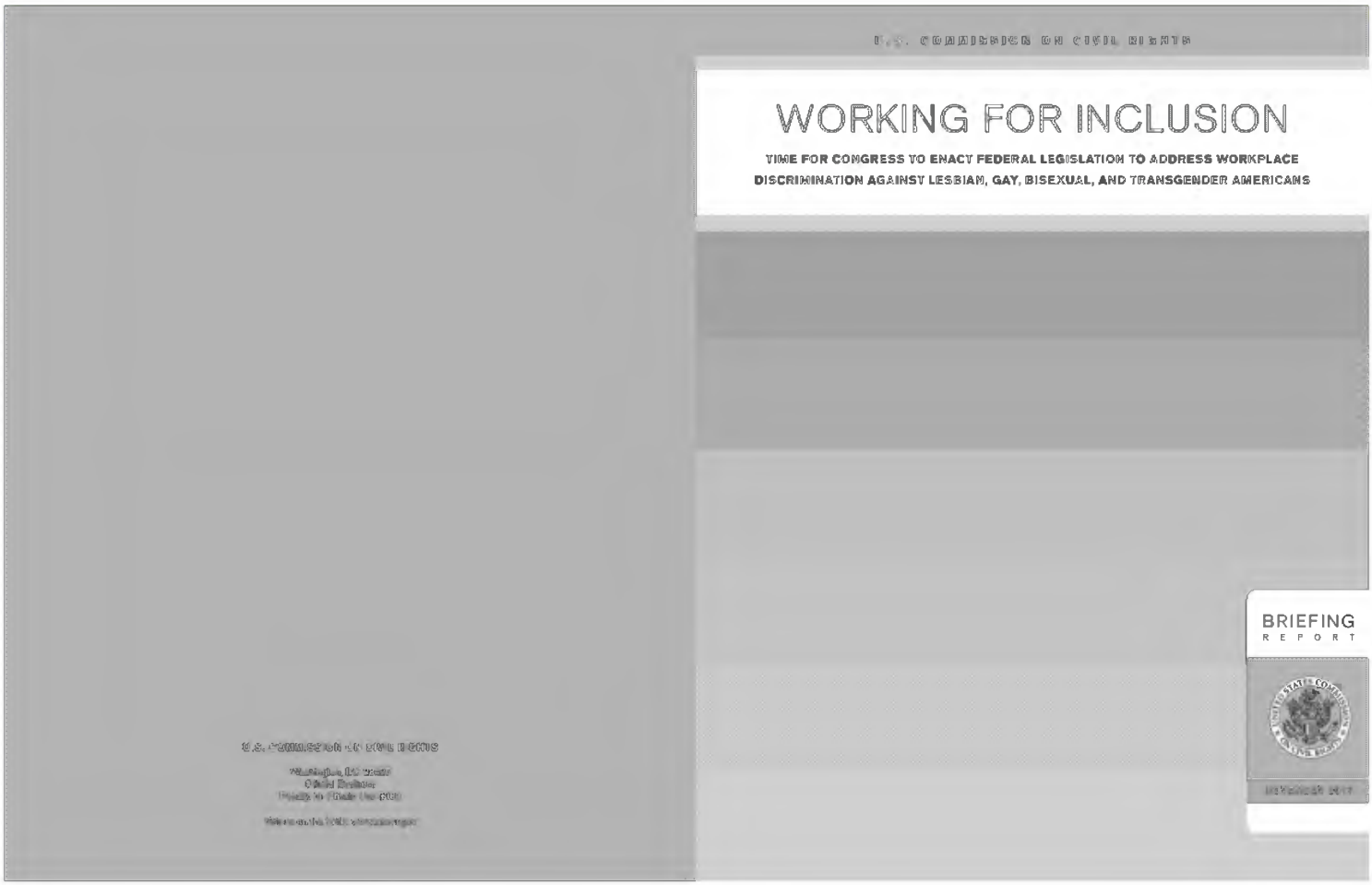

Pl. Trial Ex. 131

U.S. COMMISSION ON CIVIL RIGHTS

The U.S. Commission on Civil Rights is an independent, bipartisan agency established by Congress in 1957. It is directed to:

- Investigate complaints alleging that citizens are being deprived of their right to vote by reason of their race, color, religion, sex, age, disability, or national origin, or by reason of fraudulent practices.
- Study and collect information relating to discrimination or a denial of equal protection of the laws under the Constitution because of race, color, religion, sex, age, disability, or national origin, or in the administration of justice.
- Appraise federal laws and policies with respect to discrimination or denial of equal protection of the laws because of race, color, religion, sex, age, disability, or national origin, or in the administration of justice.
- Serve as a national clearinghouse for information in respect to discrimination or denial of equal protection of the laws because of race, color, religion, sex, age, disability, or national origin.
- Submit reports, findings, and recommendations to the President and Congress.
- Issue public service announcements to discourage discrimination or denial of equal protection of the laws.

MEMBERS OF THE COMMISSION

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Working for Inclusion: Time for Congress to Enact Federal Legislation to Address Workplace Discrimination Against Lesbian, Gay, Bisexual, and Transgender Americans

Briefing Before
The United States Commission on Civil Rights
Held in Washington, DC

Briefing Report

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UNITED STATES COMMISSION ON CIVIL RIGHTS

1331 PENNSYLVANIA AVE., NW • SUITE 1150 • WASHINGTON, DC 20425
WWW.USCCR.GOV

Letter of Transmittal

President Donald J. Trump
Vice President Mike Pence
Speaker of the House Paul Ryan
Senate Majority Leader Mitch McConnell

On behalf of the United States Commission on Civil Rights ("the Commission"), I am pleased to transmit our briefing report, *Working for Inclusion: Time for Congress to Enact Federal Legislation to Address Workplace Discrimination Against Lesbian, Gay, Bisexual, and Transgender Americans*. The report is also available in full on the Commission's website at www.usccr.gov.

The report examines the main social and economic arguments made for and against enacting federal legislation to provide federal nondiscrimination workplace protections for lesbian, gay, bisexual, and transgender (LGBT) employees.

The majority of the Commission voted for key findings including that LGBT workers have faced a long, serious, and pervasive history of official and unofficial employment discrimination by federal, state, and local governments and private employers. Such discrimination persists and has wide-ranging, damaging implications for the quality of life for many LGBT Americans, their children and families, and communities. An inconsistent and irreconcilable patchwork of state laws against LGBT workplace discrimination and federal court decisions interpreting existing federal law render LGBT employees insufficiently protected from workplace discrimination.

Our primary recommendation is directed to Congress: In order to effectively and consistently protect LGBT employees from workplace discrimination, Congress should immediately enact a federal law explicitly banning discrimination in the workplace based on sexual orientation and gender identity. We also make particular recommendations that federal agencies should issue and —where relevant—reaffirm specific guidance for federal and private employers outlining protections for LGBT individuals in the workforce, including specifically enumerating

protections for transgender persons; federal agencies should also collect workplace discrimination data about LGBT employees.

We at the Commission are pleased to share our views, informed by careful research and investigation, to help ensure that all Americans enjoy civil rights protections to which we are entitled.

For the Commission,

Catherine E. Lhamon

Chair

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EXECUTIVE SUMMARY

American employees spend a large part of our awake hours at work. At the same time, the majority of lesbian, gay, bisexual, and transgender (LGBT)[1] workers live in states that do not offer explicit LGBT-specific nondiscrimination protections in employment. The briefing testimony and written materials submitted to the Commission, along with extensive social science research and surveys, reflect the reality that many LGBT Americans are forced to deal with prejudice and discrimination every day in the workplace. Over the past several decades, there has been increasing national support for extending equal protections to LGBT individuals. According to a 2013 poll released by Project Right Side and Americans for Workplace Opportunity, a majority of people (88 percent), regardless of political affiliation, agreed that LGBT individuals should be judged based on their performance in the workplace.[2] Congress has not enacted federal antidiscrimination workplace protections for LGBT employees. This report highlights the main social and economic arguments made by proponents and opponents for enacting federal legislation and makes findings and recommendations regarding civil rights status for LGBT employees.

Over the past forty years, Congress has introduced multiple iterations of legislation that would prohibit workplace discrimination against LGBT Americans, but has not passed such legislation. On March 16, 2015, the Commission held a briefing to examine workplace discrimination against LGBT Americans.[3] The purpose of the briefing was to gather information about existing state, local, and federal laws and policies, and the impacts of discrimination on LGBT employees. The Commission also sought to hear from multiple perspectives in support of and against enacting federal legislation to address workplace discrimination against LGBT employees.[4]

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[1] This report uses the acronym of LGBT to include individuals who are lesbian, gay. bisexual, or transgender. At times, this report refers to "LGB" to refer only to those individuals because, for example, the particular study being discussed may have been limited to that sub-group.

[2] Alex Lundry, "ENDA National Poll Results," (TargetPoint Consulting, September 16, 2013), http://images.politico.com/global/2013/09/29/enda_poll_2013-09-08_natl_memo.html, p. 1; *see also* http://images.politico.com/global/2013/09/29/enda_poll_2013-09-08_50_states.html.

[3] U.S. Commission on Civil Rights. *Briefing: Examining Workplace Discrimination Against LGBT Americans,* (Washington, DC, March 16, 2015), http://www.usccr.gov/calendar/trnscrpt/Discrimination_LGBT_03-16-2015.pdf (*hereinafter cited* as Briefing Transcript).

[4] During the briefing, the Commission heard from three panels of experts. These experts discussed 1) the federal government's compliance with laws, regulations, and presidential Executive Orders that prohibit discrimination against LGBT Americans; 2) the impacts for LGBT employees who reside in states that do not have specific state nondiscrimination protections; and 3) policy issues, including whether Congress should pass federal legislation and the appropriate language for such federal legislation. *Ibid.*

Proponents in favor of a national law that specifically forbids discriminating against employees based on their sexual orientation[5] or gender identity[6] contend that federal legislation is necessary to provide LGBT workers equal rights and equal dignity in the workplace similar to other workers. Proponents of federal legislation further argue that although the federal government, states, corporations, and businesses are increasingly creating and enforcing LGBT-inclusive policies, this progress is at best sporadic and uneven. As these policies are enacted separately and independently, the lack of national legal protections leaves many to hide who they are for fear of discrimination—including termination—in the workplace. They also assert that while the nation has experienced some great strides in LGBT equality over the past several years, widespread discrimination and animus towards LGBT communities is still prevalent. Additionally, researchers have found that LGBT individuals who live in jurisdictions without worker protections also experience poverty at higher rates than heterosexuals in those jurisdictions. At the same time, lesbians and gay men living in jurisdictions that do offer employment protections were less likely to be impoverished compared to heterosexuals.[7] These findings suggest anti-discrimination protections and a social climate of acceptance may mitigate disparities.

Proponents further note that existing state and federal laws leave many LGBT employees unprotected from workplace discrimination.[8] Recently, the Equal Employment Opportunity Commission (EEOC) interpreted existing federal law prohibiting sex discrimination (Title VII of the Civil Rights Act) to include claims of discrimination based on sexual orientation and gender identity.[9] The U.S. Court of Appeals for the Seventh Circuit is currently the sole Circuit to hold that sexual orientation falls within the existing language of Title VII.[10] Yet, other Circuit Courts

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[5] Sexual orientation may be defined as "one's emotional or physical attraction to the same and/or opposite sex." Office of Personnel Management, U.S. Equal Employment Opportunity Commission, U.S. Office of Special Counsel, and Merit Systems Protection Board, *Addressing Sexual Orientation and Gender Identity Discrimination in Federal Civilian Employment: A Guide to Employment Rights, Protections, and Responsibilities*, rev. June 2015, http://www.opm.gov/policy-data-oversight/diversity-and-inclusion/reference-materials/addressing-sexual-orientation-and-gender-identity-discrimination-in-federal-civilian-employment.pdf, p. 2.

[6] Gender identity may be defined as "one's inner sense of one's own gender, which may or may not match the sex assigned at birth. Different people choose to express their gender identity differently. For some, gender may be expressed through, for example, dress, grooming, mannerisms, speech patterns, and social interactions. Gender expression usually ranges between masculine and feminine, and some transgender people express their gender consistent with how they identify internally, rather than in accordance with the sex they were assigned at birth." *Ibid.*

[7] M.V. Lee Badgett, Laura E. Durso, and Alyssa Schneebaum, "New Patterns of Poverty in the Lesbian, Gay, and Bisexual Community," Williams Institute, June 2013, https://williamsinstitute.law.ucla.edu/wp-content/uploads/LGB-Poverty-Update-Jun-2013.pdf, pp. 2–3, 4, 8–9.

[8] Sarah Warbelow and Breanna Diaz, "2016 State Equality Index," Human Rights Campaign Foundation, 2016, http://assets.hrc.org//files/assets/resources/SEI-2016-Report-FINAL.pdf?_ga=2.163800255.1465071743.1510103868-576800549.1507751318, p. 14.

[9] *See, Baldwin v. Foxx,* EEOC Doc No. 0120133080, 2015 WL 4397641 (EEOC Jul. 16, 2015) (discussing Title VII, Civil Rights Act of 1964, 42 U.S.C. § 2000e *et seq*).

[10] *Hively v. Ivy Tech Comty. Coll. of Ind.*, 853 F.3d 339, 350-51 (7th Cir. 2017). At the time of publication, this question was also pending before the U.S. Court of Appeals for the Second Circuit. See discussion *infra* in Chapter 2.

have held that Title VII does not include such protections.[11] In practice, this means that employees may or may not have access to a federal forum to hear their allegations of discrimination based on sexual orientation and gender identity. Additionally, twenty-eight states do not have state law protections prohibiting workplace discrimination based on sexual orientation, and thirty states do not have state law protections for being transgender or gender-nonconforming.[12] Proponents of federal legislation argue:

> Today, it's possible for a lesbian couple to get legally married on Saturday and then be fired on Monday for putting a wedding picture on their desk.[13]

> [D]iscrimination has no place in our nation and yet right now in 2015 in many states, like Florida, a person can be fired simply for being lesbian, gay, bisexual or transgender. As a result, millions of LGBT Americans go to work every day fearing that without any warning they could lose their jobs not because of their work performance but simply because of who they are or who they love . . . . Passing ENDA[14] would eliminate the patchwork of differing state and often absurd state legislation and provide consistent workplace protections across the country.[15]

Opponents to enactment of a specific federal non-discrimination law question whether the Constitution allows Congress to legislate non-discriminatory workplace protections for LGBT workers and argue that these protections, if any, should be governed by localities and businesses. They argue that federal legislation protecting sexual orientation and gender identity would infringe upon business owners' First Amendment rights and not permit them to run organizations that are consistent with their values.[16] Further, they argue that while all individuals should be respected, federal antidiscrimination legislation is bad policy because it is inconsistent with free-market principles protecting the freedom of contract and against overregulation by the government.[17] Ryan Anderson of the Heritage Foundation argues that a "fundamental principle" guiding American labor law is the "doctrine of 'at will' employment" that permits employers to dismiss employees

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[11] *See infra* note 134 (collecting cases).

[12] Movement Advancement Project, "Non-Discrimination Laws", http://www.lgbtmap.org/equality-maps/non_discrimination_laws/ (data current as of 10/19/17).

[13] Selisse Berry, Founder and CEO at Out and Equal Workplace Advocates, testimony, Briefing Transcript, pp. 158–59.

[14] As discussed in more detail later in this chapter, the Employment Non-Discrimination Act (ENDA) was the federal nondiscrimination legislation pending at the time of the Commission's briefing in 2015.

[15] Gina Duncan, Transgender Inclusion Director at Equality Florida, testimony, Briefing Transcript, pp. 213–14.

[16] For example, *see* Family Research Council, "The Employment Non-Discrimination Act (ENDA): A Threat to Free Markets and Freedom of Conscience and Religion," October 2013, http://downloads.frc.org/EF/EF13J68.pdf.

[17] For example, *see* Ryan Anderson, "Sexual Orientation and Gender Identity (SOGI) Laws Threaten Freedom," Heritage Foundation, November 2015, http://www.heritage.org/civil-society/report/sexual-orientation-and-gender-identity-sogi-laws-threaten-freedom, p. 2.

at any time.[18] He argues that antidiscrimination laws would threaten this principle and negatively affect the business community. Hans Bader of the Competitive Enterprise Institute claims that "[s]ince American business seldom discriminates based on sexual orientation, the potential benefits of ENDA [the Employment Non-Discrimination Act] are limited, at best. But ENDA would impose real and substantial costs on business, and it could trigger conflicts with free speech and religious freedom."[19] Bader contends that the principles of free-market competition will offer enough protections to LGBT employees, since many private companies have already prohibited discrimination on the basis of sexual orientation, and to appear anti-gay may be perceived as bad for business.[20] Finally, opponents also raise concerns about the potential for increased legal costs and workplace disruptions that they believe such federal legislation would cause.[21]

After examining the current state of LGBT workplace protections, the Commission highlights the following findings and recommendations, discussed in full in Chapter 4:

Highlighted findings:

- Historians, researchers, and courts have extensively documented that lesbian, gay, bisexual, and transgender (LGBT) workers have faced a long, serious, and pervasive history of official and unofficial employment discrimination by both federal, state, and local governments and private employers.
- Federal data sources do not effectively capture rates of LGBT employment or rates of LGBT employment discrimination.
- An inconsistent and irreconcilable patchwork of state laws against anti-LGBT workplace discrimination and federal court decisions interpreting existing federal law render LGBT employees insufficiently protected from workplace discrimination.

Highlighted recommendations:

- In order to effectively and consistently protect LGBT employees from workplace discrimination, Congress should immediately enact a federal law explicitly banning discrimination in the workplace based on sexual orientation and gender identity.
- In addition to Congressional action, federal agencies including the Departments of Justice and Labor, the Equal Employment Opportunity Commission, and the Office of Personnel Management should issue and—where relevant—reaffirm specific guidance for federal

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[18] *Ibid.* at 6.

[19] Hans Bader, "Employment Non-Discrimination Act Makes as Little Sense as Chemotherapy for a Cold," *OpenMarket Blog*, Competitive Enterprise Institute, June 2012, https://cei.org/blog/employment-non-discrimination-act-makes-little-sense-chemotherapy-cold.

[20] *Ibid.*

[21] For example, *see* Ryan Anderson, William E. Simon Fellow at the Heritage Foundation, testimony, Briefing Transcript, p. 276 ("[Nondiscrimination federal legislation] will expose employers to unimaginable liability").

and private employers outlining protections for LGBT individuals in the workforce, including specifically enumerating protections for transgender persons.

- Workplace discrimination data should be collected through the inclusion of sexual orientation and gender identity questions in population-based surveys of the workforce such as the Census, American Community Survey, and surveys fielded by the Bureau of Labor Statistics and other agencies.

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CHAPTER 1: INTRODUCTION TO LGBT EMPLOYMENT IN AMERICA

This introductory chapter: 1) seeks to quantify the number of LGBT employees in the United States, 2) discusses the extent and impact of workplace discrimination against LGBT employees, 3) lists the existing state laws addressing LGBT employees, and 4) discusses the prior efforts to enact federal legislation.

Number of Lesbian, Gay, Bisexual, and Transgender Employees

The exact number of individuals who self-identify as LGBT is not known. Historically, many national surveys have not included questions exploring sexual orientation or gender identity.[22] In fact, early estimates of LGBT couples were made by examining U.S. Census responses identifying households with cohabitating unmarried couples of the same sex.[23] Most recently, the U.S. Census Bureau sent a draft of the 2020 Census and American Community Survey collection report to Congress in March 2017.[24] It appeared that the Census Bureau was going to collect LGBT demographic information, but later that same day, the Census Bureau stated that it mistakenly included those categories for collection.[25] Advocates have argued that alongside adding LGBT questions to the Census, the American Community Survey and surveys fielded by the Bureau of Labor Statistics should include questions on sexual orientation and gender identity.[26]

A 2013 survey conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics found that 3.4 percent of Americans identify themselves as gay or lesbian (1.6 percent), bisexual (0.7 percent) or other (1.1 percent).[27] More recently, a 2017 Gallup survey found

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[22] Berry testimony, Briefing Transcript, p. 176 ("[W]e're not being counted. We're not being asked to self-identify who we are within companies or within workplaces at all.").

[23] Jaime Grant, "How Big is the LGBT Community? Why Can't I Find This Number?", National Gay and Lesbian Task Force, 2010, http://www.thetaskforce.org/static_html/downloads/release_materials/tf_lgbt_community.pdf, p. 3.

[24] U.S. Census Bureau, "Subjects Planned for the 2020 Census and American Community Survey," March 2017, https://www2.census.gov/library/publications/decennial/2020/operations/planned-subjects-2020-acs.pdf.

[25] Hansi Lo Wang, "U.S. Census to Leave Sexual Orientation, Gender Identity Questions Off New Surveys," *NPR*, March 29, 2017, https://www.npr.org/sections/thetwo-way/2017/03/29/521921287/u-s-census-to-leave-sexual-orientation-gender-identity-questions-off-new-surveys70329. The Administration for Community Living of the U.S. Department of Health and Human Services also proposed to delete a question on sexual orientation from the National Survey of Older Americans Act Participants, but decided to retain the question after many groups and individuals objected to the change. Revision of Currently Approved Collection for National Survey of Older Americans Act Participants (NSOAAP), 82 Fed. Reg. 28491 (Jun. 22, 2017).

[26] Statement of Stacey Long Simmons, Director of Public Policy & Government Affairs at National LGBTQ Task Force, U.S. Commission on Civil Rights, *Briefing: Examining Workplace Discrimination Against LGBT Americans,* (Washington, DC, March 16, 2015) at 5 (*hereinafter cited* as Simmons Statement).

[27] Brian W. Ward, James M. Dahlhamer, Adena M. Galinsky, Sarah J. Joestl, "Sexual Orientation and Health Among U.S. Adults: National Health Interview Survey, 2013," National Center for Health Statistics, 2014, https://www.cdc.gov/nchs/data/nhsr/nhsr077.pdf, p. 1. The National Health Interview Survey of 34,557 adults aged

that the portion of American adults who identified as LGBT increased from 3.5 percent in 2012 to 4.1 percent in 2016.[28] According to Gallup, these figures are from "the largest representative sample of LGBT Americans collected in the U.S."[29] This means there are an estimated 10 million adults who now identify as LGBT in the U.S., which is approximately 1.75 million more individuals than in 2012. This increase is largely due to millennials (defined as those born between 1980 and 1998) being more than twice as likely as previous generations to self-identify as LGBT.[30]

Population estimates of LGBT communities may be non-inclusive due to several factors, because of the multiple dimensions of sexuality.[31] First, self-identification is only one aspect of measuring sexual orientation and gender identity. For example, research shows that when surveys are inclusive of the complex dynamics of identity, behavior, attraction, and relationships, these surveys yield very different (and often larger) population estimates compared to those that only utilize self-identification measures.[32] Other studies suggest that sexual orientation and gender identity are on a continuum (*i.e.*, not static) for some individuals, therefore, they do not self-identify with categories that traditionally appear on surveys.[33] Thus, depending on which definition(s) and measure(s) a researcher chooses, estimates may vary. These disparate results can also be due to "how comfortable and confident survey respondents feel about the confidentiality and privacy of data collected."[34]

Based on these estimates (and considering the likelihood of underreporting, as mentioned above), it is fair to say that LGBT Americans comprise a significant portion of private and public sector employees.[35] In addition to the difficulties described above, the exact number of LGBT employees

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18–64 added questions on sexual orientation in 2013 to create an "ongoing collection of information on sexual orientation" to enable a "more consistent, long-term monitoring" of the goal of "improving the health, safety, and well-being of LGB persons." The "other" category represents the "something else" response, "don't know" response, or respondent refused to answer. *Ibid.* at 2.

[28] Gary J. Gates, "In US, More Adults Identifying as LGBT," Gallup, January 11, 2017, http://www.gallup.com/poll/201731/lgbt-identification-rises.aspx.

[29] *Ibid.* Results are based on telephone interviews with a random sample of 1,626,773 U.S. adults, 18 and older, living in all 50 states and D.C., collected from June 1, 2012 through December 30, 2016.

[30] *Ibid.*

[31] Grant, *supra* note 23, at 4-5.

[32] Identity, behavior, attraction, and relationships all capture related dimensions of sexual orientation and gender identity, but none of these measures completely address the concepts. *See* Gary Gates, "How many people are lesbian, gay, bisexual, and transgender?", Williams Institute, April 2011, https://williamsinstitute.law.ucla.edu/wp-content/uploads/Gates-How-Many-People-LGBT-Apr-2011.pdf, p. 2.

[33] *Ibid.* Judith Bradford and Jocelyn C. White, "Lesbian Health Research," in *Women and Health* (San Diego, Calif.: Academic Press, 2000), 64–78. Edward O. Laumann, John H. Gagnon, Robert T. Michael, Stuart Michaels, *The Social Organization of Sexuality: Sexual Practices in the United States* (Chicago, Ill: University of Chicago Press, 1994). Laura Dean, Ilan H. Meyer, Kevin Robinson, Randall L. Sell, Robert Sember, Vincent M.B. Silenzio, Deborah J. Bowen, et al., "Lesbian, Gay, Bisexual, and Transgender Health: Findings and Concerns," *Journal of the Gay and Lesbian Medical Association*, 4:3 (2000), p. 101, https://doi.org/10.1023/A:1009573800168.

[34] Gates, *supra* note 28.

[35] Crosby Burns, Kate Childs Graham, and Sam Menefee-Libey, "Gay and Transgender Discrimination in the Public Sector: Why It's a Problem for State and Local Governments, Employees and Taxpayers," Center for American

is also not fully known due to fear of coming out at work which could subject individuals to harassment or discrimination by colleagues or their employer. According to a survey from the Pew Research Center, "only one-third of employed LGBT adults say all or most of the people they closely work with are aware of their sexual orientation or gender identity."[36] Further, over a third of respondents say no one at work knows their sexual orientation or gender identity.[37] Only approximately 5.8 percent of self-identified bisexual survey respondents were generally open about their sexual orientation to their coworkers.[38] A 2014 report authored by the Human Rights Campaign found that most (53 percent) of LGBT employees are open about their sexuality with only a few people or are entirely "closeted" at work.[39]

Nevertheless, the best available data suggests a general range of 5.4 million to 8.2 million for estimating employees who self-identify as LGBT. The National LGBTQ Taskforce estimates there are 5.4 million LGBT workers in the United States.[40] For the upper-range, the 2015 Williams Institute report[41] estimates that up to 9.5 million adults self-identify as LGBT[42] and the 2017 Gallup poll estimates 10 million adults, or 4.1 percent of U.S. adults.[43] This puts the LGBT workforce at approximately over eight million LGBT employees. As of September 2009, state and local governments employed approximately 19.7 million workers.[44] This estimate includes about 5.2 million state employees and 14.5 million local government employees.[45] The Williams Institute

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Progress, September 2012, https://cdn.americanprogress.org/wp-content/uploads/2012/08/LGBTPublicSectorReport1.pdf, p. 6.

[36] Pew Research Center, "A Survey of LGBT Americans: Attitudes, Experiences and Values in Changing Times," June 13, 2013, http://assets.pewresearch.org/wp-content/uploads/sites/3/2013/06/SDT_LGBT-Americans_06-2013.pdf, p. 59.

[37] Brad Sears & Christy Mallory, The Williams Institute, Documented Evidence of Employment Discrimination & Its Effects on LGBT People (2011), *available at* https://williamsinstitute.law.ucla.edu/wp-content/uploads/Sears-Mallory-Discrimination-July-20111.pdf; Gary J. Gates, "Sexual Minorities in the 2008 General Social Survey: Coming Out and Demographic Characteristics," October 2010.

[38] *Ibid.*

[39] Deena Fidas and Liz Cooper, "The Cost of the Closet and the Rewards of Inclusion: Why the Workplace Environment for LGBT People Matters to Employers," Human Rights Campaign Foundation, May 2014, http://assets.hrc.org//files/assets/resources/Cost_of_the_Closet_May2014.pdf?_ga=1.25864509.1225877603.1490017176, p. 9.

[40] Stacey Long Simmons, Director of Public Policy and Government Affairs for the National LGBTQ Task Force, testimony, Briefing Transcript, p. 80. *See also* Simmons Statement, *supra* note 26, at 2.

[41] The Williams Institute is a nationally recognized think tank housed at the UCLA School of Law that specializes in research on sexual orientation and gender identity law, and public policy. It was founded in 2001 and is a respected, independent research institute that is often cited and influential in policy change, media, and nonprofit advocacy work regarding LGBTQ communities.

[42] Lauren Jow, "9.5M LGBT Adults Nationwide Would Be Protected under New Comprehensive Non-Discrimination Bill," Williams Institute, July 2015, *available at* https://williamsinstitute.law.ucla.edu/press/press-releases/9-5m-lgbt-adults-nationwide-would-be-protected-under-new-comprehensive-non-discrimination-bill/, Gary J. Gates, "LGBT Demographics: Comparisons among population-based surveys," Williams Institute, 2014, http://williamsinstitute.law.ucla.edu/wp-content/uploads/lgbt-demogs-sep-2014.pdf, p. 1.

[43] Gates, *supra* note 28.

[44] Burns, *supra* note 35, at 6.

[45] *Ibid.*

estimates that as of 2009 slightly more than 4 percent of municipal employees (585,000) and slightly more than 8 percent of state employees (418,000) are LGBT.[46] In addition, as shown in Table 1 below, data from the U.S. Bureau of Labor Statistics and the Williams Institute reflect that approximately 7 million private-sector employees—roughly 85 percent of the total LGBT workforce—are LGBT.

Table 1 Number of Gay and Transgender Employees by Secto

	Number of LGBT Employees (Est.)	Total Number of Employees	Percent out of total LGBT Workforce (Est.)
Local	585,000	14,516,000	7.13
State	418,000	5,155,000	5.09
Federal	200,000	2,829,000	2.44
Total Public	1,203,000	22,500,000	14.67
Total Private	7,000,000	107,234,000	85.33
Total Public and Private	8,203,000	129,734,000	100

Source: Crosby Burns, Kate Childs Graham, and Sam Menefee-Libey, "Gay and Transgender Discrimination in the Public Sector: Why It's a Problem for State and Local Governments, Employees and Taxpayers," Center for American Progress, September 2012, https://cdn.americanprogress.org/wp-content/uploads/2012/08/LGBTPublicSectorReport1.pdf, p. 6 (noting that the source of its data is the Williams Institute and U.S. Bureau of Labor Statistics), *accessed at* https://www.americanprogress.org/wp-content/uploads/2012/08/LGBTPublicSectorReport1.pdf, USCCR staff provided calculations for third (totals) column.

In 2012, the Office of Personnel Management (OPM) began asking federal employees to self-identify whether they are LGBT on its annual survey of federal workers.[47] As of 2015, OPM estimates that 3 percent of the federal civilian workforce is LGBT.[48] With regard to military service, the University of Southern California estimates that nearly 71,000 LGBT service members were serving in the military, or 2.8 percent of the total work force of the United States military as of 2016.[49] The Williams Institute estimates that nearly 150,000 transgender military personnel have served or are currently serving in the military.[50]

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[46] Brad Sears, Nan D. Hunter, Christy Mallory, "Documenting Discrimination on the Basis of Sexual Orientation and Gender Identity in State Employment," Williams Institute, September 2009, https://williamsinstitute.law.ucla.edu/wp-content/uploads/1_LGBTWorkforce1.pdf, p. 1.

[47] U.S. Office of Personnel Management, "2012 Federal Employee Viewpoint Survey Results: Employees Influencing Change," 2012, https://www.fedview.opm.gov/2012files/2012_Government_Management_Report.pdf, p. 21.

[48] U.S. Office of Personnel Management, "Federal Employee Viewpoint Survey Results: Employees Influencing Change," 2015, https://www.fedview.opm.gov/2015FILES/2015_FEVS_Gwide_Final_Report.PDF, p. 38.

[49] Jeremy T. Goldbach and Carl Andrew Castro, "Lesbian, Gay, Bisexual, and Transgender (LGBT) Service Members: Life After Don't Ask, Don't Tell," *Current Psychiatry Reports*, 18:56 (2016), p. 1, http://cir.usc.edu/wp-content/uploads/2016/04/GoldbachCastro-LGBT-Military.pdf.

[50] Gary J. Gates and Jody L. Herman, "Transgender Military Service in the United States," Williams Institute, May 2014, http://williamsinstitute.law.ucla.edu/wp-content/uploads/Transgender-Military-Service-May-2014.pdf, p. 1. *See also* Agnes Gereben Schaefer, Radha Iyengar, Srikanth Kadiyala, Jennifer Kavanagh, Charles C. Engel, Kayla

Extent of Discrimination Against LGBT Employees

Studies have found that discrimination in the workplace has a negative effect on LGBT employees.[51] LGBT individuals often face lower wages, increased difficulty in finding jobs, promotion denials, and/or job terminations due to their sexual orientation or gender identity. Studies have found that anywhere from 21 to 47 percent of LGBT adults faced employment discrimination because they were gay or transgender.[52] A summary of numerous studies of LGBT employee survey respondents showed that ten to 28 percent reported receiving negative performance evaluations or were passed over for promotion because they were gay or transgender, and seven to 41 percent experienced verbal and/or physical abuse in the workplace.[53] More staggering is that 90 percent of transgender employees report experiencing some form of harassment or mistreatment on the job.[54] For instance, 23 percent of employed transgender workers reported mistreatment such as "being forced to use a restroom that did not match their gender

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M. Williams and Amii M. Kress, "Assessing the Implications of Allowing Transgender Personnel to Serve Openly," RAND Corporation, 2016, https://www.rand.org/pubs/research_reports/RR1530.html (finding that somewhere between 1,320 and 6,630 transgender individuals then served in the military and a more precise estimate was not possible given current data limitations).

[51] *See e.g.,* Deborah Vagins, "Working in the Shadows: Ending Employment Discrimination for LGBT Americans," American Civil Liberties Union, September 2007, https://www.aclu.org/files/pdfs/lgbt/enda_20070917.pdf; Sears, *supra* note 37; Jennifer C. Pizer, Brad Sears, Christy Mallory, and Nan D. Hunter, *Evidence of Persistent and Pervasive Workplace Discrimination Against LGBT People: The Need for Federal Legislation Prohibiting Discrimination and Providing for Equal Employment Benefits*, 45 Loy. L.A. L. Rev. 715 (2012), *available at* http://williamsinstitute.law.ucla.edu/wp-content/uploads/Pizer-Mallory-Sears-Hunter-ENDA-LLR-2012.pdf.

[52] Movement Advancement Project, Center for American Progress, and Human Rights Campaign, "A Broken Bargain: Discrimination, Fewer Benefits and More Taxes for LGBT Workers," June 2013, http://www.lgbtmap.org/file/a-broken-bargain-full-report.pdf, p. 27 (estimating that 38% of LGBT employees who were "out at work" had experienced discrimination or harassment); Preston Mitchum, "Workplace Discrimination Series: Brooke Waits," Center for American Progress, Aug. 5, 2013, *available at* http://www.americanprogress.org/issues/lgbt/news/2013/08/05/71447/workplace-discrimination-series-brooke-waits/; Burns, *supra* note 35, at pp. 7–8 (collecting data from four different surveys that reflected that, at the low end, 13 percent of gay public-sector workers "reported being denied a promotion or receiving a negative job evaluation" to, at the high end, 47% of respondents in on a survey on transgender Americans reported experiencing "some sort of adverse job outcome"). Michigan Department of Civil Rights, *Report on LGBT Inclusion Under Michigan Law, With Recommendations for Action,* 43–44, (Jan. 28, 2013,) *available at* https://www.michigan.gov/documents/mdcr/MDCR_Report_on_LGBT_Inclusion_409727_7.pdf; Hon. Jared Polis, U.S. Representative of Second District of Colorado, testimony, Briefing Transcript, p. 257 (stating that "[f]orty-two percent of LGBT Americans have experienced mistreatment of harassment on their job just due to their sexual orientation").

[53] M.V. Lee Badgett, Holning Lau, Brad Sears, Deborah Ho, "Bias in the Workplace: Consistent Evidence of Sexual Orientation and Gender Identity Discrimination," Williams Institute, 2007, https://williamsinstitute.law.ucla.edu/wp-content/uploads/Badgett-Sears-Lau-Ho-Bias-in-the-Workplace-Jun-2007.pdf, p. 2.

[54] U.S. Department of Labor, "DOL Policies on Gender Identity: Rights and Responsibilities," July 2013, https://www.dol.gov/oasam/programs/crc/20130712GenderIdentity.htm (citing Jaime M. Grant, Lisa A. Mottet, and Justin Tanis, "Injustice at Every Turn: A Report of the National Transgender Discrimination Survey," National Center for Transgender Equality and National Gay and Lesbian Task Force, 2011, http://www.thetaskforce.org/static_html/downloads/reports/reports/ntds_full.pdf, p. 3).

identity, being told to present in the wrong gender in order to keep their job, or having a boss or coworker share private information about their transgender status without their permission."[55]

Discrimination against LGBT employees can begin with the job application process. Researchers found discrimination against LGBT employee applicants, for example, in a study when researchers sent two sets of matched resumes to major employers, where one resume suggested the applicant was gay (*e.g.*, by disclosing leadership experience at an LGBT student organization), employers were far less likely to positively receive "gay" applicants than "straight" ones. Results revealed that those with indications of being LGBT received approximately 30 percent fewer callbacks.[56]

Discrimination against LGBT employees affects all occupations. LGBT individuals across the country and in a variety of professions report being discriminatorily terminated from their jobs. As with all discrimination claims, there may be conflicting narratives between employee and employer. Pointing to either administrative (*i.e.*, EEOC) or court rulings to determine rates of discrimination is also difficult: the EEOC only recently ruled that people claiming discrimination on the basis of sexual orientation or gender identity have the right to sue under Title VII. As discussed in more detail below, only one Circuit has held that sexual orientation claims may be brought under Title VII, and the Circuit courts are divided on whether claims of gender identity fall under Title VII.

At the same time, there is evidence that discrimination is occurring. Every year (since January 2013 when the EEOC began collecting data), there has been a steady increase in the number of merit resolutions rulings and reasonable cause claims reported to the EEOC for LGBT plaintiffs (see Table 2). While the EEOC does not publish their decisions, these numbers suggest that these cases had favorable outcomes to LGBT plaintiffs alleging discrimination or the EEOC determined that there was reasonable cause to believe discrimination occurred based upon investigation.

Results from the 2008 General Social Survey (GSS)[57] found that 42 percent of LGB employees experienced at least one form of employment discrimination at some point in their lives.[58] Moreover, the survey found 25 percent of LGB-identified respondents employed by federal, state, or local governments reported having experienced workplace discrimination due to their sexual orientation in the prior five years.[59]

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[55] Sandy E. James, Jody L. Herman, Susan Rankin, Mara Keisling, Lisa Mottet, and Ma'ayan Anafi, "The Report of the 2015 U.S. Transgender Survey," National Center for Transgender Equality, December 2016, http://www.transequality.org/sites/default/files/docs/usts/USTS%20Full%20Report%20-%20FINAL%201.6.17.pdf, p. 10–11.

[56] Emma Mishel, Discrimination against Queer Women in the U.S. Workforce: A Résumé Audit Study, *Socius*, p. 6, (2016), http://journals.sagepub.com/doi/pdf/10.1177/2378023115621316.

[57] The GSS is conducted by the National Opinion Research Center at the University of Chicago, and has been a reliable source for monitoring social and demographic changes in the United States since 1972.

[58] Pizer, *supra* note 51, at 722-23.

[59] *Ibid.* at 723.

Table 2 LGBT-Based Sex Discrimination Charges				
	FY 2013*	**FY 2014**	**FY 2015**	**FY 2016**
Receipts	808	1,100	1,412	1,768
Resolutions	337	846	1,135	1,649
Resolutions By Type				
Settlements	31	71	96	118
	9.2%	8.4%	8.5%	7.2%
Withdrawals w/Benefits	17	46	57	74
	5.0%	5.4%	5.0%	4.5%
Administrative Closures	69	164	203	282
	20.5%	19.4%	17.9%	17.1%
No Reasonable Cause	216	544	737	1,114
	64.1%	64.3%	64.9%	67.6%
Reasonable Cause	4	21	42	61
	1.2%	2.5%	3.7%	3.7%
Successful Conciliations	1	13	13	26
	0.3%	1.5%	1.1%	1.6%
Unsuccessful Conciliations	3	8	29	35
	0.9%	0.9%	2.6%	2.1%
Merit Resolutions	52	138	195	253
	15.4%	16.3%	17.2%	15.3%
Monetary Benefits (Millions)	**$0.9**	**$2.2**	**$3.3**	**$4.4**

*The data for FY 2013 is for the last three quarters only. EEOC began tracking information on charges filed alleging discrimination related to gender identity and/or sexual orientation for charges received on or after January 1, 2013. Note: Charges may have multiple allegations under multiple statutes, so totals will not tally with breakdowns of specific bases or issues and are subject to updates. Monetary benefits include amounts which have been recovered exclusively or partially on non-LGBT claims included in the charge.
Source: Jeanne Goldberg (Senior Attorney Advisor, Office of the Legal Counsel, EEOC), in discussion with USCCR staff, April 17, 2017.

According to the Williams Institute, in 2008 approximately 38 percent of LGB people who were open about their sexual orientation in the workplace have experienced discrimination or harassment in the workplace.[60] Seven percent of LGB Americans report losing jobs because of their sexual orientation.[61] According to the National Center for Transgender Equality and the National Gay and Lesbian Task Force, for transgender employees the statistics are significantly higher, with 90 percent reporting experiencing harassment, mistreatment, or discrimination at

[60] *Ibid.*
[61] *Ibid.*

work, or taking actions to avoid it (*e.g.*, hiding their identity), due to their gender identity.[62] In addition, 2013 data from the Pew Research Center indicates that 21 percent of LGBT Americans feel that an employer has treated them unfairly due to their sexual orientation or gender identity.[63]

Employment discrimination also significantly affects LGBT youth and their long-term career opportunities. Bill Bettencourt from the Center for the Study of Social Policy explained that "[t]he lack of sufficient supportive career options for LGBT young people unfortunately leads to a path that impacts our criminal system and society as a whole."[64] According to a 2011-2012 Williams Institute survey, approximately 40 percent of homeless youth are LGBT.[65] Respondents most frequently cited family rejection of their sexual orientation or gender identity as a factor leading to their homelessness,[66] and 32 percent indicated abuse from their families as a reason cited for leaving.[67] Bettencourt argued that "[n]o matter what kinds of system improvements we put in place to support these young people in achieving some independence and becoming responsible citizens, without workplace supports we are doomed to fail them. Even when they can get jobs, if they cannot be themselves in the workplace, too often their productivity is impacted, as well as their ability to keep a job."[68]

ECONOMIC IMPACTS FROM WORKPLACE DISCRIMINATION

Workplace discrimination against LGBT communities can cause job instability and high turnover, resulting in greater unemployment and poverty rates as well as substantial wage gaps between LGBT and heterosexual workers. On average gay men earn from ten to 32 percent less than similarly qualified heterosexual males.[69] Older gay and lesbian adults experience higher poverty rates than their heterosexual counterparts.[70] In the 2015 U.S. Transgender Survey released by the

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[62] Grant, *supra* note 54, at 51.

[63] Pew Research Center, *supra* note 36, at 1. Pew Research Center surveyed "a nationally representative sample of 1,197 self-identified lesbian, gay, bisexual, and transgender adults 18 years of age or older. The sample comprised 398 gay men, 277 lesbians, 479 bisexuals, and 43 transgender adults." *Ibid.* at 3.

[64] Public Comment of Bill Bettencourt, Senior Associate, Center for the Study of Social Policy, U.S. Commission on Civil Rights, *Briefing: Examining Workplace Discrimination Against LGBT Americans* (Washington, DC, March 16, 2015) (submitted March 11, 2015).

[65] Laura E. Durso and Gary J. Gates, "Serving Our Youth: Findings from a National Survey of Services Providers Working with Lesbian, Gay, Bisexual, and Transgender Youth Who Are Homeless or At Risk of Becoming Homeless," Palette Fund, True Colors Fund, and Williams Institute, July 2012, https://williamsinstitute.law.ucla.edu/wp-content/uploads/Durso-Gates-LGBT-Homeless-Youth-Survey-July-2012.pdf, p. 3.

[66] *Ibid.* at 4 (finding that 46% of respondents cited this factor, the highest of any factor cited by the youth).

[67] *Ibid.*

[68] Bettencourt Comment, *supra* note 64.

[69] Lee Badgett, *supra* note 53, at 1.

[70] Movement Advancement Project Services & Advocacy for Gay, Lesbian, Bisexual & Transgender Elders, and Center for American Progress, "LGBT Older Adults: Falling Through the Safety Net," September 2010, https://cdn.americanprogress.org/wp-content/uploads/issues/2010/09/pdf/lgbt_safetynet.pdf, p. 1. Randy Albelda, M.V. Lee Badgett, Alyssa Schneebaum, Gary J. Gates, "Poverty in the Lesbian, Gay, and Bisexual Community."

National Center for Transgender Equality, transgender individuals were three times as likely to be unemployed and more than twice as likely to live in poverty compared to general rates in the U.S.[71] Nearly 30 percent of respondents in the survey reported being homeless.[72] The National Commission on Employment Policies estimated that discrimination against LGBT employees can be quantified as causing a $47 million loss in annual profits, attributable to training expenditures and unemployment benefits. Others have estimated that hostile work environments cost companies $1.4 billion in lost output per year due to a decline in productivity.[73]

Financially, discrimination also creates a large burden on national economic growth. Discrimination can lead to increased turnover for a business. For instance, approximately 53 percent of LGBT employees are "closeted."[74] Closeted LGBT employees "who felt isolated at work" are 73 percent more likely than their heterosexual counterparts to leave a position within three years.[75] Due to direct and indirect costs (*e.g.*, exit interviews, severance pay, temporary staffing, loss of productivity, training new employees) replacing employees can be quite costly.[76] Replacing employees due to discrimination can cost anywhere from $5,000 to $10,000 for an hourly worker, and between $75,000 to $211,000 for an executive who makes $100,000 a year.[77] Another analysis found the annual cost of employee turnover due to various forms of workplace discrimination could cost U.S. employers upwards of $64 billion annually.[78] There are also legal costs associated with discrimination for all businesses. Employers who find themselves tied up in discrimination lawsuits can experience significant financial costs. In 2010, the Annual Workplace Class Action Litigation Report found that the cost of the top-ten private plaintiff employment discrimination lawsuits totaled $346.4 million, which increased from $84.4 million just a year

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Williams Institute, March 2009, *available at*: http://escholarship.org/uc/item/2509p8r5; Crosby Burns and Jeff Krehely, "Gay and Transgender People Face High Rates of Workplace Discrimination and Harassment: Data Demonstrate Need for Federal Law," Center for American Progress, May 2011, *available at* https://cdn.americanprogress.org/wp-content/uploads/issues/2011/06/pdf/workplace_discrimination.pdf.

[71] James, *supra* note 55, at 3.

[72] *Ibid.*

[73] Kenneth A. Kovach and Peter E. Millspaugh, *Employment Non Discrimination Act: On the Cutting Edge of Public Policy*, 39 Bus. Horizon 65, 70 (1996). *See also* Jeremy S. Barber, Comment, Re-Orienting Sexual Harassment: Why Federal Legislation is Needed to Cure Same-Sex Sexual Harassment Law, 52 AM. U. L. REV. 493, 531 & n. 238 (2002).

[74] Fidas, *supra* note 39, at 2. HRC Staff, "HRC Study Shows Majority of LGBT Workers Closeted at the Workplace," Human Rights Campaign, HRC Blog, May 7, 2014, *available at* http://www.hrc.org/blog/entry/hrc-study-shows-majority-of-lgbt-workers-closeted-on-the-job.

[75] Pizer, *supra* note 51, at 14.

[76] Heather Boushey and Sarah Jane Glynn, "There Are Significant Business Costs to Replacing Employees," Center for American Progress, November 2012, https://cdn.americanprogress.org/wp-content/uploads/2012/11/16084443/CostofTurnover0815.pdf, p. 5.

[77] Gail Robinson and Kathleen Dechant, "Building a business case for diversity," *The Academy of Management Executive*, 11.3: 21, August 1997, http://cursos.itam.mx/sastre/casos%20y%20ejercicios/diversidadrobinsonydechant97.pdf, p. 23.

[78] The Level Playing Field Institute, "The Corporate Leavers Survey," January 2007. http://www.workforcediversitynetwork.com/docs/corporate-leavers-survey.pdf, p. 4.

before.[79] In 2013, the cost of the top-ten private plaintiff employment discrimination lawsuits totaled $638 million.[80]

Studies have found that policies protecting against discrimination on the basis of sexual orientation and/or gender identity have a positive impact on businesses in terms of employee morale, the work environment, and profits. Utilizing data from the Organization for Economic Co-operation and Development (OECD), Out Now Global estimates that—as a nation—the U.S. could save $8.93 billion if LGBT workers felt comfortable being out at work.[81] They argue these savings would be the result of LGBT workers being able to be out to all of their colleagues without fear of harassment or discrimination. Further, the report estimates that businesses would have a direct benefit as well. Out Now Global found that for businesses with 10,000 employees their savings could be between $127 thousand and $944 thousand; for businesses with 50,000 employees, their savings estimated between $633 thousand and $4.7 million; businesses with 100,000 employees, $1.3 million and $9.4 million; and for those with 250,000 employees, $3.2 million and $23.6 million in savings.[82]

Businesses have also cited that having a diverse staff positively affects office operations. Such benefits include: recruitment and retention, ideas and innovation, customer service, productivity, customer base, and employee relations and morale.[83] Additionally, nondiscrimination policies have positive effects on LGBT workers, including high job satisfaction, high commitment to the company, high life satisfaction, high psychological adjustment, and less conflict between work

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[79] Seyfarth Shaw LLP, "Annual Workplace Class Action Litigation Report," January 2011, http://www.seyfarth.com/dir_docs/publications/2016WCARfinal.pdf.

[80] Chris DiMarco, "Top 10 most expensive discrimination settlements of 2013," *Corporate Counsel*, July 8, 2014, http://www.insidecounsel.com/2014/07/08/top-10-most-expensive-discrimination-settlements-o.

[81] Ian Johnson and Darren Cooper, "LGBT Diversity: Show Me The Business Case," Out Now, February 2015, http://www.outnowconsulting.com/media/13505/Report-SMTBC-Feb15-V17sm.pdf, p. 47 (data source: Out Now Global LGBT 2020 Study). This calculation uses the midpoint between the Center for American Progress' estimate of 16.1% of annual salary to replace low-skilled employees and Oxford Economics' estimate of 120% of annual salary to replace average to high-skilled employees. Boushey, *supra* note 76, at p. 2; Oxford Economics, "The Cost of Brain Drain: Understanding the financial impact of staff turnover," February 2014, http://www.oxfordeconomics.com/my-oxford/projects/264283. The calculation is for moving the "out to none" population to being "out to all" for the national full time workforce, with 38% of U.S. respondents stating they are currently "out to all," assuming that the LGBT community comprises 6% of the adult population. Lukenbill, G, "Untold millions: Positioning your business for the gay and lesbian consumer revolution" Harper Collins: New York; U.S. Census Bureau, "Annual estimates of the population by five-year age groups and sex for the United States," May 2007.

[82] The achievable savings for companies of the sizes indicated where the lower amount is if all workers are defined as low-skilled (Boushey, *supra* note 76, at 2), and the upper level in the calculation is the average figure found in 2014 as the costs to replace staff (Oxford Economics, *supra* note 81).

[83] Brad Sears and Christy Mallory, "Economic Motives for Adopting LGBT-Related Workplace Policies," Williams Institute, October 2011, http://williamsinstitute.law.ucla.edu/wp-content/uploads/Mallory-Sears-Corp-Statements-Oct2011.pdf, p. 2–3.

and home.[84] A 2014 Human Rights Campaign report found that one in four LGBT employees reported staying at a job specifically because of its inclusive environment.[85]

Implementing these policies affects employee morale and satisfaction, thereby affecting productivity. Of the top 50 Fortune 500 companies that implemented nondiscrimination policies, a majority of those companies stated that these policies increased overall profitability.[86] When polled, a majority of small business owners believe laws that prohibit discrimination against LGBT employees can improve their bottom line.[87] Further, more than two-thirds of small business owners believe there should be a federal law prohibiting employment discrimination against LGBT individuals.[88]

INTENSIFIED DISCRIMINATION AGAINST TRANSGENDER INDIVIDUALS

Due to the lack of cultural awareness on transgender issues and stigma, many transgender workers face particular difficulty obtaining jobs, retaining jobs, and receiving promotions. Mara Keisling, Executive Director of the National Center for Transgender Equality, offered testimony to the Commission explaining some of the hardships that the transgender community faces:

> [W]hat I think is important for everybody to understand -- that right now in 2015, more than at any time in my 15-year career -- in this moment, transgender people are traumatized. They are traumatized economically, they are traumatized culturally and they are very much traumatized physically. . . . We are really a resilient and determined people. You have to be when you are as marginalized as transgender people are, and . . . our testimony shows how transgender people are under siege and traumatized economically with an unemployment rate twice the national average or four times [more] likely than non-trans people to live on less than $10,000 a year.[89]

The Commission also received testimony that showed how these difficulties are "exacerbated for transgender people who are also members of other vulnerable communities, such as being a person

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[84] Kristin Griffith and Michelle Hebl, "The Disclosure Dilemma for Gay Men and Lesbians: 'Coming Out' at Work," *Journal of Applied Psychology*, 87(6):1191–99 (2002), pp. 1195–96.
[85] Fidas, *supra* note 39, at 23.
[86] U.S. Congress, Joint Economic Committee Democratic Staff, "Economic Consequences of Discrimination Based on Sexual Orientation and Gender Identity", November 2013, p. 2.
[87] Small Business Majority, "Opinion Poll: Small Businesses Support Workplace Nondiscrimination Policies," June 4, 2013, https://www.smallbusinessmajority.org/sites/default/files/research-reports/060413-workplace-nondiscrimination-poll-report.pdf, p. 4.
[88] *Ibid.*
[89] Mara Keisling, Executive Director of the National Center for Transgender Equality, testimony, Briefing Transcript, pp. 215–16.

of color; undocumented; living with HIV/AIDS; or a senior or youth."[90] A survey by the National Center for Transgender Equality and the National Gay and Lesbian Task Force found that 44 percent of transgender employees were passed over for a job, 23 percent were denied a promotion, and 26 percent were fired due to their gender identity.[91] Respondents, who reported having lost a job due to bias, further reported being currently unemployed at much higher percentages than the general population (26 to seven percent respectively).[92] This finding suggests that transgender individuals struggle to regain employment after they have been discriminatorily terminated.

Transgender individuals are unemployed at three times the rate of the general population,[93] and transgender people of color are jobless at up to four times the rate of the general population, according to the National Transgender Discrimination Survey.[94] The same survey found that employment discrimination negatively affects transgender workers in many ways. These issues include hiring, retention, promotion, and suffering from underemployment. Further, many transgender workers report experiencing hostile work environments where they are often mistreated, harassed, physically or sexually assaulted, forced to present as a gender they do not identify with, asked inappropriate questions, and deliberately taunted by the use of incorrect pronouns by their coworkers.[95] Due to the increased stigma of being transgender and these barriers listed above, unemployment is particularly detrimental to transgender individuals. Further, many transgender individuals consider themselves underemployed because they are overqualified for their position. For example, transgender people report often taking such jobs because of difficulties of being hired. According to a 2011 report, transgender respondents who were unemployed have nearly double the rate of engaging in survival sex work, four times the rate of homelessness, and 85 percent more incarceration compared to those who were employed.[96] In addition, they are disproportionately more likely to be HIV positive, smoke, use drugs or drink heavily, and have multiple suicide attempts.[97]

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[90] Statement of Ilona Turner, Legal Director at Transgender Law Center, U.S. Commission on Civil Rights, *Briefing: Examining Workplace Discrimination Against LGBT Americans,* (Washington, DC, March 16, 2015) at 2 (*hereinafter cited* as Turner Statement).

[91] Grant, *supra* note 54, at 53.

[92] *Ibid.*

[93] James, *supra* note 55, at 140.

[94] Grant, *supra* note 54, at 55.

[95] *Ibid.* at 56-62. *See, e.g., Bost v. Sam's East, Inc.*, E.E.O.C. Charge Number 430-2014-01900, Determination (Aug. 4, 2017), *available at* http://transgenderlegal.org/media/uploads/doc_729.pdf. In this case, the EEOC issued a determination that a transgender employee of Sam's Club "was subjected to a hostile work environment because of her sex," after the evidence demonstrated that the employee "was harassed in that [employer] officials repeatedly referred to [the employee] by using masculine pronouns when speaking with her or providing her written correspondence. Despite [the employee's] complaints to have this behavior stopped, the derogatory masculine references continued."

[96] Grant, *supra* note 54, at 65.

[97] *Ibid.*

Data released in 2016 from the largest national survey of transgender Americans by the National Center for Transgender Equality show:[98]

1. In the past year, 30 percent of respondents who had a job claimed they were fired, denied a promotion, or experienced other forms of mistreatment (*e.g.*, verbal harassment, physical or sexual assault at work) due to their gender identity; 13 percent of respondents claimed a lost job.
2. In the past year, 15 percent of respondents were verbally harassed, physically attacked, and/or sexually assaulted while at work.
3. 77 percent of respondents who had a job in the past year hid their gender identity, delayed their transition, or quit their job, due to fear of negative repercussions.
4. Due to perceived bias in employment, 20 percent of those surveyed felt forced to have to work in the "underground economy" (*e.g.*, sex work or dealing drugs).

Kylar Broadus, a transgender man and the Senior Public Policy Counsel with the National LGBTQ Task Force, presented some of these findings along with his personal experiences of discrimination before the United States Senate in 2012 and again at the March 2015 briefing of the U.S. Commission on Civil Rights. After announcing his transition to coworkers, Broadus reported that he was harassed daily, forbidden from talking to certain individuals, and heavily monitored by his supervisor, despite the fact that his work performance had not suffered. Six months later, Broadus lost his job. He was unemployed for a year before finding another job and suffered post-traumatic stress disorder because of the negative treatment at work.[99] Fifteen years later, he stated that he is still dealing with the financial repercussions due to extended underemployment and has not been able to pay off his student loans.[100]

As a part of the National LGBTQ Task Force, he seeks to ensure that there are clear directives to employers regarding protections for LGBT Americans. In his own words:

> [W]hile we worked hard, all of us, to provide protections there are not enough protections and they're slim, particularly for transgender individuals, and [] there are unclear directives. And as we've seen with past laws enacted in the United States, when there are unclear directives to employers then the laws that are there become very murky . . . We

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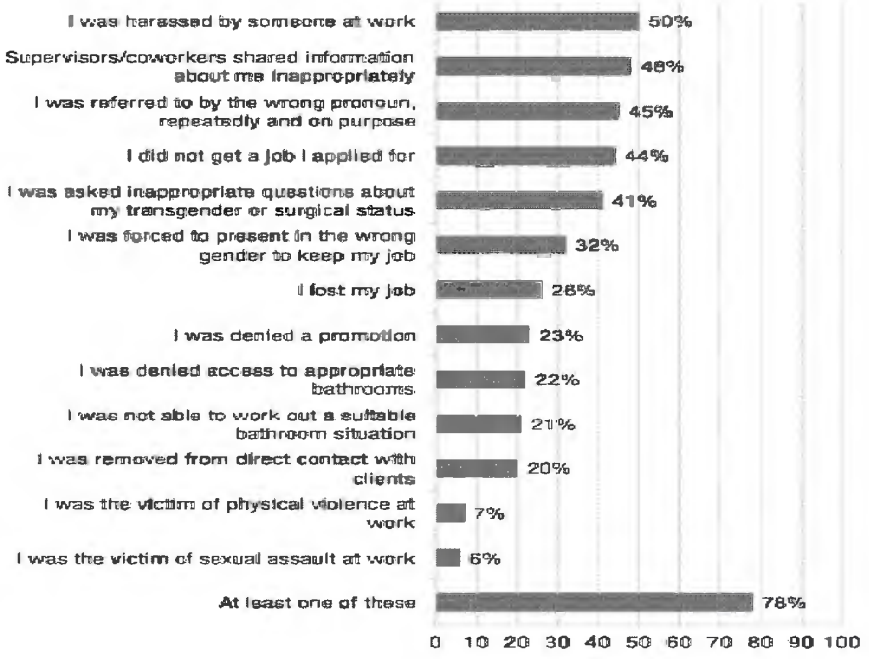
[98] James, *supra* note 55, at 10-11.
[99] Statement of Kylar W. Broadus, Senior Public Policy Counsel of the Transgender Civil Rights Project at the National LGBTQ Task Force, U.S. Commission on Civil Rights, *Briefing: Examining Workplace Discrimination Against LGBT Americans,* (Washington, DC, March 16, 2015) at 4-5 (*hereinafter cited* as Broadus Statement).
[100] *Ibid.*

need clear expressed federal protections for transgender Americans. After all, we are people and we are human beings and we deserve the right to make a living.[101]

Broadus' experiences are not unique; many transgender individuals have reported enduring similar mistreatment in the workplace (Figure 1). Further, they report feeling forced to take jobs for which they are overqualified and to make significantly less money compared to cisgender[102] individuals. Figure 2 shows the large disparity in the percentage of transgender individuals with household incomes less than $10,000 compared to the general population.

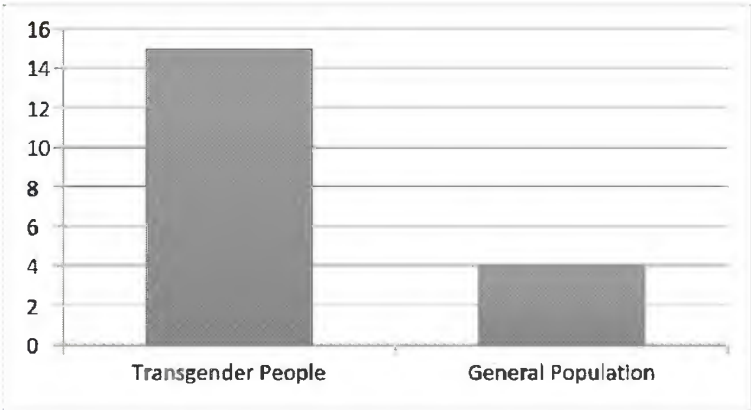
Figure 1. Transgender Workers—Mistreatment and Workplace Discrimination



Source: Jaime M. Grant, Lisa A. Mottet, and Justin Tanis. "Injustice at Every Turn: A Report of the National Transgender Discrimination Survey," National Center for Transgender Equality and National Gay and Lesbian Task Force, 2011, http://www.thetaskforce.org/static_html/downloads/reports/reports/ntds_full.pdf, p. 56.

[101] Kylar W. Broadus, Senior Public Policy Counsel of the Transgender Civil Rights Project at the National LGBTQ Task Force, testimony, Briefing Transcript, pp. 225–26.
[102] Cisgender is a term referring to individuals whose gender identity is congruent with the sex they were assigned at birth.

FIGURE 2. Percent of People with Household Incomes under $10,000



Source: Jaime M. Grant, Lisa A. Mottet, and Justin Tanis, "Injustice at Every Turn: A Report of the National Transgender Discrimination Survey," National Center for Transgender Equality and National Gay and Lesbian Task Force, 2011.
http://www.thetaskforce.org/static_html/downloads/reports/reports/ntds_full.pdf, p. 51.

Recently, additional issues transgender individuals face in the workplace have become more prominent in national media. These news accounts cover efforts from transgender individuals to be treated fairly and have their gender identities recognized, which includes the use of their correct names and pronouns as well as being allowed to adhere to the appropriate dress code.[103] OPM encourages federal agencies to eliminate "gender-specific dress and appearance rules" to ensure that all employees are comfortable.[104] Additionally, many advocates are fighting for employer-provided healthcare benefits to include sex reassignment surgery, counseling, and hormone therapy.[105]

Existing State Laws for LGBT Employees

Most states use Title VII of the Civil Rights Act of 1964 as the model for state anti-discrimination laws. Accordingly, most states have enacted legislation to prohibit discrimination on the basis of

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[103] Ellen Chang, "Transgender Employees Seeking Greater Workplace Protection," *The Street*, July 27, 2017, https://www.thestreet.com/story/13157435/1/transgender-employees-seeking-greater-workplace-protection.html.
[104] U.S. Office of Personnel Management, "Guidance Regarding the Employment of Transgender Individuals in the Federal Workplace Diversity and Inclusion," Diversity & Inclusion: Reference Materials, https://www.opm.gov/policy-data-oversight/diversity-and-inclusion/reference-materials/gender-identity-guidance/.
[105] R. Nick Gorton, "Transgender Health Benefits: Collateral Damage in the Resolution of the National Health Care Financing Dilemma," *Sexuality Research and Social Policy*, December 2007, Vol 4(4): 81-91, *available at* http://www.deanspade.net/wp-content/uploads/2010/08/gorton.pdf; Human Rights Campaign Foundation, "Corporate Equality Index 2017: Rating Workplaces on Lesbian, Gay, Bisexual and Transgender Equality," http://assets.hrc.org//files/assets/resources/CEI-2017-FinalReport.pdf?_ga=1.92925597.1225877603.1490017176, pp. 24–27; Jennifer Wong, *Recasting Transgender-Inclusive Healthcare Coverage: A Comparative Institutional Approach to Transgender Healthcare Rights*, 31 Law & Ineq. 471 (2013), *available at*: http://scholarship.law.umn.edu/lawineq/vol31/iss2/6.

race, sex, and religion along with other protections provided by federal law. Some states have adopted protections against discrimination based on sexual orientation and/or gender identity, but a sizable minority of states have not extended any anti-discrimination protections to LGBT individuals. Where they exist, these state protections may be in the form of a state statute, a state executive order, an administrative order, or state policy for state employees. Such legislation or orders vary between states. Local jurisdictions (such as cities or counties) may also have passed ordinances. Twenty states plus the District of Columbia have state laws that offer employment protections for all LGBT employees.[106] An additional two states have laws prohibiting sexual orientation discrimination, but exclude transgender protections.[107] Eight states have an executive order, administrative order, or a state policy that protects only LGBT state employees. An additional three states offer LGB protections to state employees, but do not address transgender employees. And 17 states offer no protections on the basis of sexual orientation or gender identity, but cities and local municipalities may offer their own protections (see Table 3).[108]

Table 3 Employment Protection Laws by State

Sexual Orientation & Gender Identity Statute (LGBT)*	Sexual Orientation Only (LGB)**	Executive Order for State Employees	Administrative Order for State Employees	Government Policy for State employees	No LGBT protections
California	New Hampshire	Arizona (LGB)	Alaska (LGB)	Indiana (LGBT)	Alabama
Colorado	Wisconsin	N.C. (LGBT)***			Arkansas
Connecticut		Kentucky (LGBT)			Florida
Delaware		Michigan (LGBT)			Georgia
District of Columbia		Missouri (LGB)			Louisiana
Hawaii		Montana (LGBT)			Idaho
Illinois		Ohio (LGBT)			Mississippi
Iowa		Pennsylvania (LGBT)			Nebraska
Maine		Virginia (LGBT)			Kansas
Maryland					North Dakota
Massachusetts					Oklahoma

[106] Movement Advancement Project, "Non-Discrimination Laws: Employment," data current as of October 19, 2017, http://www.lgbtmap.org/equality-maps/non_discrimination_laws; Human Rights Campaign, "State Maps of Laws & Policies: Employment," updated April 25, 2017, http://www.hrc.org/state-maps/employment.

[107] *Ibid.*

[108] Movement Advancement Project, "Non-Discrimination Laws: Employment," data current as of October 19, 2017, http://www.lgbtmap.org/equality-maps/non_discrimination_laws.

Minnesota					South Carolina
Nevada					South Dakota
New Jersey					Tennessee
New Mexico					Texas
New York					West Virginia
Oregon					Wyoming
Rhode Island					
Utah					
Vermont					
Washington					

Source: Movement Advancement Project, "Non-Discrimination Laws: Employment," data current as of October 19. 2017, http://www.lgbtmap.org/equality-maps/non_discrimination_laws; Human Rights Campaign, "State Maps of Laws & Policies: Employment," updated April 25, 2017, http://www.hrc.org/state-maps/employment. Table created by USCCR staff.
* "LGBT" indicates that the state offers both sexual orientation and gender identity protections.
** "LGB" indicates that the state offers only sexual orientation protections. ***N.C.'s Ex. Or. does not protect transgender bathroom acessibility.

Failed Efforts to Enact Federal Legislation

Since 1974, seven separate pieces of legislation to prohibit LGBT employment discrimination on the basis of actual or perceived sexual orientation or gender identity have been introduced in Congress. Table 4 below summarizes introduced LGBT workplace protection legislation from 1974 through 2017 (see Appendix A for full explanation and language of the various legislation). The first two iterations of this federal legislation—frequently dubbed the Employment Non-Discrimination Act (ENDA) or the Equality Act—prohibited employment discrimination on the basis of sexual orientation alone.[109] In 2009, gender identity protections were added and if enacted, the legislation would offer protections for all LGBT individuals.[110] These proposed bills sought to provide employment protections to LGBT workers as well as to offer a legal avenue for employees to file formal complaints alleging sexual orientation and gender identity discrimination in the workplace.[111] Closely modeled after existing civil rights legislation such as Title VII of the Civil Rights Act and the Americans with Disabilities Act, the various incarnations of these bills sought to enhance protections beyond those provided by local policies and state laws.[112]

[109] Equality Act, H.R. 14752, 93rd Cong. (1974), *available at* https://www.congress.gov/bill/93rd-congress/house-bill/14752; Employment Non-Discrimination Act of 1994, H.R. 4636, 103rd Cong. (1994), *available at* https://www.congress.gov/bill/103rd-congress/house-bill/4636.
[110] Employment Non-Discrimination Act of 2009, H.R. 3017, 111th Cong. (2009), *available at* https://www.congress.gov/bill/111th-congress/house-bill/3017.
[111] *Id.*
[112] Seth Althauser and Sarah Greenberg, "FAQ: Employment Non-Discrimination Act: What You Need to Know," Center for American Progress, July 2011, https://www.americanprogress.org/issues/lgbt/news/2011/07/19/9988/faq-the-employment-non-discrimination-act/#r1.

No version has ever successfully passed both the House and the Senate (see Table 4).[113] The failure of these bills can be attributed to opponents against enacting new federal legislation, and after the Supreme Court's *Hobby Lobby* decision, some prominent LGBT activist organizations opposed the breadth of the exemptions afforded to religious groups.[114] For instance, some opponents to enacting federal legislation prohibiting employment discrimination argue that the expansion of these laws would constitute another example of government overreach against private businesses.[115] In his testimony to the Commission, Roger Clegg of the Center for Equal Opportunity stated his opposition to ENDA on the premise that:

> [p]eople should be able to use their private property the way that they want to use their private property—and that employers should be able to make personnel decisions without interference from the government . . . . And there should be a presumption against the government, at any level, stepping in and saying . . . we know better than you whom you should hire and whom you should promote. And there should be an especially strong presumption against the federal government passing a law that second guesses employers in this regard.[116]

Others argue that passing federal legislation prohibiting sexual orientation and gender identity discrimination creates a new protected class on the basis of someone's choice. For instance, at the 2009 House Education and Labor Committee Hearing, Rep. John Kline of Minnesota argued that it would create "an entirely new protected class that is vaguely defined and often subjective . . . . Attempting to legislate individual perceptions is truly uncharted territory and it does not take a legal scholar to recognize that such vaguely defined protections will lead to an explosion in litigation and inconsistent judicial decisions."[117]

In response to the 2015 version of the bill, some LGBT groups such as the National LGBTQ Task Force withdrew support because they felt that the religious exemptions were too broad. Other

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[113] Jerome Hunt, "History of the Employment Non-Discrimination Act: It's Past Time to Pass This Law," Center for American Progress, July 2011, *available at* https://www.americanprogress.org/issues/lgbt/news/2011/07/19/10006/a-history-of-the-employment-non-discrimination-act/.

[114] Ed O'Keefe, "Gay Rights groups withdraw support of ENDA after Hobby Lobby decision," *The Washington Post*, July 8, 2014, https://www.washingtonpost.com/news/post-politics/wp/2014/07/08/gay-rights-group-withdrawing-support-of-enda-after-hobby-lobby-decision/?utm_term=.004df929e6bf.; Tierney Sneed, "Why LGBT Groups Turned on ENDA," *U.S. News*, July 9, 2014, https://www.usnews.com/news/articles/2014/07/09/why-lgbt-groups-turned-on-enda?int=news-rec.

[115] Walter Olson, "Against ENDA," *Cato At Liberty Blog*, November 1, 2013, https://www.cato.org/blog/against-enda.

[116] Roger Clegg, President and General Counsel at the Center for Equal Opportunity, Briefing Transcript, pp. 107-08.

[117] For example, *see* H.R. 3017, Employment Non-Discrimination Act of 2009, Hearing Before the House Comm. on Ed. and Labor, 111th Congress (2009), *transcript available at* https://www.gpo.gov/fdsys/pkg/CHRG-111hhrg52242/pdf/CHRG-111hhrg52242.pdf.

groups such as the American Civil Liberties Union (ACLU), Lambda Legal, the National Center for Lesbian Rights, and the Transgender Law Center all raised similar concerns and wanted the bill to offer the same amount of protections given to other minority groups (*e.g.*, minority races, religions).[118] Ian Thompson, a legislative representative at the ACLU, stated that "[i]n none of those other categories is there this kind of broad, sweeping religious exemption that gives a stamp of legitimacy to discrimination, and we feel adamantly that there should not be for this type of discrimination against LGBT people."[119]

Table 4 Summary of Introduced LGBT Employment Non-Discrimination Legislation[a]

		Protected Classes		Protected Venues	
	Congressional Actions	**LGB**	**Gender Identity***	**Workplace**	**Other**
1974 Equality Act	Not voted out of committee Reintroduced 1975–1991	Sex, Marital status, Sexual orientation	No	Yes, including: Employers, Employment agencies, Labor unions, Joint labor-management committees Exempt: < 15 employees	Public accommodations, Public facilities, Federally assisted programs
1994 ENDA	Not voted out of committee. Reintroduced in 1996, then failed Senate 49–50. Not voted upon in House Same version reintroduced 1997-2004 Not introduced in 2005-2006	Yes	No	As above. Exempt: Faith-based organizations Armed forces	
2007 ENDA	Passed House 235–184 Not introduced in Senate	Yes	Yes, but removed from voted-upon House bill	As above	No preferential treatment, No quotas
2009 ENDA	Not voted out of committee	Yes	Yes	As above	

[118] Sneed, *supra* note 114.
[119] *Ibid.*

Table 4 Summary of Introduced LGBT Employment Non-Discrimination Legislation[a]					
		Protected Classes		Protected Venues	
	Congressional Actions	LGB	Gender Identity*	Workplace	Other
2013 ENDA	Passed Senate 64–32 Not voted upon in House	Yes	Yes	As above.	
2015 Equality Act	Introduced 7/23/15	Yes	Yes	As above. Religious exemption changes to incorporate existing Title VII exemption.	Public accommodations, federally funded programs, housing, federal jury service, credit
2017 Equality Act	Reintroduced 5/2/17	Yes	Yes	As above.	As above.

[a] LGB = lesbian, gay, bisexual. ENDA = Employment Non-Discrimination Act. *Gender Identity = Transgender, Gender Non-conforming or pertaining to anyone who does not adhere to the gender binary. Source: U.S. Commission on Civil Rights staff

In May 2017, 241 Democratic members of Congress reintroduced the Equality Act in both the Senate and House.[120] If this bill passes, it would include broad societal protections on the basis of sex (including pregnancy and childbirth), sexual orientation, and gender identity in employment, housing, public accommodations, federal jury service, and public education.[121] One of the co-sponsors of the bill, Rep. David Cicilline of Rhode Island, stated: "The Equality Act represents a simple idea that everyone, including members of the LGBT community, is entitled to equal treatment under the law, and the right to live free of discrimination."[122] Unlike other iterations of this bill, this version does not have religious exemptions. The bill states that the Religious Freedom Restoration Act (RFRA) cannot be used to block protections against discrimination. The bill states: "The Religious Freedom Restoration Act of 1993 (42 U.S.C. 2000bb et seq.) shall not provide a claim concerning, or a defense to a claim under, a covered title, or provide a basis for challenging the application or enforcement of a covered title."[123] A more detailed discussion on the advantages and disadvantages of federal legislation can be found in Chapter 3.

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[120] Equality Act, H.R. 2282, 115th Cong. (2017). *available at* https://www.congress.gov/bill/115th-congress/house-bill/2282; Equality Act, S. 1006, 115th Cong. (2017), *available at* https://www.congress.gov/bill/115th-congress/senate-bill/1006.

[121] *Id.*

[122] Jeff Taylor, "241 members of Congress just announced their support for full LGBT equality," *LGBTQ Nation*, May 2, 2017, https://www.lgbtqnation.com/2017/05/democrats-take-stand-lgbtq-rights-reintroducing-equality-act/.

[123] Equality Act, H.R. 2282, 115th Cong. (2017), *available at* https://www.congress.gov/bill/115th-congress/house-bill/2282; Equality Act, S. 1006, 115th Cong. (2017), *available at* https://www.congress.gov/bill/115th-congress/senate-bill/1006.

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CHAPTER 2: EXISTING FEDERAL NON-DISCRIMINATION LAW

Title VII of the Civil Rights Act and LGBT Employees

Title VII of the Civil Rights Act of 1964 states: "It shall be an unlawful employment practice for an employer (1) to fail or refuse to hire or to discharge any individual, or otherwise to discriminate against any individual with respect to his compensation, terms, conditions, or privileges of employment, because of such individual's race, color, religion, sex, or national origin."[124] As discussed below, the question for LGBT employees is whether discrimination based on sexual orientation or gender identity falls within Title VII's prohibition against discriminating on the basis of "sex."

The EEOC's "congressionally mandated role is to enforce Title VII of the Civil Rights Act of 1964, as well as the other federal employment non-discrimination laws."[125] Employees who believe that they have been discriminated against can file claims for discrimination with the EEOC. The EEOC has authority to issue administrative decisions and resolve charges of discrimination. While the EEOC receives all claims, the Department of Justice (DOJ) enforces Title VII in cases involving state or local government employees.[126] In January 2013, the EEOC began tracking information on filed claims alleging discrimination on the basis of sexual orientation or gender identity.[127] The data for claims (or charges) based on LGBT discrimination filed with the EEOC FY 2013-2016 can be found above in Chapter 1.

Title VII contains a religious exemption that recognizes the right of religious organizations to preferentially hire individuals of a particular religion.[128] The Supreme Court recognized in *Corporation of the Presiding Bishop of the Church of Jesus Christ of Latter-day Saints v. Amos*

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[124] 42 U.S.C. § 2000e-2(a). Of note, Title VII's protections do not apply to all employers. Congress exempted employers with 15 or fewer employees, 42 U.S.C. § 2000e(a), and certain religious employers from Title VII. 42 U.S.C. § 2000e-1(a).

[125] Jeanne Goldberg, Senior Attorney Advisor, Office of Legal Counsel at EEOC, testimony, Briefing Transcript, p. 10.

[126] U.S. Department of Justice, Laws Enforced by the Employment Litigation Section, https://www.justice.gov/crt/laws-enforced-employment-litigation-section (last updated Oct. 25, 2017).

[127] Mary Beth Maxwell, Principal Deputy Assistant Secretary for Policy at the Department of Labor, testimony, Briefing Transcript, p. 30.

[128] Title VII states its provisions do not apply to "a religious corporation, association, educational institution, or society with respect to the employment of individuals of a particular religion to perform work connected with carrying on of the corporation, association, educational institution, or society of its activities." 42 U.S.C § 2000e-1(a). Under the statute, religion is defined to include "all aspects of religious observance and practice, as well as belief." 42 U.S.C § 2000e(j). The EEOC defines religious practices "to include moral or ethical beliefs as to what is right and wrong which are sincerely held with the strength of traditional religious views." 29 C.F.R. § 1605.1.

that the scope of this exemption is not limited to jobs that might be considered primarily religious, but includes "all activities of religious employers."[129]

In *Hosanna-Tabor v. E.E.O.C.*, the Supreme Court also recognized that the "ministerial exception" to antidiscrimination laws is required by the Religious Clauses of the First Amendment.[130] The Supreme Court ruled that having to "accept or retain an unwanted minister, or punishing a church for failing to do so," would infringe on the Free Exercise Clause, which "protects a religious group's right to shape its own faith and mission through its appointments," and the Establishment Clause, "which prohibits government involvement in such ecclesiastical decisions."[131] Determining whether the ministerial exception applies in a particular case requires a fact-specific analysis, but *Hosanna-Tabor* makes clear that it is not limited to only those who meet the popular conception of clergy.[132]

"Because of Sex" Court and Administrative Decisions

TITLE VII AND SEXUAL ORIENTATION

In April 2017, the Seventh Circuit held that claims of discrimination based on sexual orientation could be brought under the existing language of Title VII.[133] Until then, all federal circuit courts of appeals that had considered the question had uniformly rejected claims that workplace actions based upon sexual orientation constitute discrimination under Title VII.[134] In May 2017, in *Zarda*

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[129] 483 U.S. 327, 339 (1987).

[130] *Hosanna-Tabor Evangelical Lutheran Church and School v. E.E.O.C.*, 565 U.S. 171, 188 (2012).

[131] *Id.* at 188-89.

[132] *See id.* at 192-95. For more discussion about the religious exemptions, please see the Commission's report on the subject. U.S. Commission on Civil Rights, "Peaceful Coexistence: Reconciling Nondiscrimination Principles with Civil Liberties," September 2016, http://www.usccr.gov/pubs/Peaceful-Coexistence-09-07-16.PDF. In October 2017, Attorney General Jeff Sessions issued guidance "interpreting religious liberty protections in federal law," pursuant to President Trump's Executive Order No. 13798 (May 4, 2017). Attorney General, Memorandum for All Executive Departments and Agencies re Federal Law Protections for Religious Liberty, Oct. 6, 2017, *available at* https://www.justice.gov/opa/press-release/file/1001891/download.

[133] *Hively*, 853 F.3d at 350-51 (holding that "the logic of the Supreme Court's decisions, as well as the common-sense reality that it is actually impossible to discriminate on the basis of sexual orientation without discriminating on the basis of sex" meant that discrimination on the basis of sexual orientation is actionable under Title VII.). The employer in the *Hively* case has not asked the Supreme Court to review the Seventh Circuit's decision, and the time for seeking a petition of *certiorari* has passed.

[134] *See, e.g., Christiansen v. Omnicom Group, Inc.*, 852 F.3d 195, 199 (2d Cir. 2017) (declining to revisit past circuit precedent that holds sexual orientation discrimination does not fall under Title VII); *Evans v. Georgia Regional Hospital*, 850 F.3d 1248, 1255 (11th Cir. 2017) ("[T]here is no sexual orientation action under Title VII."); *Vickers v. Fairfield Med. Ctr.*, 453 F.3d 757, 764 (6th Cir. 2006) ("[R]ecognition of Vickers' claim would have the effect of *de facto* amending Title VII to encompass sexual orientation as a prohibited basis for discrimination."); *Medina v. Income Support Div., New Mexico*, 413 F.3d 1131, 1135 (10th Cir. 2005) ("Title VII"s protections . . . do not extend to harassment due to a person's sexuality."); *Bibby v. Phila. Coca Cola Bottling Co.*, 260 F.3d 257, 261 (3d Cir. 2001) (affirming decision of district court granting summary judgment to defendant where plaintiff claimed he was harassed on the basis of his sexual orientation); *Higgins v. New Balance Athletic Shoe, Inc.*, 194 F.3d 252, 259 (1st Cir. 1999) ("Title VII does not proscribe harassment simply because of sexual orientation."); *Hopkins v. Balt. Gas &*

v. Altitude Express, the U.S. Court of Appeals for the Second Circuit voted to review *en banc* whether Title VII protects against discrimination on the basis of sexual orientation.[135] Even where courts rejected sexual orientation claims, in some courts, allegations based on gender non-conformity were deemed actionable.[136] Those courts that have held that discrimination based on gender non-conformity is actionable have generally relied on the rationale that discrimination based on "sex stereotyping" is actionable, as the Supreme Court found in *Price Waterhouse v. Hopkins*. In *Price Waterhouse v. Hopkins*, the Supreme Court held that sex discrimination includes employment decisions based upon a woman's failure to conform to "sex stereotypes."[137] Hopkins was a female senior manager whose firm denied her partnership because the partners believed she did not act sufficiently feminine. The firm advised Hopkins she would have a better chance at being elected partner if she would, among other things, "take a course at charm school," "walk more femininely," "talk more femininely," and "wear makeup."[138]

In an earlier decision, the Supreme Court held that "[i]n forbidding employers to discriminate against individuals because of their sex, Congress intended to strike at the entire spectrum of disparate treatment of men and women resulting from sex stereotypes."[139] The Supreme Court therefore reasoned that "[a]n employer who objects to aggressiveness in women but whose positions require this trait places women in an intolerable and impermissible catch 22: out of a job if they behave aggressively and out of a job if they do not. Title VII lifts women out of this bind."[140] "[W]e are beyond the day," concluded the Court, "when an employer could evaluate employees by assuming or insisting that they matched the stereotype associated with their group."[141] In 1998, the Supreme Court also held that Title VII sexual harassment of an employee by a person of the same sex is actionable, regardless of the victim's or harasser's sex.[142]

Elec. Co., 77 F.3d 745, 751 (4th Cir. 1996) ("Title VII does not prohibit conduct based on the employee's sexual orientation[.]"); *Williamson v. A.G. Edwards & Sons, Inc.*, 876 F.2d 69, 70 (8th Cir. 1989) ("Title VII does not prohibit discrimination against homosexuals."); *DeSantis v. Pacific Tel. & Tel Co., Inc.*, 608 F.2d 327, 329-30 (9th Cir. 1979) (Title VII does not prohibit discrimination based upon homosexuality), *overruled on other grounds by Nichols v. Azteca Restaurant Enterprises, Inc.*, 256 F.3d 864, 875 (9th Cir. 2001); *Blum v. Gulf Oil Corp.*, 597 F.2d 936, 938 (5th Cir. 1979) ("Discharge for homosexuality is not prohibited by Title VII[.]").

[135] *Zarda et al. v. Altitude Express et al.*, Case No. 15-3775, Dkt. 271 (2nd Cir. May 25, 2017).

[136] *See, e.g., Schwenk v. Hartford*, 204 F.3d 1187 (9th Cir. 2000), discussed *infra*.

[137] 490 U.S. 228, 251 (1989).

[138] *Id.* at 235 (internal quotation marks omitted).

[139] *Id.* at 251 (*quoting Los Angeles Dept. of Water and Power v. Manhart*, 435 U.S. 702, 707 n. 13 (1978)) (further citations omitted).

[140] *Id.* at 251.

[141] *Id.*

[142] *Oncale v. Sundowner Offshore Servs., Inc.*, 523 U.S. 75, 79-80 (1998). The plaintiff in *Oncale* worked on an oil platform crew, and was forcibly subjected to sex-related humiliating actions by co-workers in the presence of the rest of the crew. The Court focused on "whether members of one sex are exposed to disadvantageous terms or conditions of employment to which members of the other sex are not exposed." *Id.* at 80 (quoting *Harris v. Forklift Sys., Inc.*, 510 U.S. 17, 25 (1993) (Ginsburg, J., concurring)). Justice Scalia, writing for the Court, recognized this ruling expanded the textual meaning of "sex" beyond what the sponsors of the law may have intended:

In practice, some courts have found that the distinctions among sex stereotyping, sexual orientation, gender non-conformity, same-sex harassment, and gender identity are confusing, difficult to apply, and depending on the facts, not necessarily distinct.[143] "The challenge facing the lower courts since *Price Waterhouse* is finding a way to protect against the entire spectrum of gender stereotyping while not protecting against the stereotype that people should be attracted only to those of the opposite gender."[144] The Seventh Circuit recently described the efforts of courts to sort through the distinction between sexual orientation discrimination versus gender non-conformity discrimination as follows:

> [C]ourts have gone about this task in different ways—either by disallowing any claims where sexual orientation and gender non-conformity are intertwined, (and, for some courts, by not allowing claims from lesbian, gay, or bisexual employees at all), or by trying to tease apart the two claims and focusing only on the gender stereotype allegations. In both methods, the opinions tend to turn circles around themselves because, in fact, it is exceptionally difficult to distinguish between these two types of claims.[145]

In 2015, the Equal Employment Opportunity Commission concluded that a person's claim alleging sexual orientation discrimination falls within Title VII on the basis of alleged sex discrimination.[146] The practical impact of the EEOC's ruling is that all employees covered by EEOC jurisdiction may now file administrative claims under Title VII before the agency alleging discrimination based on sexual orientation. The EEOC's decision is not binding on courts, however courts may, and often do, defer to the EEOC. In its decision, the EEOC identified the following three legal bases for recognizing sexual orientation discrimination under Title VII:

- First, the EEOC concluded that "sexual orientation is inherently a 'sex-based consideration,' and an allegation of discrimination based on sexual orientation is necessarily an allegation of sex discrimination under Title VII."[147] The very concept of sexual orientation is based upon a person's sexual attractions, and cannot be defined or

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> As some courts have observed, male-on-male sexual harassment in the workplace was assuredly not the principal evil Congress was concerned with when it enacted Title VII. But statutory prohibitions often go beyond the principal evil to cover reasonably comparable evils, and it is ultimately the provisions of our laws rather than the principal concerns of our legislators by which we are governed.

Id. at 79.

[143] *See, e.g.*, *Videckis et al. v. Pepperdine University*, Case No. 2:15-CV-00298, Dkt. 41 (C.D. Cal. Dec. 15, 2015), *available at* http://documents.latimes.com/judge-pregerson-ruling-sexual-orientation-discrimination/.

[144] Brian Soucek, Perceived Homosexuals: Looking Gay Enough for Title VII, 63 Am. U. L. Rev. 715, 726 (2014).

[145] *Hively v. Ivy Tech Cmty. Coll.*, 830 F.3d 698, 705 (7th Cir. 2016), *overruled by Hively*, 853 F.3d at 350-51.

[146] *Baldwin v. Foxx*, EEOC Doc No. 0120133080, 2015 WL 4397641 (EEOC Jul. 16, 2015).

[147] 2015 WL 4397641 at *5 (quoting *Price Waterhouse*, 490 U.S. at 242).

understood without reference to "sex." Therefore, sexual orientation is "inseparable from and inescapably linked to sex."[148]

- Second, the EEOC determined that sexual orientation discrimination is associational discrimination on the basis of sex. "For example, a gay man who alleges that his employer took an adverse employment action against him because he associated with or dated men states a claim for sex discrimination under Title VII; the fact that the employee is a man instead of a woman motivated the employer's discrimination against him."[149] In other words, "an employee alleging discrimination on the basis of sexual orientation is alleging that his or her employer took his or her sex into account by treating him or her differently for *associating* with a person of the same sex."[150] The EEOC compared such discrimination to associational race discrimination courts have long recognized.[151]
- Third, the EEOC clarified that there is little to no distinction between sexual orientation discrimination and gender stereotype discrimination (which is actionable under *Price Waterhouse*). According to the EEOC, gender stereotypes involve more than assumptions about over-masculine or feminine behavior: "Sexual orientation discrimination and harassment '[are] often, if not always, motivated by a desire to enforce heterosexually defined gender norms.'"[152]

TITLE VII AND GENDER IDENTITY

Courts' view of claims based on sex stereotyping and gender identity have changed over time, with some courts allowing these claims to proceed under Title VII and some finding that Title VII does not cover these claims. For its part, the EEOC held in 2012 that claims based on gender identity may be brought under Title VII's prohibition against discrimination "because of sex."[153] In 2017, Attorney General Jeff Sessions withdrew guidance issued by Attorney General Eric Holder in 2014 and stated that going forward the Department of Justice would take the position that Title VII "encompasses discrimination between men and women but does not encompass discrimination based on gender identity *per se*, including transgender status."[154]

In the late 1970s and early 1980s, the first circuit courts to consider Title VII claims brought by plaintiffs seeking protection from discrimination based on their gender identities adopted the

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[148] *Id.*
[149] *Id.* at *6.
[150] *Id.* (emphasis in original).
[151] *Id.* (citing *Floyd v. Amite Cnty. School Dist.*, 581 F.3d 244, 249 (5th Cir. 2009); *Holcomb v. Iona Coll.*, 521 F.3d 130, 138 (2d Cir. 2008)).
[152] *Id.* at *8 (quoting *Centola v. Potter*, 183 *F. Supp.* 2d 403, 410 (D. Mass. 2002)) (alteration in original).
[153] *Macy v. Holder*, EEOC Doc No. 0120120821, 2012 WL 1435995 (EEOC Apr. 20, 2012).
[154] Attorney General, Memorandum re Revised Treatment of Transgender Employment Discrimination Claims Under Title VII of the Civil Rights Act of 1964, Oct. 4, 2017.

position that the plain meaning of the term "sex" did not extend to discrimination based on "transsexualism."[155] In *Holloway*, an employee of Arthur Andersen who was assigned male at birth brought suit under Title VII, alleging her employer discharged her after she began her transition from living as a man to living as a woman.[156] The Ninth Circuit held that "[a] transsexual individual's decision to undergo sex change surgery does not bring that individual, nor transsexuals as a class, within the scope of Title VII."[157]

Similarly, in the *Sommers* case—where a transgender woman was discharged because she "misrepresented herself as an anatomical female when she applied for the job"[158]—the Eighth Circuit viewed "the major thrust of the 'sex' amendment was towards providing equal opportunities for women."[159] The Eighth Circuit court held, "[b]ecause Congress has not shown an intention to protect transsexuals, we hold that discrimination based on one's transsexualism does not fall within the protective purview of the Act."[160] Thus, the focus of these early cases was on what Congress intended the scope of the term "sex" to encompass.

As discussed above, in 1989, in *Price Waterhouse*, the Supreme Court held that sex discrimination includes employment decisions based upon a woman's failure to conform to "sex stereotypes."[161] Of importance here, in *Price Waterhouse*, the Supreme Court used the terms "sex" and "gender" interchangeably.[162] With regard to congressional intent, the Supreme Court stated that "Congress' intent to forbid employers to take *gender* into account in making employment decisions *appears on the face of the statute*."[163]

After *Price Waterhouse*, courts began analyzing gender identity discrimination claims under Title VII in two ways. The first approach recognizes open identification as a member of the opposite sex as a deviation from preconceived gender norms. This category is an extension of the *Price Waterhouse* framework whereby it is unlawful to discriminate against an individual for failing to conform to sex stereotypes. An example of cases falling into the first category is the Ninth Circuit's decision in *Schwenk v. Hartford*.[164] The Ninth Circuit relied on the "logic and language of *Price*

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[155] *See Holloway v. Arthur Andersen & Co.*, 566 *F.2d* 659, 663 (9th Cir. 1977); *Sommers v. Budget Mktg., Inc.*, 667 F.2d 748, 750 (8th Cir. 1982).
[156] *Holloway*, 566 F.2d at 661.
[157] *Id.* at 664.
[158] *Sommers*, 667 F.2d at 748.
[159] *Id.* at 750 (citations omitted).
[160] *Id.*
[161] *Price Waterhouse*, 490 U.S. at 248-51.
[162] In concluding an employer cannot discharge an employee for deviations from "sex stereotypes," the Supreme Court held "an employer who acts on the basis of a belief that a woman cannot be aggressive, or that she must not be, has acted on the basis of *gender*." *Id. at* 250 (emphasis added). Likewise, the Supreme Court viewed the words "because of . . . *sex*" to mean "*gender* must be irrelevant to employment decisions." *Id.* at 240 (emphasis added).
[163] *Id.* at 239 (emphasis added).
[164] 204 F.3d at 1187.

Waterhouse" to conclude that openly expressing one's identity as a member of the opposite sex is therefore no different from the failure to conform with sex stereotypes in *Price Waterhouse*.[165]

Under the second approach, courts have continued to analyze cases using the pre-*Price Waterhouse* view of differentiating between "sex" and "gender," and associating transgender status with one or the other. The cases interpreting "sex" to include "gender identity" hold transgender status is protected, whereas the cases interpreting "sex" to mean biological sex hold it is not. The Tenth Circuit followed this approach in *Etsitty v. Utah Transit Auth.*:

> [T]here is nothing in the record to support the conclusion that the plain meaning of "sex" encompasses anything more than male and female. In light of the traditional binary conception of sex, transsexuals may not claim protection under Title VII from discrimination based solely on their status as a transsexual.[166]

The court did suggest, without deciding, that an actionable claim may arise based on discrimination against a transgender individual for failing to conform to the gender stereotypes of his or her biological sex.[167] More recently courts have, even while differentiating between "sex" and "gender," held the analysis employed by *Etsitty* to be too narrow.[168]

Currently, six federal circuit courts of appeals have adjudicated the merits of a Title VII claim asserted by transgender individuals. The Sixth, Ninth, and Eleventh Circuits all hold Title VII prohibits discrimination against a transgender employee on the basis of the reasoning announced in *Price Waterhouse*.[169] In contrast, the Seventh, Eighth, and Tenth Circuits have held there is no Title VII protection for transgender individuals.[170]

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[165] *Id.* at 1201-02. *See also Smith v. City of Salem*, 378 F.3d 566, 574 (6th Cir. 2004); *Glenn v. Brumby*, 663 F.3d 1312, 1316 (11th Cir. 2011) ("'The very acts that define transgender people as transgender are those that contradict stereotypes of gender-appropriate appearance and behavior.' There is thus a congruence between discriminating against transgender and transsexual individuals and discrimination on the basis of gender-based behavioral norms.") (quoting Ilona M. Turner, *Sex Stereotyping Per Se: Transgender Employees and Title VII*, 95 Cal. L. Rev. 561, 563 (2007)) (alteration and internal citations omitted).

[166] 502 F.3d 1215, 1222 (10th Cir. 2007).

[167] *Id.* at 1224.

[168] For example, the court in *Fabian v. Hosp. of Cent. Conn.* reasoned the definition of "sex" extends beyond the biological distinctions between male and female, but also to the social and cultural manifestations associated with a particular biological sex. 172 F.Supp.3d 509, 526 (D. Conn. 2016). An unlawful adverse employment action is also made "because of . . . sex" when motivated by a recent gender reassignment surgery. *Schroer v. Billington*, 577 F.Supp.2d 293, 308 (D.D.C. 2008) ("[T]he Library's refusal to hire Schroer after being advised that she planned to change her anatomical sex by undergoing sex reassignment surgery was *literally* discrimination 'because of . . . sex.'") (emphasis in original).

[169] *See Smith*, 378 F.3d at 574; *Schwenk*, 204 F.3d at 1201-02; *Glenn*, 663 F.3d at 1316.

[170] *See Ulane v. Eastern Airlines, Inc.*, 742 F.2d 1081, 1084 (7th Cir. 1984); *Sommers*, 667 F.2d at 750; *Etsitty*, 502 F.3d at 1222. Both the *Ulane* and *Sommers* decisions, however, were decided pre-*Price Waterhouse*, and the continued force of those opinions is therefore uncertain.

NON-DISCRIMINATION AND RELIGIOUS BELIEFS

The right to be free of discrimination at work may conflict with other protected rights of co-employees and/or employers. For example, in *Cruzan v. Special Sch. Dist. No. 1*, a female employee alleged the employer's policy allowing a transgender woman to use the women's restroom created a hostile work environment and discriminated against her on the basis of religion.[171] The court upheld the lower court's grant of summary judgment to the employer because the evidence was not sufficient to show a hostile work environment and because the employee did not notify the employer of her religious objections.[172]

More recently, a district court in the Eastern District of Michigan granted summary judgment to a funeral home that terminated a transgender woman who was willing to comply with the female, but not the male, dress code. The court held enforcement of Title VII in these circumstances was not allowed because under the Religious Freedom Restoration Act, it imposed a substantial burden on the owner's sincerely held religious belief that a person's sex is a "God-given gift" and people should not deny or attempt to change their sex.[173]

Additional Legal Protections for LGBT Employees in the Federal Workplace

Multiple federal departments have responsibilities for ensuring non-discrimination against LGBT employees working within the federal government. For instance, the Department of Labor has made efforts to protect LGBT employees from discrimination and remove barriers for the LGBT workforce through policy, education, and training.[174] To this end, the Office of Diversity and Inclusion within OPM has issued publications regarding the treatment of LGBT employees in the federal workplace. Additionally, same-sex marriage benefits in federal employment are addressed in agency-specific EEO policies following the *U.S. v. Windsor* and *Obergefell v. Hodges* decisions to ensure equal benefits for same-sex married couples. For instance, the Department of Labor changed its policies to ensure implementation and compliance where necessary.[175]

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[171] 294 F.3d 981, 982-83 (8th Cir. 2002).
[172] *Id.* at 984.
[173] *EEOC v. R.G. & G.R. Harris Funeral Homes*, 201 F.Supp.3d 837, 856 (E. D. Mich. 2016), *appeal docketed*, No. 16-2424 (6th Cir. Oct. 13, 2016). For more discussion about the Religious Freedom Restoration Act, please see the Commission's report. Peaceful Coexistence, *supra* note 132.
[174] Maxwell testimony, Briefing Transcript at 22–23.
[175] *Ibid.* at 21-23.

PRESIDENTIAL EXECUTIVE ORDERS

Since the late 1960s, Presidents have issued Executive Orders to address workplace discrimination within the executive branch and/or by federal contractors and subcontractors. Presidents use executive orders "to achieve policy goals, set uniform standards for managing the executive branch, or outline a policy view intended to influence the behavior of private citizens."[176] Executive orders provide a uniform policy for the federal government, but generally are not enforceable in courts.

In 1969, President Nixon issued Executive Order 11,478, which required all executive department and agencies to adopt an affirmative program to prohibit employment discrimination.[177] In 1998, President Clinton amended Nixon's Executive Order to include "sexual orientation."[178] On the same day, President Clinton issued a caveat noting that the amended Executive Order "does not and cannot create any new enforcement rights (such as the ability to proceed before the Equal Employment Opportunity Commission)."[179] The Clinton Executive Order did play a significant role toward employment equality within federal agencies.[180] For example, it directed agencies to revise their policies to ensure that employment decisions for federal civilian employees are not made on the basis of sexual orientation.

In 2014, President Obama issued Executive Order 13,672, reaffirming non-discrimination against employees in all aspects of federal employment, including upgrades, demotions, promotions, transfers, recruitment, recruitment advertising, layoff, termination, pay and other forms of compensation, and selection for various types of training.[181] This Executive Order added "gender identity" to the list of categories already protected from employment discrimination and thus

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[176] Vivian S. Chu and Todd Garvey, "Executive Orders: Issuance, Modification and Revocation," Congressional Research Service, April 16, 2014 at Summary, *available at* http://fas.org/sgp/crs/misc/RS20846.pdf.

[177] Exec. Order No. 11,478, Equal Employment Opportunity in the Federal Government, 3 C.F.R. § 803 (Aug. 8, 1969) (stating "[i]t is the policy of the Government of the United States to provide equal opportunity in Federal employment for all persons, to prohibit discrimination in employment because of race, color, religion, sex, national origin, handicap, or age, and to promote the full realization of equal employment opportunity through a continuing affirmative program in each executive department and agency.").

[178] Exec. Order No. 13,087, Further Amendment to Executive Order 11478, Equal Employment Opportunity in the Federal Government, 3 C.F.R. § 30097.

[179] William J. Clinton, *Statement on Signing an EO on Equal Employment Opportunity in the Federal Government*, May 28, 1998, Gerhard Peters and John T. Woolley, eds., American Presidency Project, *available at* http://www.presidency.ucsb.edu/ws/?pid=56040.

[180] U.S. Equal Employment Opportunity Commission (EEOC), *Discrimination Based on Sexual Orientation, Status as a Parent, Marital Status and Political Affiliation*, (Fact Sheet, Dec. 29, 2009), *available at* http://www.eeoc.gov/federal/upload/otherprotections.pdf.

[181] E.O. 13,672, July 21, 2014, Further Amendment to Executive Order 11,478, Equal Employment Opportunity in the Federal Government, and Executive Order 11,246, Equal Employment Opportunity, July 21, 2014, *available at* https://obamawhitehouse.archives.gov/the-press-office/2014/07/21/executive-order-further-amendments-executive-order-11478-equal-employmen. *See also* Remarks by the President at Signing of Executive Order on LGBT Workplace Discrimination, July 21, 2014, *available at* https://obamawhitehouse.archives.gov/the-press-office/2014/07/21/remarks-president-signing-executive-order-lgbt-workplace-discrimination.

clarified that protections extend protection to transgender individuals.[182] In support of the Executive Order, the White House issued a statement saying that prohibiting LGBT employment discrimination is not only critical to promoting equality, but also plays an important role in supporting businesses and strengthening the economy.[183]

Additionally, the Obama Executive Order prohibits federal contractors from engaging in discrimination on the bases of both gender identity and sexual orientation.[184] The Department of Labor enforces this provision, and in 2014, the Office of Federal Contract Compliance Programs issued a regulation governing non-discrimination by federal contractors and subcontractors.[185] To satisfy their obligations under the final rule, federal contractors or federally assisted contractors must: 1) include an updated equal opportunity clause in new or modified subcontracts and purchase orders, 2) ensure that applicants and employees are not discriminated against by reason of their sexual orientation and gender identity, 3) update the equal opportunity language in job solicitations, and 4) post updated notices.[186] Only federal contracts entered into after April 8, 2015, are impacted by the Final Rule.[187]

The development of the Obama Executive Order was criticized by several religious organizations, which fought for inclusion of a religious exemption.[188] While the Obama Executive Order did not specifically grant exemptions to religious contractors, it did not amend President Bush's Executive Order 13,279, which protects the right of faith-based social service programs receiving federal funding to limit "employment of individuals [to] a particular religion."[189]

Further, opponents of extending federal legislation were supportive of President Trump's Executive Order that revoked President Obama's Executive Order 13,673, also known as the Fair Pay and Safe Workplaces order, which required federal contracting agencies to consider violations of federal and state labor laws when considering contract rewards.[190] In 2016, the Department of Labor regulations implementing Executive Order 13,673 required companies seeking federal contracts to report workplace law violations, including Title VII violations, which the Department

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[182] *Id.*
[183] White House, Office of the Press Secretary, FACT SHEET: Taking Action to Support LGBT Workplace Equality Is Good for Business.
[184] *Id.*
[185] DOL, Office of Federal Contract Compliance Programs, Implementation of Executive Order 13672 Prohibiting Discrimination by Contractors and Subcontractors (Washington DC: GPO, 2014), 79 Fed. Reg. 72985 (Dec. 9, 2014).
[186] 41 C.F.R. Parts 60-1, 60-2, 60-4, and 6-50.
[187] *Id.*
[188] Julie Hirschfeld Davis and Erik Eckholm, "Faith Groups Seek Exclusion from Bias Rule," *New York Times,* July 8, 2014, http://www.nytimes.com/2014/07/09/us/faith-groups-seek-exclusion-from-bias-rule.html?_r=0.
[189] E.O. 13,672 *supra* note 181; E.O. 13,279, Equal Protection of the Laws for Faith-Based and Community Organizations, 3 C.F.R. §§ 77141–77144 (Dec. 12, 2002).
[190] Exec. Order No. 13,673, 79 Fed. Reg. 45309 (Jul. 31, 2014).

had previously interpreted as banning discrimination based on sexual orientation and gender identity.[191] Camilla Taylor, Senior Counsel for Lambda Legal, argued that while President Trump did not specifically overturn the order that protected LGBT employees who work for federal contractors, he made the policy increasingly difficult to enforce.[192]

TRANSGENDER GUIDANCE FOR FEDERAL AGENCIES

In March 2015, OPM issued "Guidance Regarding the Employment of Transgender Individuals in the Federal Workplace," which defines terms and addresses questions agencies may have related to the employment of transgender individuals within the Federal workforce:

> The guidance outlines a series of core concepts including gender identity, transgender, and transition and defines common terms related to the transition process. The guidance also provides information on issues such as employee confidentiality and privacy, dress and appearance, sanitary and related facilities, recordkeeping, and insurance benefits.[193]

OFCCP has also issued guidance stating that the current laws banning discrimination on the basis of sex should include transgender workers.[194] At the Commission's briefing, Mary Beth Maxwell, Principal Deputy Assistant Secretary for Policy at the DOL, stated that former Secretary Thomas Perez directed DOL to update enforcement protocols and antidiscrimination guidance to clarify that "we provide the full protection of the federal nondiscrimination laws that we enforce to transgender individuals."[195]

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[191] Guidance for Executive Order 13673, "Fair Pay and Safe Workplaces," 81 Fed. Reg. 58653 (Aug. 25, 2016), *available at* https://www.federalregister.gov/documents/2016/08/25/2016-19678/guidance-for-executive-order-13673-fair-pay-and-safe-workplaces.

[192] Mary Emily O'Hara, "LGBTQ Advocates Say Trump's New Executive Order Makes Them Vulnerable to Discrimination," *NBC News*, Mar. 29, 2017, https://www.nbcnews.com/news/us-news/lgbtq-advocates-say-trump-s-news-executive-order-makes-them-n740301.

[193] Statement, U.S. Office of Personnel Management at 1, March 25, 2015 (*hereinafter* OPM Statement); U.S. Office of Personnel Management, Diversity & Inclusion Reference Materials: Guidance Regarding the Employment of Transgender Individuals in the Federal Government, http://www.opm.gov/policy-data-oversight/diversity-and-inclusion/reference-materials/gender-identity-guidance/.

[194] U.S. Department of Labor, DOL Policies on Gender Identity: Rights and Responsibilities, http://www.dol.gov/oasam/programs/crc/20130712GenderIdentity.pdf.

[195] Adam Edelman, "Labor Department to update discrimination protection guidance for federal transgender workers," *New York Daily News*, July 1, 2014, http://www.nydailynews.com/news/politics/labor-department-update-anti-discrimination-protection-guidance-federal-transgender-workers-article-1.1851248; *see also* Maxwell testimony, Briefing Transcript at 23.

FEDERAL AGENCIES' EMPLOYMENT POLICIES INCLUSIVE OF GENDER IDENTITY AND SEXUAL ORIENTATION

Federal agencies' Equal Employment Opportunity (EEO) policies and No Fear Act statements generally list prohibitions of discrimination based on race, color, sex, religion, national origin, age, disability, marital status, or political affiliation. Many federal agencies now also specifically include gender identity or sexual orientation.

Of the ten federal agencies with the largest numbers of employees, all have gender identity and/or sexual orientation language within their EEO policies. OPM guidance encourages federal agencies to update their EEO statements and policies to include prohibitions against discrimination based on sexual orientation and gender identity.[196]

Table 5 depicts information regarding EEO and No Fear Act policies of the ten largest federal agencies by number of employees. The Notification and Federal Antidiscrimination and Retaliation Act of 2002 (No Fear Act) was implemented in October 2003. The EEOC states that the Act "imposes additional duties upon Federal agency employers intended to reinvigorate their longstanding obligation to provide a work environment free of discrimination and retaliation."[197]

Table 5 EEO/No Fear Language Ten Largest Federal Departments by Number of Employees

Department	EEO Policy/No Fear Act Contains Gender Identity or Sexual Orientation Language	Language Listed in Policy	Additional Findings
Justice	Yes, Both[198]	Discrimination on the basis of sex, gender identity, sexual orientation	N/A
Agriculture	Yes, Both[199]	Discrimination on the basis of sex, gender identity, sexual orientation	Policy states that not all prohibited bases will apply to all programs and/or employment activities

[196] Office of Personnel Management, *supra* note 5.
[197] U.S. Equal Employment Opportunity Commission, "No FEAR Act," https://www.eeoc.gov/eeoc/statistics/nofear/qanda.cfm.
[198] U.S. Department of Justice, "U.S. Department of Justice Equal Employment Opportunity Policy," https://www.justice.gov/jmd/file/790081/download, *available from* https://www.justice.gov/jmd/policy (last updated Oct. 31, 2015).
[199] U.S. Department of Agriculture, "Non Discrimination Statement," https://www.usda.gov/non-discrimination-statement (last visited Nov. 12, 2017).

Table 5 EEO/No Fear Language—Ten Largest Federal Departments by Number of Employees			
Department	**EEO Policy/No Fear Act Contains Gender Identity or Sexual Orientation Language**	**Language Listed in Policy**	**Additional Findings**
Veterans Affairs	Yes, Both[200]	Discrimination on the basis of sex, gender identity, sexual orientation, transgender status	N/A
Homeland Security	Yes, Both[201]	Discrimination on the basis of sex, sexual orientation and gender identity	N/A
Treasury	Yes, Both[202]	Discrimination on the basis of sex (including gender identity, sexual orientation, and pregnancy)	
Health & Human Services	Yes, Both[203]	Discrimination on the basis of sex, gender identity, sexual orientation	N/A
Interior	Yes, Both [204]	Discrimination on the basis of sex, gender, sexual orientation, gender identity	
Transportation	Yes, Both[205]	Discrimination on the basis of sex, sexual orientation, gender identity and transgender	N/A

[200] U.S. Department of Veterans Affairs, "EEO, Diversity and Inclusion, No FEAR, and Whistleblower Rights and Protection Policy Statement," Jul. 5, 2017, https://www.diversity.va.gov/policy/statement.aspx.
[201] U.S. Department of Homeland Security, "Revised DHS Anti-Discrimination Policy Statement," Jun. 12, 2014, https://www.dhs.gov/sites/default/files/publications/DHS%20Anti-Discrimination%20Policy%20Statement%20-%206.12.14_1.pdf.
[202] U.S. Department of the Treasury, "EEO and Civil Rights Policies," May 31, 2017, https://www.treasury.gov/about/organizational-structure/offices/Mgt/Documents/FY%202017.EEO%20Policy%20FY2017%20Draft%203.30.17.pdf.
[203] U.S. Department of Health and Human Services, "Department of Health and Human Services Equal Employment Opportunity Policy," Apr. 29, 2016, https://www.hhs.gov/about/agencies/asa/eeo/policy/index.html.
[204] U.S. Department of the Interior, "Employment Complaints and Adjudication Division," https://www.doi.gov/pmb/eeo/Complaints-Processing.
[205] U.S. Department of Transportation, "DOT Discrimination Policy—Complaint Process," Oct. 4, 2016, https://www.transportation.gov/civil-rights/complaint-resolution/equal-employment-opportunity-complaint-process.

Table 5 EEO/No Fear Language—Ten Largest Federal Departments by Number of Employees			
Department	**EEO Policy/No Fear Act Contains Gender Identity or Sexual Orientation Language**	**Language Listed in Policy**	**Additional Findings**
Labor	Yes, Both[206]	Discrimination on the basis of sex (including gender identity) and sexual orientation.	
Defense	Yes, Both[207]	Discrimination on the basis of sex, sexual orientation and gender identity	N/A

Source: Compiled by U.S. Commission on Civil Rights staff.

Private Workplace Protections for LGBT Employees

Many private companies have adopted and implemented workplace policies or practices that prohibit discrimination on the basis of sexual orientation and/or gender identity.[208] According to written testimony by The Leadership Conference on Civil and Human Rights to the Senate, by 2012, 86 percent of Fortune 500 companies prohibited sexual orientation discrimination and more than 50 percent also prohibited discrimination based on gender identity.[209]

For the past fifteen years, the Human Rights Campaign has released a list that ranks the Fortune 500, Fortune 1000, and the top 200 revenue-grossing law firms on the basis of the "best places to work for LGBT equality."[210] The ranking is based on what they call the "corporate equality index" (CEI) that utilizes several criteria.[211] First, businesses are rated if they have equal employment opportunity policies that include: sexual orientation and gender identity for all operations (domestic and global), and contractor/vendor standards that include sexual orientation and gender identity. The second set of criteria is based on employment benefits that are equivalent to spousal and partner benefits such as equivalent medical benefits (*e.g.*, dental, vision, legal dependent

[206] U.S. Department of Labor, "U.S. Department of Labor Policy on Equal Employment Opportunity," Feb. 24, 2015, https://www.dol.gov/oasam/programs/crc/crc-internal/2015EEOPolicy.pdf.
[207] U.S. Department of Defense, "Directive 1020.02E: Diversity Management and Equal Opportunity in the DoD," Nov. 29, 2016, http://www.esd.whs.mil/Portals/54/Documents/DD/issuances/dodd/102002e_dodd_2015.pdf.
[208] Human Rights Campaign Foundation, *supra* note 105, at 2.
[209] Senate Hearing 112-915, "Equality at Work: The Employment Non-Discrimination Act," Hearing of the Committee on Health, Education, Labor, and Pensions, June 2012, *available at* https://www.gpo.gov/fdsys/pkg/CHRG-112shrg92383/html/CHRG-112shrg92383.htm.
[210] Human Rights Campaign Foundation, *supra* note 105, at 10. Commission staff is unaware of other reports that are as comprehensive and robust as the HRC's CEI reports regarding the inclusive private employers' policies, practices, and benefits for LGBT employees in the United States. Started in 2002, these reports are nationally recognized benchmarks for businesses to gauge their level of LGBT workplace inclusion against competitors.
[211] *Ibid.* at 16-18. A tool established by the Human Rights Campaign that rates U.S. businesses on their treatment of gay, lesbian, bisexual, and transgender employees, consumers, and investors.

coverage, COBRA) and other "soft" benefits (*e.g.*, bereavement leave, employer-provided supplemental life insurance for partner, adoption assistance, qualified joint and survivor annuity for partners).

Regarding transgender protections specifically, the Human Rights Campaign rates corporations on the basis of providing transgender employees equal health coverage. This includes use of insurance contracts and/or policy documentation that are based on the World Professional Association for Transgender Health Standards of Care, use of documentation that clearly communicates inclusive insurance options, and whether such coverage is readily available to employees. They state that benefits should include services related to gender transition (*e.g.*, medically necessary services related to sex affirmation/reassignment such as short-term medical leave, pharmaceutical coverage, coverage for medical visits, coverage for reconstructive surgical procedures related to sex reassignment, and coverage for routine non-transition services).[212]

According to the Human Rights Campaign 2017 CEI report, as of 2016, 92 percent of Fortune 500 companies included sexual orientation and 82 percent included gender identity in their non-discrimination policies.[213] Half of these Fortune 500 companies offer transgender-inclusive health care benefits, including surgical procedures. For the 2017 CEI report, the 327 Fortune 500 companies that submitted surveys had an average score of 91 out of a possible 100. However, when analyzing the scores of all Fortune 500 companies, it found substantially lower scores. The average score for all Fortune 500 companies (reporting and non-reporting) was 66; and those companies that did not respond to the survey had an average score of 14 (see Table 6).[214]

Table 6 Equality at Fortune-Ranked Companies

	All Fortune 500	Fortune 500 Participants	Fortune 500 Non-Responders
Sexual Orientation in U.S. Non-Discrimination Policy	92%	99%	75%
Gender Identity in U.S. Non-Discrimination Policy	82%	98%	49%
Domestic Partner Benefits	61%	81%	19%
Transgender-Inclusive Benefits	50%	74%	0%
Organizational LGBT Competency	57%	83%	0%
Public Commitment to the LGBT Community	47%	69%	0%

[212] *Ibid.* at 14.
[213] *Ibid.* This report discusses the 2017 CEI report. The Human Rights Campaign recently published the 2018 CEI report, which is available at https://www.hrc.org/campaigns/corporate-equality-index.
[214] *Ibid.* at 7.

Source: Human Rights Campaign Foundation, Corporate Equality Index 2017, http://assets.hrc.org//files/assets/resources/CEI-2017-FinalReport.pdf?_ga=1.92925597.1225877603.1490017176

Some question whether the high percentages of the United States' largest companies having antidiscrimination policies evidences nondiscrimination and equality. For instance, there is only one openly gay chief executive officer (CEO) of a Fortune 500 company, which is Apple's Tim Cook.[215] Todd Sears, a former financial advisor at Merrill Lynch who now runs Out on the Street, an organization that helps companies recruit and retain LGBT employees, argues that, "when people see that 90 percent of companies have nondiscrimination policies in place, that's great. But to me, a better indicator, is, how many senior leaders are there who are gay and who are out? If LGBT people look around and they don't see other LGBT people who are out, if they don't hear inclusive messages, they're not going to feel valued."[216]

[215] Benjamin Snyder, "Apple's CEO becomes the Fortune 500's only openly gay CEO. Here are 11 other workplace stats," *Fortune*, Oct. 30, 2014, http://fortune.com/2014/10/30/apples-ceo-becomes-the-fortune-500s-only-openly-gay-ceo-here-are-11-more-workplace-stats/.

[216] Hunter Stuart, "U.S. Companies Less LGBT-Friendly Than They'd Like You To Believe," *The Huffington Post*, Jun. 27, 2014, http://www.huffingtonpost.com/2014/06/27/lgbt-employees-equality-discrimination-protection-at-work_n_5526746.html.

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CHAPTER 3: VIEWPOINTS IN FAVOR AND AGAINST FEDERAL LEGISLATION

Ensuring Equal Rights and the Normative Argument

Advocates who favor federal legislation protecting employees against discrimination based on sexual orientation and gender identity assert that passing comprehensive protections for LGBT Americans that include anti-discrimination employment provisions is essential to ensure equal rights for all citizens.[217] Selisse Berry from Out and Equal Workplace Advocates, a panelist at our briefing, noted that "we live in an interesting time. LGBT people can be married in 37 states and we can still be fired in 29 states simply because of who we love and who we are."[218] At the time of the briefing, in March 2015, same-sex marriage was a state-by-state determination. Since that time, the Supreme Court has determined that states must license marriage between two people of the same sex and recognize same-sex marriages performed in other states.[219] Kate Kendell, the Executive Director for the National Center for Lesbian Rights, stated that "[b]oth methodological and anecdotal information enforces that LGBT, particularly transgender employees, even in this moment of great acceleration of LGBT rights, [still] suffer in the employment realm."[220]

The debate concerning extending specific anti-discrimination protections to LGBT Americans often draws comparisons to enacting the Civil Rights Act and issues of racial discrimination in the United States. Opponents of enacting federal legislation argue that discrimination against LGBT communities is not analogous to discrimination based on race or sex. For instance, the Family Research Council argues that unlike race and sex which are considered "inborn, involuntary and immutable" sexual orientation and gender identity are not.[221] Further, these opponents argue, unlike historical discrimination against an individual's race or sex, the LGBT community cannot make similar discrimination claims. Peter Sprigg of the Family Research Council argues that

> [t]he bad name given to the word 'discrimination' relates primarily to our country's shameful history of racial discrimination, including over two centuries of slavery and

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[217] For example, *see* Senate Hearing 112-915. "Equality at Work: The Employment Non-Discrimination Act," Hearing of the Committee on Health, Education, Labor, and Pensions, June 2012, *available at* https://www.gpo.gov/fdsys/pkg/CHRG-112shrg92383/html/CHRG-112shrg92383.html; Human Rights Campaign, "Federal Legislation," http://www.hrc.org/resources/federal-legislation; Neera Tanden and Ted Strickland, "We Need A Federal LGBT Non-Discrimination Act," *Newsweek*, Dec. 10, 2014, http://www.newsweek.com/we-need-federal-lgbt-non-discrimination-act-290907; Shalyn Caulley, *The Next Frontier to LGBT Equality: Securing Workplace-Discrimination Protections*, 2017 U. Ill. L. Rev. 909 (2017); Sarah Warbelow, Legal Director for Human Rights Campaign, testimony, Briefing Transcript at 75.

[218] Berry testimony, Briefing Transcript at 158.

[219] *Obergefell v. Hodges*, 576 U.S. __, 135 S. Ct. 2584 (2015).

[220] Kate Kendell, Executive Director of the National Center for Lesbian Rights, testimony, Briefing Transcript at 70.

[221] Family Research Council, *supra* note 16.

> another century of segregation. Homosexuals can claim no comparable disadvantage. Until less than a century ago, women were not even granted the most fundamental right of voting. Again, homosexuals have no comparable claim. Protecting against religious discrimination advances the cause of religious liberty which was enshrined in our nation's Constitution at the Founding. No comparable guarantee of sexual liberty is found in the Constitution.[222]

Thus, they argue that members of LGBT communities do not need federal legislation to prohibit workplace discrimination. During his testimony before the Commission, Ryan Anderson of the Heritage Foundation argued that "[t]he Civil Rights Act of 1964 barring discrimination on the basis of race was a proper response. America has no similar history of society-wide legal prohibition on employment based on sexual orientation or gender identity."[223]

Proponents argue discrimination against LGBT communities is similar to historical discrimination based on race and sex. Many studies support the claim of historic and continuing employment discrimination against employees on the basis of sexual orientation and gender identity. Historians, researchers, and the courts have all recognized that LGBT workers have faced a long, serious, and pervasive history of employment discrimination.[224] Scholars have argued that not only did LGBT individuals face societal stigma, but also faced various forms of institutional discrimination including being barred from federal or state government employment.[225] Gary Gates, the Research Director at UCLA Law School's Williams Institute, found that judicial opinions from appellate courts in seven states—California, Connecticut, Iowa, Maryland, Montana, Oregon, and Washington, including six of those states' highest courts—have all agreed that LGBT individuals have faced a long history of discrimination, regardless of how the court ultimately ruled on whether sexual orientation is a suspect classification.[226] For example, Maryland's highest court in 2007 recognized that "[h]omosexual persons have been the object of societal prejudice by private actors as well as by the judicial and legislative branches of federal and state governments."[227] Additionally the court found that "homosexual persons, at least in terms of contemporary history, have been a

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[222] S. M., "Indiscriminate," *The Economist, Democracy in America blog*, Jul. 12, 2013, http://www.economist.com/blogs/democracyinamerica/2013/07/gay-rights-workplace (quoting Peter Sprigg, "Homosexuality is Not a Civil Right," Family Research Council, 2007).

[223] Anderson testimony, Briefing Transcript at 280-281.

[224] Sears, *supra* note 46; *Conaway v. Deane*, 932 A.2d 571, 609 (Md. 2007). Christine Michelle Duffy and Denise Visconti, eds., *Gender Identity and Sexual Orientation Discrimination in the Workplace: A Practical Guide*, Bloomberg BNA, October 2014; Pizer, *supra* note 51.

[225] Stephanie Rotondo, eds., "Employment Discrimination against LGBT Persons," 16 Geo. J. Gender & L. 103 (2015); Alison Lorenzo, "Constitutional Law—Equal Rights Amendment, Equal Protections, and Due Process—The Right of Same-Sex Marriage is Not Fundamental, Prohibiting Same-Sex Marriage Does Not Constitute Gender-Based Discrimination, and Restrictions on the Right of Marriage are Rationally Related to the State's Interest in Regulation of Marriage," 39 Rutgers L.J. 1003, nn. 122–124 (2008).

[226] Sears, *supra* note 46, at Chapter 6, https://williamsinstitute.law.ucla.edu/wp-content/uploads/6_FindingsCourtsScholars.pdf.

[227] *Conaway*, 932 A.2d at 609.

disfavored group in both public and private spheres of our society."[228] In 2004, a concurring opinion filed by a justice of the Supreme Court of Montana described how LGBT people have been marginalized by their "government and institutions," and cited a number of cases documenting discrimination by state and local governments to demonstrate how "gays and lesbians historically have been the focus of discriminatory treatment in the workplace."[229]

The Supreme Court and federal courts have also recognized that LGBT employees have historically faced issues of workplace discrimination. For instance, the Ninth Circuit held that "[d]iscrimination against homosexuals has been pervasive in both the public and private sectors. Legislative bodies have excluded homosexuals from certain jobs and schools, housing, churches, and have prevented homosexual marriage."[230] The court concluded that "the discrimination faced by homosexuals in our society is plainly no less pernicious or intense than the discrimination faced by other groups already treated as suspect classes, such as aliens or people of a particular national origin."[231]

The Sixth Circuit in 1995 concluded "[h]omosexuals have suffered a history of pervasive irrational and invidious discrimination in government and private employment, in political organization and in all facets of society in general, based on their sexual orientation."[232] Additionally, that same year, a District of Columbia Court of Appeals judge cited examples of such discrimination in a dissent, including that: "[b]eing identified with homosexuality has been the basis of refusals to hire, the ruin of careers, undesirable military discharges, denials of occupational licenses, denials of the right to adopt, to the custody of children and visitation rights, denials of national security clearances and denials of the right to enter the country."[233]

Further, according to Congressional testimony by M.V. Lee Badgett, economist and research director of the Williams Institute and director of the Center for Public Policy and Administration, following over a decade of research and twelve studies, gay male workers were paid significantly less on average than their heterosexual male counterparts.[234] Data on the earnings for lesbians tend to be more inconsistent. Several studies show that lesbian or bisexual women do not earn less than

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[228] *Id.* at 610.
[229] *Snetsinger v. Mont. Univ. Sys.*, 104 P.3d 445, 455 (Mont. 2004) (Nelson, J., specially concurring).
[230] *Watkins v. U.S. Army*, 875 F.2d 699, 724 (9th Cir. 1989), *cert. denied*, 498 U.S. 957 (1990).
[231] *Id.*
[232] *Equal. Found. of Greater Cincinnati v. City of Cincinnati*, 54 F.3d 261, 264 n.1 (6th Cir. 1995) (quoting trial court findings), *cert. granted, judgment vacated*, 518 U.S. 1001 (1996).
[233] *Dean v. D.C.*, 653 A.2d 307, 334 (D.C. 1995) (quoting Elvia Arriola, Sexual Identity and the Constitution: Homosexual Persons as a Discrete and Insular Minority, 10 Women's Rts. L. Rep. 143, 157 (1988)).
[234] Testimony on H.R. 2015, The Employment Non-Discrimination Act of 2007: Hearing on H.R. 2015 Before the House Committee on Education & Labor and the House Subcommittee on Health, Employment, Labor & Pensions, 110th Cong. 4 (2007) (statement of M.V. Lee Badgett), *available at*: http://williamsinstitute.law.ucla.edu/wp-content/uploads/Badgett-HR2015-testimony-Sept-2007.pdf.

heterosexual women.[235] Badgett et al., argue that this does not imply the absence of employment discrimination. They argue that these findings suggest that since lesbians may not be constrained by the same gender expectations that result from being in relationships with men, they may make different decisions than heterosexual women (*e.g.*, choosing to delay or not have children, invest more into training, go into male-dominated professions) which may hide effects of discrimination.[236] Regardless, lesbian, bisexual, and heterosexual women all earn less than either gay or heterosexual men.[237] Moreover, when transgender individuals are surveyed separately the disparities are even more apparent. In six surveys conducted between 1996 and 2006, 20 percent to 57 percent of transgender respondents reported having experienced employment discrimination during some point in their life. At the time of the report, no detailed wage and income studies have been conducted regarding the transgender community, but convenience samples of the transgender population find that six percent to 60 percent of respondents report being unemployed, and 22 percent to 64 percent earn less than $25,000 per year.[238]

Another argument for extending LGBT protections is grounded in the principle of equal access to public markets and equal dignity of persons. Some researchers argue that as a society we have implemented legal safeguards intended to ensure equal access to necessities (*e.g.*, food, shelter, work) through federal and state statutes and common law principles.[239] This demonstrates that, as a society, we acknowledge the necessity for all citizens to have access to public accommodations, housing, and employment regardless of arbitrary characteristics like race, religion, nationality, disability, sex, and—with increasing consistency—sexual orientation and gender identity. Thus, the argument is that discrimination against LGBT persons is a clear violation of the normative principle of equal access and ultimately is dangerous and dehumanizing.

Conversely, Richard Epstein, Professor of Law at New York University School of Law and Senior Fellow at The Hoover Institution, argues that workplace antidiscrimination legislation would interfere with business owners' freedom of contract.[240] Epstein argues that in a free market society,

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[235] Arabshebani, G. Reza, Alan Marin and Jonathan Wadsworth. 2007. "Variations in Gay Pay in the USA and the UK," in M. V. Lee Badgett and Jefferson Frank, eds. "Sexual Orientation Discrimination: An International Perspective." London: Routledge; Badgett, M. V. Lee. 1995. "The Wage Effects of Sexual Orientation Discrimination." Industrial and Labor Relations Review 48(4): 726-739; Black, Dan A., Hoda R. Makar, Seth G. Sanders, and Lowell J. Taylor. 2003. "The Effects of Sexual Orientation on Earnings." Industrial and Labor Relations Review 56(3): 449-469.

[236] Lee Badgett, *supra* note 53.

[237] M.V. Lee Badgett and Alyssa Schneebaum, "The Impact of Wage Equality on Sexual Orientation Poverty Gaps," Williams Institute, June 2015, https://williamsinstitute.law.ucla.edu/wp-content/uploads/Impact-of-Wage-Equality-on-Sexual-Orientation-Poverty-Gaps-June-2015.pdf.

[238] *Ibid.*

[239] Isaac Saidel-Goley, "The Right Side of History: Prohibiting Sexual Orientation Discrimination in Public Accommodations, Housing, and Employment," 31 Wisc. J. of L., Gender & Soc'y 2 (2017).

[240] Richard Epstein, "Freedom of Association and Antidiscrimination Law: An Imperfect Reconciliation," *Liberty Law Forum*, Jan. 2, 2016, http://www.libertylawsite.org/liberty-forum/freedom-of-association-and-antidiscrimination-law-an-imperfect-reconciliation/.

the markets will correct the injustices of discrimination and discriminatory practices by punishing those who discriminate (*e.g.*, loss of profits, loss of qualified workforce), and thus result in economic equality for all.[241] In addition, he argues that antidiscrimination legislation is too costly, burdensome, and inefficient for the federal government to legislate over business practices.[242] In a somewhat similar vein, Andrew Koppelman, Professor of Law and Political Science at Northwestern University, argues that "[t]he general principle governing transactions between private parties should be freedom of association, for reasons of both liberty and efficiency. Any departure from that rule, such as a prohibition of discrimination, has the burden of proof."[243] However, Koppelman argues that Epstein does not consider the pervasive nature of discrimination and prejudice in our culture.[244] While some groups may be subject to historic and current pervasive discrimination, Epstein argues that economic equality cannot be achieved because those who choose not to prohibit discrimination still comprise the majority share of the market as a whole. Koppelman argues that when discriminators dominate the market, which at the present time it is for LGBT employees, then legal intervention is arguably justified.[245] He posits that not only can antidiscrimination laws help mitigate a society's pattern of stigma and marginalization that marks some members in society as inferior to others; but also, since "[h]abits of discrimination are hard to break, and legal intervention can help to break them."[246]

Further, the principle of the equal dignity of persons incorporates the "fundamental assumption that human beings are to be treated with dignity and respect"[247] and the equally fundamental assumption that all humans are to be treated with "equal dignity in the eyes of the law."[248] This principle is perhaps one of the most basic and foundational tenets of a free and democratic society, and a cornerstone of American society.[249] One viewpoint holds that "we can all accept that invidious sex discrimination violates equal dignity, and it is logically impossible to accept that notion without also accepting that sexual orientation [and gender identity] discrimination violates equal dignity."[250] Likewise, as stated by panelist Kylar Broadus, "[t]he bottom line is that it boils

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[241] *Ibid.* at 207.
[242] *Ibid.*
[243] Andrew Koppelman, "Richard Epstein's Imperfect Understanding of Antidiscrimination Law," *Liberty Law Forum*, Jan. 12, 2016, *available at* http://www.libertylawsite.org/liberty-forum/richard-epsteins-imperfect-understanding-of-antidiscrimination-law/.
[244] *Ibid.* at 208.
[245] *Ibid.*
[246] *Ibid.*
[247] Joseph William Singer, *Normative Methods for Lawyers*, 56 UCLA L. Rev. 899, 959 (2009).
[248] *Obergefell*, 135 S. Ct. at 2608.
[249] *Id.*
[250] Saidel-Goley, *supra* note 239, at 126.

down to we're all human beings on this planet and that in the United States you have to have a job to survive and that protections are needed."[251]

Employment discrimination can have long-lasting material effects, especially if it hinders individuals from securing steady employment. Those who suffer from chronic and cyclical under- and unemployment are more likely to be impoverished and often have secondary effects (*e.g.*, long-term earnings losses, declines in psychological and physical well-being, social withdrawal, family disruption) that can create additional difficulties for individuals and their families.[252] According to a 2015 study, Badgett and Schneebaum found that non-married gay and bisexual men earn less than non-married heterosexual men.[253] Looking at the poverty rates among same-sex and opposite-sex couples, same-sex white male couples tend to fare better (3.3 percent),[254] but the researchers found that lesbian couples have higher rates of poverty (7.9 percent) than heterosexual couples (5.8 percent). Critically, breaking these numbers down by race exposes even deeper inequities. Researchers found that African American lesbian couples have a poverty rate of 24.7 percent and gay African American couples have a rate of 14.5 percent, making them 3.1 and 1.8 times more likely to be in poverty compared to heterosexual African American couples (eight percent), respectively.[255]

Researchers have shown that state-employment protections for LGBT workers correlate with reduced poverty rates for those workers. In 2013, researchers found that in states where employment protections exist for LGBT workers, the poverty rate for both married opposite-sex couples and same-sex (both female and male) couples decreased.[256] In contrast, in states without protections, male same-sex couples tend to have slightly lower rates than opposite-sex couples, however, female same-sex couples are nine percent more likely to be in poverty than married opposite-sex couples.[257] Throughout the report, researchers found that employment discrimination protections seem to have a positive effect on all workers, but especially LGBT workers. For instance, poverty rates for both heterosexual and LGBT workers were shown to be lower in states with employment discrimination protections as opposed to states without protections, where

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[251] Broadus testimony, Briefing Transcript at 224-25.
[252] Jennie Brand, "The Far-Reaching Impact of Job Loss and Unemployment," *Annual Review of Sociology*, Vol 41, 359-375; Lindsey Hanson and Timothy Essenburg, eds., "The New Faces of American Poverty: A Reference Guide to the Great Recession," ABC-CLIO, 2014.
[253] Lee Badgett, *supra* note 237.
[254] This is largely due to their demographic makeup because white men are still on average the highest earners in the U.S.
[255] Lee Badgett, *supra* note 237.
[256] Lee Badgett, *supra* note 7.
[257] *Ibid.*

LGBT poverty is significantly higher than the poverty rate of heterosexual citizens.[258] Kate Kendell, Executive Director of the National Center for Lesbian Rights, noted

> many of the calls that we get are from individuals in these 29 States where there are no protections. If they live in a State where there are protections, it's an easy answer for them. We encourage them to file a complaint. We refer them to attorneys that do LGBT employment discrimination cases. There is recourse they can take. And then our resource is really just to hook them up with the knowledge base and with someone who can be their advocate. Most of what we—the calls that we get are in States where there is no protection. And it's only been recently in light of the EEOC's Macy ruling that we've seen an expansion of Title VII perhaps being available as a vehicle. Many, many times the most difficult answer that we give to people when they call saying that they've suffered some adverse employment action is, I'm sorry, there is nothing we can do. There is no protection in your State.[259]

Some opponents argue that discrimination against LGBT Americans has declined to the point that federal legislation has become unnecessary.[260] However, Coffman et al., argue that the magnitude of antigay sentiment is substantially underestimated.[261] They found that many individuals when asked sensitive questions are less likely to answer honestly, especially if the opinion is considered socially undesirable. When Coffman et al., utilized a "veiled" methodology[262] they found that antigay sentiments were reported at much higher rates. Specifically regarding the workplace, they found that respondents were 67 percent more likely to disapprove of an openly gay manager and 71 percent more likely to say it should be legal to discriminate in hiring on the basis of sexual orientation. In FY 2015, the EEOC received 1,412 claims alleging sex discrimination based on sexual orientation and/or gender identity/transgender status.[263] This represented an overall increase of approximately 28 percent of the total LGBT charges filed in 2014 (1,100).

Gina Duncan, the Transgender Inclusion Director of Equality Florida, the state's largest LGBT advocacy organization, touted the work of her organization in increasing legislative employment

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[258] *Ibid.*

[259] Kendell testimony, Briefing Transcript at 95–96.

[260] For example, *see* Anderson testimony, Briefing Transcript at 281 (arguing that "American businesses seldom discriminat[e] based on sexual orientation") (quoting Hans Bader of the Competitive Enterprise Institute).

[261] Katherine Coffman, Lucas Coffman, Keith Marzilla Ericson, "The Size of the LGBT Population and the Magnitude of Anti-gay sentiment are Substantially Underestimated," *National Bureau of Economic Research*, (2013), *available at* http://www.nber.org/papers/w19508.pdf.

[262] The researchers refer to their methodology as "veiled" to mean that they utilized a method to reduce social desirability bias by being able to obscure a participant's identity from being matched to their answers. They utilized the item count technique that has been proven effective by Miller, JD, "A new survey technique for studying deviant behavior," PhD Diss. G Wash U, 1984.

[263] U.S. Equal Employment Opportunity Commission, "What You Should Know About EEOC and the Enforcement Protections for LGBT Workers," *available at* https://www.eeoc.gov/eeoc/newsroom/wysk/enforcement_protections_lgbt_workers.cfm.

protections,[264] but at the Commission's briefing, she expressed concerns regarding the continued opposition she faced:

> The gender identity and expression piece of most legislation passed and pending has come under the most scrutiny and opposition and, frankly, the understanding of the transgender community is minimal among our elected officials, locally and at the statewide level. In lobbying in Tallahassee for legislation, I am often told I'm the first transgender person a lawmaker has ever met and I say, that you know of. The issue of public accommodations, *i.e.*, public bathrooms, as they relate to transgender citizens is always the baseless point of opposition that we must overcome to pass fully inclusive laws in Florida and in states across the country.[265]

Members of Congress have also made equal rights arguments in favor of passing a non-discrimination federal statute to extend workplace protections to all members of LGBT communities. For example, Rep. Alan Lowenthal sees the Equality Act as providing the same protections that all persons have under the 1964 Civil Rights Act, related to race. He stated that passing the Act would give

> the lesbian, gay, and trans community the same civil rights status as those other groups that had been denied equal access and equal opportunity under the law. I think it's the most comprehensive and sweeping way to ensure equal opportunities and equal protection under the law for all people. I think it's the right thing to do, because if you don't do it under the Equality Act, you're going to have to do [it] piece by piece, through piecemeal legislation. That's what's happened up until now.[266]

What Does Existing Federal Law (Title VII) Mean for Additional Federal Legislation?

Some proponents of workplace protection legislation argue that the primary need for federal legislation stems from the need to halt inconsistent and irreconcilable decisions which exist under the growing patchwork of employment discrimination decisions across the nation. As discussed in detail above, "courts have not taken a uniform position by any means with respect to the interpretations of Title VII discrimination."[267] The court decisions, in particular, are often

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[264] Ms. Duncan stated that Equality Florida has worked to pass fully inclusive human rights ordinances across the state and that as of the time of the briefing, over 55% of the population of Florida is now protected against discrimination in employment, housing, and public accommodations. Duncan testimony, Briefing Transcript at 209.
[265] *Ibid.* at 209-210.
[266] John Riley, "Exclusive: Rep. Alan Lowenthal on why Congress must pass the Equality Act," *Metro Weekly*, Mar. 23, 2017. http://www.metroweekly.com/2017/03/congressman-alan-lowenthal-on-why-congress-must-pass-the-equality-act/. *See also* U.S. Congress, *supra* note 86 (stating that "Workplace discrimination on the basis of sexual orientation and gender identity remains a problem in the American workplace and carries significant economic consequences.").
[267] Goldberg testimony, Briefing Transcript at 32.

confusing and contradictory regarding whether discrimination based on sexual orientation or gender identity can be alleged under Title VII, as reported to the Commission:

1. Jeanne Goldberg, Senior Attorney Advisor in the Office of the Legal Counsel of the EEOC, stated that court decisions are "not consistent," especially "on the sexual orientation issue." She went on to state that what federal legislation "would add as a general proposition is explicit protections and would therefore provide clarity and consistency across the country for our stakeholders, both employees and employers." She concluded that "at this point in time," such clarity does not exist.[268]
2. Kate Kendell, Director of the National Center for Lesbian Rights, put it more starkly: "Most of . . . the calls that we get are in States where there is no protection . . . Many, many times the most difficult answer that we give to people when they call saying that they've suffered some adverse employment action is, I'm sorry, there is nothing we can do. There is no protection in your State."[269]

Debates have also arisen as to what extent federal legislation protecting against discrimination based on sexual orientation and gender identity should replicate existing federal legislation terms—specifically whether the *bona fide* occupational qualification exception or the religious exemption found in Title VII should be included. Discussion in this area also concerns whether such federal legislation is constitutional, with proponents relying on the court decisions holding that the Civil Rights Act was constitutional, and opponents arguing that the histories and policies surrounding protections of race are different than for protections based on a person being LGBT. These points of view are discussed further herein.

BONA FIDE OCCUPATIONAL QUALIFICATION EXCEPTION

Title VII of the Civil Rights Act allows for employment decisions to be made on the basis of sex, religion, or national origin (but not race or color) if sex, religion, or national origin is a *bona fide* occupational qualification reasonably necessary for the operation of the business.[270] This is a "narrow" exception that allows an employer to "discriminate on the basis of 'religion, sex, or national origin in those certain instances where religion, sex, or national origin is . . . reasonably necessary to the normal operation of that particular business or enterprise.'"[271] The employer bears

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[268] *Ibid.* at 33-34.

[269] Kendell testimony, Briefing Transcript at 96.

[270] 42 U.S.C. § 2000e-2(e)(1).

[271] *Automobile Workers v. Johnson Controls, Inc.*, 499 U.S. 187, 200–01, 111 S. Ct. 1196 (1991) (*"Johnson Controls"*) (quoting 42 U.S.C. § 2000e–2(e)(1)). In *Johnson Controls,* a female plant worker in a battery manufacturing plant sued her employer because of a company policy that prohibited all women from working near lead—which entailed a health risk of harm to any fetus carried by a female employee—unless the employee documented her infertility. The Supreme Court held that even "the professed moral and ethical concerns about the welfare of the next generation do not suffice to establish a BFOQ of female sterility. Decisions about the welfare of

the burden of establishing the affirmative defense that a particular qualification falls within the exception.[272] The 2017 version of the Equality Act (and ENDA) did not include such an exception to discriminate on the basis of sexual orientation, and modifies the BFOQ exception as to sex to state that "individuals are recognized as qualified in accordance with their gender identity."[273] While some have argued that any federal legislation should include this exception,[274] a representative of the EEOC indicated that employers have not raised the issue in the cases she is aware of.[275] In Goldberg's testimony to the Commission, she stated that employers generally do not raise BFOQ exceptions as an excuse.[276] Thus, with the infrequency of this qualification, it makes it unlikely to be relevant regarding this specific issue. Others have argued that sexual orientation and gender identity more closely align with race, and thus, there are no *bona fide* reasons to discriminate.[277] Some would support only an extremely narrow exception similar to the BFOQ exception for discrimination based on gender.[278] Of note, courts have held that a customer preference invokes the exception only when it is based on the company's inability to perform the primary function or service it offers.[279]

RELIGIOUS LIBERTY AND FREE EXERCISE CONCERNS

Title VII of the Civil Rights Act allows a religious employer to discriminate on the basis of religion when it hires an employee.[280] For example, a Christian organization may require its employees to

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future children must be left to the parents who conceive, bear, support, and raise them rather than to the employers who hire those parents." *Id.* at 206. It further stated "our cases have stressed that discrimination on the basis of sex because of safety concerns is allowed only in narrow circumstances." *Id.* at 202.

[272] *See Dothard v. Rawlinson*, 433 U.S. 321 (1977), in which a prison rejected the application of female correctional counselor (prison guard) because she failed to meet the minimum 120-pound weight requirement of an Alabama statute. In deciding for the employee, the Court determined that the employer failed to rebut the *prima facie* case of discrimination on the basis that the height and weight requirements are job-related in that they have a relationship to the strength essential to efficient job performance as a correctional counselor, produced no evidence correlating such requirements with the requisite amount of strength thought essential to good job performance and, in fact, had not offered evidence of any kind in specific justification of the statutory standards.

[273] https://www.congress.gov/bill/115th-congress/house-bill/2282/text.

[274] Clegg testimony, Briefing Transcript at 148.

[275] Goldberg testimony, Briefing Transcript at 50.

[276] *Ibid.*

[277] Kylie Byron, "Natural Law and *Bona Fide* Discrimination: The Evolving Understanding of Sex, Gender, and Transgender Identity in Employment," 6 Wash. U. Jur. Rev. 343 (2014), *available at*: http://openscholarship.wustl.edu/law_jurisprudence/vol6/iss2/4; Laura Underkuffler, "Odious Discrimination and the Religious Exemption Question," 32 Cardozo L. Rev. 2069 (2011), *available at*: http://cardozolawreview.com/content/32-5/Underkuffler.32-5.pdf.

[278] Sarah Warbelow, Briefing Transcript at 154.

[279] *See Diaz v. Pan-Am*, 442 F.2d 385 (5th Cir. 1971) ("Similarly, we do not feel that the fact that Pan Am's passengers prefer female stewardesses should alter our judgment [that the *bona fide* occupational exception applies]. On this subject, EEOC guidelines state that a BFOQ ought not be based on 'the refusal to hire an individual because of the preferences of co-workers, the employer, clients or customers.'").

[280] Title VII of the Civil Rights Act of 1964 (Pub. L. 88-352).

be Christians.[281] The previously introduced version of ENDA (2013) included a religious exemption based upon the Title VII religious exemption.[282] The inclusion of this provision was criticized by some as not sufficiently protective of religious liberty. According to Ryan Anderson of the Heritage Foundation, "[w]hile ENDA provides some religious liberty protections, they are inadequate and vaguely defined . . . The religious liberty language in ENDA has been subject to repeated litigation with conflicting rulings by different courts as to which religious institutions are considered religious enough . . . the bill would not protect those who wish to run their businesses and other organizations in keeping with their moral or religious values."[283]

There are also multiple, conflicting viewpoints within the LGBT community on whether any religious exemption should be included. Many, but not all, LGBT advocacy groups withdrew their support for the religious exemption in ENDA after the Supreme Court's decision in *Hobby Lobby*.[284] The heart of these advocacy groups' concerns is that:

> ENDA's discriminatory provision, unprecedented in federal laws prohibiting employment discrimination, could provide religiously affiliated organizations—including hospitals, nursing homes and universities—a blank check to engage in workplace discrimination against LGBT people. The provision essentially says that anti-LGBT discrimination is different—more acceptable and legitimate—than discrimination against individuals based on their race or sex. If ENDA were to pass and be signed into law with this provision, the most important federal law for the LGBT community in American history would leave too many jobs, and too many LGBT workers, without protection. Moreover, it actually might lessen non-discrimination protections now provided for LGBT people by Title VII of CRA and very likely would generate confusion rather than clarity in federal law. Finally, such a discrimination provision in federal law likely would invite states and municipalities to follow the unequal federal lead. All of this is unacceptable.

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[281] 42 U.S.C. § 2000e-1. *See also Amos*, 483 U.S. at 327 (holding that a gym operated by the Mormon Church could legally require their staff to be Mormons in good standing).

[282] 42 U.S.C. § 2000e -1; Employment Non-Discrimination Act of 2013, S. 815, 113th Cong. (2013) (as passed by Senate November 7, 2013).

[283] Anderson testimony, Briefing Transcript at 281-82.

[284] *See, e.g.*, David Badash, "After Hobby Lobby, Seven Top LGBT and Civil Rights Orgs Drop Support for ENDA," New Civil Rights Movement, July 8, 2014, *available at* http://www.thenewcivilrightsmovement.com/breaking_after_hobby_lobby_six_top_lgbt_and_civil_rights_orgs_drop_support_for_enda; "ACLU Withdraws Support for ENDA," American Civil Liberties Union, July 8, 2014, *available at* https://www.aclu.org/lgbt-rights/aclu-withdraws-support-enda; and Chris Johnson, "Nadler 'Concerned,' Wants to Narrow ENDA's Religious Exemption," Washington Blade, July 8, 2014, *available at* http://www.washingtonblade.com/2014/07/08/rep-nadler-says-enda-religious-exemption-overbroad/. David Badash, "HRC Charts Lone Course, Reiterates Support for ENDA Despite Religious Exemptions," New Civil Rights Movement, July 8, 2014, *available at* http://www.thenewcivilrightsmovement.com/hrc_standing_alone_reiterates_support_for_enda_despite_religious_exemptions.

> The Supreme Court's decision in Hobby Lobby has made it all the more important that we not accept this inappropriate provision. Because opponents of LGBT equality are already misreading that decision as having broadly endorsed rights to discriminate against others, we cannot accept a bill that sanctions discrimination and declares that discrimination against LGBT people is more acceptable than other kinds of discrimination.[285]

Finally, some would use the exact same language as found in Title VII and have argued that the existing Title VII case law properly defines the line for which religious organizations should be able to use such an exception. As Alan Brownstein, law professor at University of California, Davis, testified before the Commission:

> I've written that there's a parallel between religion and sexual orientation both because there's a conduct dimension to both religion and sexual orientation, because both are relational and involve obligations based on relationships, because the protection of both religious liberty and the rights of the LGBT community are usually challenged by the same kind of slippery slope arguments that have been used to defeat both. So, I think there's some basis for saying not that discrimination against LGBT people is somehow sui generis and unique, and we need a separate regime of exemptions for the LGBT community. But I think one could argue that there's an analogy and a parallel between religion and sexual orientation so that the same religious exemptions that would apply with regard to discrimination on the basis of religion in hiring ought also to apply with regard to discrimination on the basis of sexual orientation.[286]

Constitutionality of Federal Legislation

Although not a focus of the Commission's investigation, opponents of legislation affording workplace nondiscrimination protections to LGBT Americans question the constitutionality of such a law.[287] In particular, they object to use of the Commerce Clause and Section 5 of the Fourteenth Amendment as the constitutional basis.[288] Article 1, Section 8, clause 3 of the U.S.

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[285] "Joint Statement on Withdrawal of Support for ENDA and Call for Equal Workplace Protections for LGBT People," American Civil Liberties Union, Gay & Lesbian Advocates and Defenders, Lambda Legal, National Center for Lesbian Rights, and Transgender Law Center, July 8, 2014, *available at* https://www.aclu.org/sites/default/files/assets/joint_statement_on_enda.pdf.

[286] Alan Brownstein, Law Professor at University of California, Davis, Briefing Transcript, pp. 284-85.

[287] Clegg testimony, Briefing Transcript at 101-104.

[288] Section 5 of the 14th Amendment provides Congress "power to enforce, by appropriate legislation, the provisions of this [amendment]" which, in Section 1, provides that, "No State shall make or enforce any law which shall abridge the privileges or immunities of citizens of the United States; nor shall any State deprive any person of life, liberty, or property, without due process of law; nor deny to any person within its jurisdiction the equal protection of the laws." Section 5 of the 14th Amendment provides Congress the power to enforce, by appropriate legislation, the substantive provisions of the Amendment. U.S. CONST., amend. XIV, sec. 5.

Constitution describes the enumerated power of Congress "[t]o regulate Commerce with foreign Nations, and among the several States, and with the Indian Tribes."[289] In *U.S. v. Lopez*,[290] the U.S. Supreme Court articulated that one test for determining whether an activity is within Congress' power to regulate under the Commerce Clause is "whether it substantially affects interstate commerce." Organizations and individuals who oppose this legislation believe that "Congress is going to have a hard time meeting those standards."[291] The Supreme Court also opined that "the power of Congress to promote interstate commerce also includes the power to regulate the local incidents thereof, including local activities in both the States of origin or destination, which might have a substantial and harmful effect upon that commerce."[292]

Proponents of anti-discrimination workplace protections for LGBT Americans counter that the interconnectedness of our national economy strengthens the argument that LGBT workplace protections affect interstate commerce:

> More so than ever, our economy is interconnected. We no longer live in a world in which goods and services are produced in one particular area; they stay in that area. Mom and pop shops are virtually a thing of the past when you're talking about production that is solely within a given area.[293]

Similarly, as discussed throughout this report, LGBT employees work throughout the United States and are employed by corporations that conduct business across state lines. For example, Northrop Grumman employs LGBT workers and "is located in all 50 states."[294] Such factual evidence seems to support the use of the Commerce Clause as the basis for federal anti-discrimination legislation.

In sum, as stated by briefing panelist Brownstein, "we fought that battle [about interstate commerce and nondiscrimination laws] and we've concluded as a society that the rights of employees, and the rights of people who seek public accommodations outweigh the rights of employers."[295]

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[289] U.S. CONST., art. I § 8, cl. 3.
[290] 514 U.S. 549 (1995).
[291] Clegg testimony, Briefing Transcript at 101 ("Now, it was certainly arguable in 1964 that the widespread and systemic discrimination against blacks in large parts of the country had a substantial effect on interstate commerce. But can it be credibly argued that, in 2015, discrimination against homosexuals has a "substantial" effect on interstate commerce? I don't think so.").
[292] *Heart of Atlanta Motel, Inc. v. U.S.*, 379 U.S. 241, 258 (1964).
[293] Warbelow testimony, Briefing Transcript at 99.
[294] Sylvester Mendoza, Global Director of Global Inclusion and Strategic Alliance at Northrop Grumman, testimony, Briefing Transcript, p. 172.
[295] Brownstein testimony, Briefing Transcript at 295.

Are Existing Public Sector Protections Enough?

While there have been formal restrictions and barriers in the private sector against LGBT employees, there also has been a long history of LGBT workers being barred from employment in the federal government.[296] The Merit Systems Protections Board cited a 2012 OPM survey that "found that lesbian, gay, bisexual, and transgender federal employee perceptions of the workplace were generally less positive than other employees."[297] When surveying federal LGBT employees, scholars Lewis and Pitts found that many LGBT workers do not believe they are given the same treatment as their heterosexual colleagues. They gave more negative responses to every question about their jobs, organizations, leaders, and co-workers.

> LGBT employees are 1 to 3 percentage points less likely than heterosexuals to think their performance appraisals are fair and to be satisfied with their pay; 3 to 6 points less likely to be satisfied with their advancement opportunities or to feel that merit drives rewards in their agencies; 4 to 6 points less likely to think highly of their immediate supervisors, agency leadership, or organizations; and 4 to 8 points less likely to be satisfied with their agencies' treatment of diversity, [prohibited personnel practices] and employee empowerment. They are also 3 to 8 percentage points more likely to say that they are planning to look for a new job outside their agency. Given the low percentages reporting dissatisfaction, LGBTs are one quarter more likely than heterosexuals to express dissatisfaction on most measures.[298]

Additionally, outside of reporting EEOC claims, the federal government does not appear to collect data regarding whether the efforts to ensure federal anti-discrimination policies are fully implemented. Advocates argue that it would be helpful if "every federal agency [were] charged with collecting information on sexual orientation and gender identity in all of their surveys."[299] According to the National LGBTQ Task Force, collecting additional data on sexual orientation and gender among LGBT federal employees, federal contractors, and federally assisted contractors could be "spearheaded by a presidential Executive Order calling for agencies to determine best methods for integrating these demographic questions into their data collection instruments" and to examine the "levels of filing" of complaints and what is happening in federal enforcement and oversight.[300] It is worth noting that adding demographic measures may not be a wanted change for all LGBT people in fear of privacy concerns. Due to the societal stigma of embodying an LGBT

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[296] Sears, *supra* note 224.
[297] Merit Systems Protection Board, *Sexual Orientation in the Federal Workplace, Policy and Perspective*, (May 2014) (discussing and citing the Office of Personal Management's 2012 Employee Viewpoint Survey at iii).
[298] Gregory B. Lewis and David W. Pitts, "LGBT–Heterosexual Differences in Perceptions of Fair Treatment in the Federal Service," *American Review of Public Administration*, 1-19 (2015), p. 15.
[299] Simmons testimony, Briefing Transcript at 82-83.
[300] *Ibid.* at 93.

identity and the fear of prejudice, some LGBT individuals may not want to disclose their sexual orientation or gender identity in surveys.

Outside of federal employment, an estimated one million LGBT employees work in the public sector for state and local governments.[301] Of these employees, only 45 percent of American workers live in a jurisdiction prohibiting sexual orientation discrimination in employment, and only 34 percent of workers live in a jurisdiction prohibiting gender identity discrimination.[302] These workers may face a patchwork of employment protections, depending on what state or local jurisdiction they work for. For instance, Lisa Howe, Executive Director of the Nashville LGBT Chamber of Commerce, explained at the briefing how state-by-state protections do not offer adequate protections for all LGBT workers. She reported that in Tennessee there are "very few protections . . . for contractors or anything like that. So in Nashville the metro government did pass a policy to extend sexual orientation, gender identity onto the employment—the discrimination policies for their contractors and the state overturned it and said that local governments do not have that authority."[303]

Even though some states have policies for state and local LGBT employees, researchers have found that discrimination is still pervasive and occurs nearly as frequently as discrimination in the private sector.[304] Looking at public sector complaints in 123 jurisdictions, Mallory and Sears found that the rate of discrimination complaints filed by LGB state and local employees was slightly lower than, but similar to, that of filings by LGB employees in the private sector.[305] They found that the frequency is similar with state and local government employment, but state filings are slightly lower (2.8 complaints for state government and 3.2 complaints for local government for every 10,000 LGB employees). Mallory and Sears found the rate of sexual orientation and gender identity complaints occurred at a similar rate as discrimination claims based on race and sex.[306] They further discussed that the actual rate of discrimination against LGBT employees may be drastically underreported for several reasons. First, some state and local agencies lack the resources and staff necessary to effectively enforce nondiscrimination laws. Panelist Roger Clegg brought up this point in his testimony, stating that having to resort to litigation and regulation is "very

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[301] Chris Mallory and Brad Sears. "Discrimination Against State and Local Government LGBT Employees." *LGBTQ Policy Journal*, Volume 4, (2012).
[302] Lee Badgett et al., "Executive Order to Prevent Discrimination Against LGBT Workers," Center for American Progress and Williams Inst., 4 (Feb. 2013), https://www.americanprogress.org/issues/lgbt/reports/2013/02/19/53931/an-executive-order-to-prevent-discrimination-against-lgbt-workers/.
[303] Howe testimony, Briefing Transcript at 173.
[304] Lee Badgett, *supra* note 53.
[305] Mallory and Sears, *supra* note 301. Three per every 10,000 LGB public sector employee compared to 4.1 per every 10,000 LGB private sector employee.
[306] *Ibid.* at 46-47 (four per every 10,000 LGB employee, 3.9 per every 10,000 racial minority employee, 5.2 per every 10,000 female employee).

expensive and distortive media."[307] This argument may be likely to have bipartisan support for those in favor and those who oppose federal legislation. Second, LGBT people may be hesitant to file complaints because of a perception of judicial unresponsiveness. Third, LGBT people may choose not to file complaints in order to avoid further "outing" themselves and thus risk suffering further negative consequences in the workplace.

Are Private Sector Policies Enough?

Opponents of federal legislation assert that "while racial integration might not have been forthcoming apart from the Civil Rights Act, in the case of sexual orientation, voluntary actions and market forces have emerged that undermine the clamor for federal action."[308] Proponents of federal legislation disagree, arguing that although the federal government, corporations, and businesses are increasingly creating and enforcing LGBT-inclusive policies, LGBT workers still lack an array of national legal protections, leaving many to hide who they are for fear of discrimination in the workplace. These proponents note that private sector policies are necessary, but not sufficient to create a national climate of inclusion. Proponents for federal legislation argue that voluntary measures implemented by some major corporations are not enough, since the effects of workplace discrimination against members of the LGBT community remain very serious. For individuals, workplace discrimination can drastically increase psychological stress and other mental health problems. A fifth of LGBT respondents to the Human Rights Campaign Foundation's 2014 survey reported feeling exhausted from expending time and energy hiding their identities and a third felt distracted from their duties at work due to negative workplace environments.[309] As the Director of Human Rights Campaign's Workplace Equality Program has stated "[t]he inclusive policies coming from the boardroom have not fully made it into the everyday culture of the American workplace."[310]

Further, business policies are not enforceable in courts, and businesses may decide not to follow their own policies. The Director of the Public Policy at the National LGBTQ Task Force shared the story of an insurance company receptionist, who was terminated the same day an agency executive saw him kiss his partner in the work parking lot.[311] The employer had a general company policy of non-discrimination; yet according to testimony before the Commission, the employee perceived that he had no recourse to challenge the termination decision. This case occurred in 2002, therefore it was before the EEOC's decision to extend workplace protections based on sexual

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[307] Clegg testimony, Briefing Transcript at 108.
[308] Anderson testimony, Briefing Transcript at 281.
[309] Fidas, *supra* note 39, at 3.
[310] "HRC Study Shows Majority of LGBT Workers Closeted on the Job," News release, HRC, May 7, 2014.
[311] Simmons Statement at 7.

orientation. Panelist Long-Simmons used this example to highlight the importance of enacting federal legislation to protect LGBT workers since businesses merely having a stated policy may not offer these employees full protections.

Lastly, even though the EEOC has held that claims of discrimination based on sexual orientation and gender identity can be brought under Title VII, for employees to "truly benefit from these legal protections, explicit statutes must be enacted to make sure that the law is clear to everyone, including employers, workers, and courts."[312] "Courts are not strictly bound to follow the [EEOC's] interpretation of the law."[313] Given the current inconsistent Circuit court decisions, should a private employer in some jurisdictions not agree with the EEOC's decision, it could refuse to abide by it, which may result in a court overturning the EEOC's decision.[314]

How Would Federal Legislation Impact the Economy?

ECONOMIC SUPPORT OF FEDERAL LEGISLATION

There is substantial support for federal legislation in the business community. As Mary Beth Maxwell, the former Principal Deputy Assistant Secretary for Policy at the Department of Labor put it, "Equality in the workplace is not only the right thing to do; it turns out to be good business."[315] Sylvester Mendoza, Director of Global Inclusion and Strategic Alliances at Northrop Grumman, stated that discrimination "has no place in the workplace, and we believe in doing everything possible to eliminate discrimination against any employee, including members of the LGBT community."[316] Northrop Grumman's zero tolerance policy offers protections to their employees from "discrimination based on sex, gender, gender identity, expression, and sexual orientation."[317] They feel that diversity and inclusion are strengths necessary to a global corporation. By providing an inclusive working environment, Northrop Grumman believes that employees "bring their whole authentic selves to work every day, contributing diverse ideas, perspectives, and talents to solve our customers' toughest challenges."[318] While this policy is an example of a positive and inclusive step towards workplace equality for LGBT employees, this policy only protects Northrop's workers from discrimination. Thus, this example illustrates how

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[312] Mendoza testimony, Briefing Transcript at 193; Ilona Turner, Legal Director at the Transgender Law Center, testimony, Briefing Transcript, p. 204.
[313] Turner testimony, Briefing Transcript at 207. As discussed in more detail above, only one circuit court has followed EEOC's lead and held that Title VII permits sexual orientation lawsuits.
[314] *See ibid.* at 207-08.
[315] Maxwell testimony, Briefing Transcript at 21.
[316] Mendoza testimony, Briefing Transcript at 166.
[317] *Ibid.* at 167.
[318] *Ibid.*

the need to eliminate patchwork protections for LGBT employees is imperative so all employees can have the reassurance of being protected from discrimination.

There are many companies like Northrop Grumman who believe that discrimination against LGBT employees and applicants leads to less qualified staff.[319] Discrimination lowers motivation to invest in future education. Not only does this affect individuals, it also lowers a company's overall skilled staff and the entire U.S. labor force. Furthermore, this leads to a decrease in productivity and, therefore, a decrease in profit and economic growth. LGBT and heterosexual employees alike who work for businesses that discriminate show high rates of absenteeism and are generally less committed to their respective businesses.[320] Accordingly, many businesses support federal legislation:

1. 63 percent of small businesses support legislation to legally protect LGBT employees regardless of employer's religious beliefs.[321]
2. Almost six in ten small-business owners also believe that employment nondiscrimination laws improve or would improve their businesses' bottom lines by allowing access to the most talented individuals, regardless of sexual orientation or gender identity.[322]

Employment protection policies often cost companies little to nothing to implement or maintain antidiscrimination policies. Eighty-six percent of small businesses that do not already have such an antidiscrimination policy state that these policies cost them "nothing or next to nothing," while only two percent of small businesses with such policies say there is a "small but significant" cost associated with antidiscrimination policies. None of the businesses surveyed reported a substantial cost. [323]

Furthermore, findings suggest there are economic benefits in extending LGBT employees' equal benefits and adding protective inclusion and diversity policies. As discussed previously, employees perceive these policies as positive, thus contribute positively to business profits. Moreover, with the increasing numbers of same-sex households, the buying power of LGBT consumers is also growing. Studies suggest there has been a 20 percent increase in LGBT market growth from 2006 to 2012, which equates to approximately $790 billion.[324] Further, surveys suggest that consumers (both LGBT and allies) see acceptance and tolerance positively, thereby

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[319] Mendoza testimony, Briefing Transcript at 166-67. Human Rights Campaign Foundation, *supra* note 105.
[320] Out & Equal, Harris Interactive, and Witeck Combs Communications, "Out & Equal Workplace Culture Report," 2008.
[321] Small Business Majority, *supra* note 87.
[322] *Ibid.*; Movement Advancement Project, *supra* note 52.
[323] Small Business Majority, *supra* note 87.
[324] Witeck-Combs Communications, "America's LGBT 2012 Buying Power Projected at $790 Billion," 2012.

increasing customer flow and money earned for the economy.[325] A majority of heterosexual and LGBT consumers state that friendliness and support of equal rights for the LGBT community influence the decision to purchase products or services from a business. In a national survey in 2011, 87 percent of LGBT individuals and 75 percent of heterosexuals say they consider choosing a brand known to provide equal benefits to employees regardless of sexual orientation or gender identity.[326] In the same survey, researchers found that brand loyalty is important to LGBT consumers. They found that 71 percent LGBT adults said that they are likely to remain loyal if the business is believed to be "very friendly" and "supportive" of the LGBT community, regardless if the less-friendly company is cheaper and/or more conveniently located.[327]

Conversely, the potential for boycotts of a company's products or services has impacted many businesses' view of supporting LGBT rights. For decades, most companies rarely targeted or advertised to the LGBT community, choosing instead to stay away from partisan issues to avoid taking a position that might isolate a segment of their customer base.[328] Today though, customers increasingly see their dollars as an extension of their power in the voting booth.[329] Social media campaigns have bolstered boycotts, which have allowed people around the country to organize protests and boycott products.[330] As the Chief Executive of the Center for Talent Innovation has noted "[t]here's enormous value in figuring out how to be seen and to act as a LGBT-friendly company."[331] However, even with the positive voluntary measures that companies have implemented to end discrimination against LGBT employees, as stated previously, many people are not covered and discrimination remains a significant problem for these communities.

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[325] Ogilvy, "LGBT-Inclusive Advertising Is Driving Business Yet Consumers Demand Authenticity According to Ogilvy Survey," June 28, 2017, https://www.prnewswire.com/news-releases/lgbt-inclusive-advertising-is-driving-business-yet-consumers-demand-authenticity-according-to-ogilvy-survey-300481056.html, Harris Interactive, "LGBT Adults Strongly Prefer Brands That Support Causes Important to Them and That Also Offer Equal Workplace Benefits," *PR Newswire*, Jul. 18, 2011, http://www.prnewswire.com/news-releases/lgbt-adults-strongly-prefer-brands-that-support-causes-important-to-them-and-that-also-offer-equal-workplace-benefits-125742178.html.

[326] Harris Interactive, *supra* note 325.

[327] *Ibid.*

[328] Katherine Sender, *Business, Not Politics: The Making of the Gay Market*, Columbia University Press, February 2005; Samantha Felix, "15 Ads That Changed the Way We Think About Gays and Lesbians," *Business Insider*, Oct. 13, 2012, http://www.businessinsider.com/15-ads-that-changed-the-way-we-think-about-gays-and-lesbians-2012-10?op=1.

[329] Amanda Hoover, "Major Companies Back Transgender Teen in Supreme Court Case: A New Trend?", *Christian Science Monitor*, Mar. 2, 2017, https://www.csmonitor.com/USA/2017/0302/Major-companies-back-transgender-teen-in-Supreme-Court-case-a-new-trend.

[330] Americus Reed and Judith Samuelson, "When Do Consumer Boycotts Work?", *New York Times, Opinion Pages, Room for Debate*, Feb. 7, 2017, https://www.nytimes.com/roomfordebate/2017/02/07/when-do-consumer-boycotts-work.

[331] Hoover, *supra* note 329.

ECONOMIC OPPOSITION TO FEDERAL LEGISLATION

Opponents of the Employment Non-Discrimination Act and the Equality Act argue that anti-discrimination laws against LGBT people will prove economically disadvantageous to businesses and the economy.[332] Some believe that anti-discrimination laws will be counterproductive and result in less frequent hiring of LGBT employees because of the risk of costly lawsuits. Their concern is that employers will hire a non-LGBT person over an LGBT person because the former does not present the risk of later lawsuits claiming discrimination.[333] Additionally, opponents argue that employers may not want to lay off employees who are protected by the Employment Non-Discrimination Act, even if the layoff is for legitimate reasons, because the employee could sue for wrongful termination. Because of this, opponents argue businesses will be stuck with "unproductive or superfluous workers," which will cause further economic stress.[334] Opponents believe this reluctance to fire people would also result in hiring fewer LGBT individuals because employers feel such employees cannot be fired. The end result of federal legislation on hiring and firing employees, according to those opposed to federal legislation, will be less job creation in the market as a whole.[335]

Opponents of federal legislation are concerned that there may be additional litigation due to what they perceive as the subjective nature of sexual orientation and gender identity, which is more difficult for an employer to identify than sex or race. According to some opponents, this means that an LGBT employee who is fired could, theoretically, bring more lawsuits against a former employer, which could harm all businesses, including those that already have antidiscrimination policies in place.[336] One author asserts that, even if the employer were to win a wrongful termination suit, the business would still have to pay at least $250,000 in attorney fees. Additional costs, though minimal, could also come from training seminars on a new federal law and the cost of following strict guidelines.[337]

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[332] For example, *see* Ryan Anderson, "ENDA Threatens Fundamental Civil Liberties," Heritage Foundation, November 2013, http://www.heritage.org/civil-society/report/enda-threatens-fundamental-civil-liberties; Heritage Action For America, "'No' On the Employment Non-Discrimination Act (ENDA), November 2013, *available at* http://heritageaction.com/key-votes/employment-non-discrimination-act-enda/. The U.S. Chamber of Commerce did not take a position either for or against the Employment Non-Discrimination Act when it was debated in 2013. Chris Johnson, "U.S. Chamber of Commerce stays neutral on ENDA," *Washington Blade*, Sept. 18, 2013, http://www.washingtonblade.com/2013/09/18/chamber-stays-neutral-enda/.

[333] Courtney Michaluk and Daniel Burnett, "Gayconomics 101: Why the Latest LGBT Rights Legislation Could Be the 'ENDA' the Road for Some Job Seekers," *Huffington Post*, Nov. 25, 2013, http://www.huffingtonpost.com/courtney-michaluk/enda_b_4326767.html.

[334] Anderson, *supra* note 332.

[335] *Ibid.*

[336] For example, *see* Hans Bader, "Employment Non-Discrimination Act Makes as Little Sense as Chemotherapy for a Cold," Competitive Enterprise Institute, June 13, 2012, https://cei.org/blog/employment-non-discrimination-act-makes-little-sense-chemotherapy-cold.

[337] Michaluk, *supra* note 333; Small Business Majority, *supra* note 87.

At the Commission's briefing, panelists noted that in states that have enacted LGBT anti-discrimination protections, there has not been a flood of litigation in response. Kate Kendell stated:

> We have a number of states that have passed laws that prohibit discrimination based on gender identity . . . And there hasn't been some—there hasn't been a huge flood of litigation, nor has there been inane interpretations. What these laws do, is they set a tone for how we think people should be treated on the job. And by existing, they stop the very discrimination that they're meant to redress. And then in extreme cases, people then are free and have the ability to bring cases. The ability to answer the question, what kind of country do we want to live in? With the statute that says, we want to live in a country where people, all sorts of people, including people based on sexual orientation or gender live free, honored for who they are and able to do their jobs to the highest of their ability. And their ability is what matters, not who they are. That seems to me to be a good thing for this country to do.[338]

Of note, the number of EEOC claims alleging sexual orientation and/or gender identity discrimination counters against the narrative of additional lawsuits. The EEOC reports that it "receives close to 95,000 charges a year on all of the statutes we enforce . . . in those three quarters of fiscal year 2013 and looking at a snapshot of 2014, we are talking about a fraction, really small fraction—talking about 800 charges altogether raising these issues, and, obviously, a number of them may not be meritorious."[339] After the EEOC held that sexual orientation and gender identity fall within Title VII, the number of charges filed alleging discrimination on these bases did rise to 1,768 for FY 2016, which is approximately 1.8 percent of all charges filed with the EEOC.

Another concern about the effect of federal legislation and additional federal regulation on business hiring and firing could negatively impact the free market system.[340] The "at-will" employment concept in which businesses fire and rehire at any time follows this economy philosophy. They argue that businesses hire the most qualified regardless of sexual orientation or gender identity because it is in their best interest to do so.[341] This belief holds that "the free market is already correcting what bureaucratic red tape cannot fix."[342]

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[338] Kendell testimony, Briefing Transcript at 115.
[339] *Ibid.* at 55-56.
[340] Statement of Roger Clegg, President and General Counsel at Center for Equal Opportunity, U.S. Commission on Civil Rights, *Briefing: Examining Workplace Discrimination Against LGBT Americans,* (Washington, DC, March 16, 2015) at 4; *see also* Clegg testimony, Briefing Transcript at 277 (raising concerns about "government interference in the marketplace.").
[341] Clegg testimony, Briefing Transcript at 67. ("If discrimination on the basis of sexual orientation is always irrational, then employers that engage in such discrimination will be at economic disadvantage, and the market will punish them.").
[342] Michaluk, *supra* note 333.

New Developments in Federal Legislation

In May 2017, the Equality Act was reintroduced in Congress.[343] This newest version extends protections for LGBT individuals not only in the workplace, but also in public accommodations, housing, federally funded programs, jury service, and credit. This is significant and worth noting in this report since the right of transgender persons to access the bathroom that correctly aligns with their gender identity has gained national attention. Kylar Broadus, Senior Public Policy Counsel of the Transgender Civil Rights Project, at the briefing explained the frustrating dilemma in simply trying to access a bathroom. He told the Commission: "I didn't go to the bathroom for years [in public facilities] because I would be accosted by police at every place and thrown out of the women's room."[344] While a full discussion of these issues is beyond the scope of this report, we acknowledge them for contextual reasons.

Specifically regarding the workplace, transgender rights advocates argue that employers should allow transgender workers to use the restroom that conforms to their gender identity and/or allow them access to private, single user facilities.[345] And the American public seems to also agree. A 2016 survey found broad, bi-partisan support for LGBT nondiscrimination laws, with 72 percent of Americans saying they favor laws that would protect LGBT individuals from discrimination in jobs, public accommodations, and housing.[346] Further, a majority (53 percent) of Americans oppose laws that require transgender persons to use the bathroom that corresponds to their assigned sex at birth rather than their gender identity.[347] A lack of a clear policy surrounding the use of restrooms for transgender employees (and citizens more broadly) creates an uncomfortable and sometimes hostile atmosphere for transgender people. Mara Keisling from the National Center for Transgender Equality, stated the explicit connection between bathroom rights and workplace protections. In her testimony she stated: "If you're allowed to have a job and you can't be fired but they don't have to let you use a bathroom at work, you can't work."[348]

Access to restrooms for transgender people is also a health issue relevant to both employees and businesses. The Department of Labor's (DOL) Occupational Safety and Health Administration (OSHA) released guidelines in 2015 for employers to ensure all employees have access to facilities they need. The report states: "all employees, including transgender employees, should have access to restrooms that correspond to their gender identity." The department argues that lack of access

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[343] https://www.congress.gov/bill/115th-congress/house-bill/2282/text.
[344] Broadus testimony, Briefing Transcript at 224.
[345] Chang, *supra* note 103.
[346] Robert P. Jones, Betsy Cooper, Daniel Cox, and Rachel Lienesch, "Majority of Americans Oppose Laws Requiring Transgender Individuals to Use Bathrooms Corresponding to Sex at Birth Rather than Gender Identity." *PRRI*. 2016, *available at* http://www.prri.org/research/poll-lgbt-transgender-bathroom-bill-presidential-election/.
[347] *Ibid.*
[348] Keisling testimony, Briefing Transcript at 219.

to proper and hygienic restrooms can cause health problems or risks to physical safety for affected individuals.[349] For instance, the National Center for Transgender Equality found that in the past year, 8 percent of respondents reported having a urinary tract infection, kidney infection, or another kidney-related problem as a result of avoiding restrooms.[350] Further, the DOL's Office of Federal Contract Compliance Program (OFCCP) released a fact sheet stating that gender identity is protected under their policy prohibiting sex discrimination. Its new rule requires "contractors to allow workers to use bathrooms, changing rooms, showers, and similar facilities consistent with the gender with which the workers identify."[351] These policies by the Department of Labor reflect some of the ongoing policy struggles in this realm—for both state and local laws—that inhibit an individual's access to a bathroom that corresponds with the individual's gender identity (e.g., Texas and North Carolina).[352] However, some private companies have instituted their own policies regarding their public and employee bathrooms (*e.g.*, Target and Starbucks)[353] to compensate for the lack of federal protections.

Over the past several years, the business community has become more vocal about social issues, both for and against LGBT rights. Corporations have taken positions on state religious freedom restoration laws, which allow businesses to discriminate against customers on the basis of religion that many see as anti-gay. For example, corporations like Hobby Lobby and Chick-Fil-A have both come under fire by advocates for touting anti-LGBT rhetoric and adopting non-inclusive policies.[354] Conversely, many corporations have publicly declared support for extending employment protections for LGBT workers and customers. Todd Sears, founder and principal of Out Leadership, argues that these actions from the business community are "the new normal . . . [and] it's not just that companies are speaking out, there's actually a price to not speaking out."[355] For instance, after then-North Carolina Governor Pat McCory passed the HB 2 bill that blocked local governments from passing anti-discrimination laws protecting LGBT people, repealed existing municipal housing and employment protections for LGBT people, and forced transgender

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[349] U.S. Department of Labor, Occupational Safety and Health Administration, *A Guide to Restroom Access for Transgender Workers*, 2015, *available at* http://www.dol.gov/asp/policy-development/TransgenderBathroomAccessBestPractices.pdf.

[350] James, *supra* note 55.

[351] U.S. Department of Labor, Office of Federal Contract Compliance Programs, *OFCCP's Sex Discrimination Final Rule*, 2016, *available at* https://www.dol.gov/ofccp/SexDiscrimination/SexDiscrimFinalRuleFactSheet_JRFQA508c.pdf.

[352] http://www.legis.state.tx.us/tlodocs/85R/billtext/pdf/SB00006I.pdf; M.S.R., "Texas Republicans revive their 'bathroom bill,'" *The Economist*, Jul. 27, 2017, https://www.economist.com/blogs/democracyinamerica/2017/07/toilet-talk. See below for an in-depth discussion of the North Carolina legislation.

[353] Hadley Malcolm, "How other stores are handling transgender bathroom policies," *USA TODAY*, Apr. 27, 2016, https://www.usatoday.com/story/money/2016/04/27/retailers-transgender-bathroom-policy-lgbt/83560714/.

[354] The Advocate, "Chick-Fil-A," http://www.advocate.com/chick-fil (last visited Nov. 12, 2017); Emma Margolin, "How Hobby Lobby will reverberate throughout the LGBT community," *MSNBC*, Jul. 10, 2014, http://www.msnbc.com/msnbc/hobby-lobby-reverberate-throughout-lgbt-community.

[355] Hoover, *supra* note 329.

people to utilize public bathrooms based on the sex on their birth certificates rather than their gender identities, many companies refused to continue doing business in the state. When businesses and corporate investors oppose legislation, such as when the National Basketball Association pulled its 2017 All-Star Game out of North Carolina in opposition to HB 2, they are likely to influence local and state policy going forward. For example, when the Georgia state legislature attempted to pass their own religious freedom bill, Governor Nathan Deal vetoed it, stating that it would hurt Georgia business growth.[356] According to the *Associated Press*, the "bathroom bill" has cost North Carolina an estimated $3.76 billion in lost business revenue.[357] Due to the political, economic, and social backlash from HB2, now-Governor Roy Cooper promised during his 2017 gubernatorial campaign that he was going to repeal the bill. However, he did not issue a full repeal. Rather in March 2017 he offered a "compromise" in the form of House Bill 142.[358] This new bill forbids "state agencies, boards, offices, departments, institutions," and "branches of government," including public universities, from regulating "access to multiple occupancy restrooms, showers, or changing facilities."[359] HB 142 further restricts local governments, school boards, and public universities from passing their own LGBT-inclusive policies and bans any city in North Carolina from "regulating private employment practices or regulating public accommodations" until December 1, 2020.[360] This new bill has assuaged some of the concerns from HB 2, for instance the NCAA has decided to return to North Carolina despite the continued discriminatory impacts of this new bill. The NCAA governors argue that HB142 brings North Carolina laws in step with the majority of the other states.[361] However, LGBT advocates argue that the bill "literally does not do one thing to protect the LGBT community and locks in HB2's most basic and offensive provision."[362]

On May 30, 2017 the Seventh Circuit Court of Appeals ruled in favor of a transgender plaintiff regarding bathroom access.[363] The court ruled that restricting the transgender student from using

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[356] Sandhya Somashekhar, "Georgia governor to veto religious freedom bill criticized as anti-gay," *Washington Post*, Mar. 28, 2016, https://www.washingtonpost.com/news/post-nation/wp/2016/03/28/georgia-governor-to-veto-religious-freedom-bill-criticized-as-anti-gay/?utm_term=.a7a46bc15b99.

[357] Emery Dalesio and Jonathan Drew, "Price tag of North Carolina's LGBT law: $3.76B" *Associated Press*, Mar. 27, 2017, https://www.apnews.com/fa4528580f3e4a01bb68bcb272f1f0f8.

[358] Eliot McLaughlin, "North Carolina's HB142: Repeal? Compromise? What does it all mean?", *CNN*, Mar. 30, 2017, http://www.cnn.com/2017/03/30/us/north-carolina-hb2-repeal-hb142-explainer/; Mark Joseph Stern, "The HB2 "Repeal" Bill Is an Unmitigated Disaster for LGBTQ Rights and North Carolina" *Slate*, Mar. 30, 2017, http://www.slate.com/blogs/outward/2017/03/30/hb2_repeal_bill_is_a_disaster_for_north_carolina_and_lgbtq_rights.html.

[359] General Assembly of North Carolina, Session Law 2017-4, House Bill 142.

[360] *Id.*

[361] Camila Domonoske, "NCAA Returning to North Carolina After Partial Repeal of 'Bathroom Bill'", *National Public Radio*, Apr. 4, 2017, http://www.npr.org/sections/thetwo-way/2017/04/04/522579434/ncaa-returning-to-north-carolina-after-partial-repeal-of-bathroom-bill.

[362] The Observer Editorial Board, "HB2 repeal: Cooper turns back on LGBT community" *The Charlotte Observer*, Mar. 30, 2017, http://www.charlotteobserver.com/opinion/editorials/article141667999.html.

[363] *Whitaker v. Kenosha Unified Sch. Dist. No. 1 Bd. of Educ.*, 858 F.3d. 1034 (7th Cir. 2017).

the bathroom that corresponded to his gender identity was a form of sex discrimination, which is protected under Title IX.[364] While this case was specifically regarding a Wisconsin high school student, the court's decision has sweeping implications for how Title IX will be interpreted in the future, and potentially for the 14th Amendment.[365] Where courts interpret bans against sex discrimination to prohibit discrimination against transgender individuals, their reasoning offers analogies in other contexts in which bans against sex discrimination apply (*e.g.*, workplace, housing, public accommodations).

[364] Education Amendments of 1972, Pub. L. 92-318, codified at 20 U.S.C. § 1681 et seq.

[365] In February 2017, the Departments of Education and Justice rescinded earlier guidance, dated May 13, 2016, from the Departments of Education and Justice stating that Title IX's prohibition of discrimination on the basis of sex required access to sex-segregated facilities based on an individual's gender identity. Civil Rights Division of the U.S. Department of Justice and Office for Civil Rights of the U.S. Department of Education, Dear Colleague letter, Feb. 22, 2017, *available at* https://www2.ed.gov/about/offices/list/ocr/letters/colleague-201702-title-ix.docx.

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CHAPTER 4: FINDINGS AND RECOMMENDATIONS

The Commission makes the following findings and recommendations:

Findings and Recommendations

FINDINGS

1. **Overview**

   a) Historians, researchers, and courts have extensively documented that lesbian, gay, bisexual, and transgender (LGBT) workers have faced a long, serious, and pervasive history of official and unofficial employment discrimination by both federal, state, and local governments and private employers.
   b) Anti-LGBT employment discrimination persists and has wide-ranging, damaging implications for the quality of life for many LGBT Americans, their children and families, and communities.
   c) In the absence of explicit federal statutory nondiscrimination protections, LGBT workers face serious barriers to both gaining and keeping jobs and promotions. Workplace discrimination against LGBT communities can cause job instability and high turnover, resulting in greater unemployment and poverty rates as well as substantial wage gaps between LGBT workers and workers outside the LGBT community. Studies have shown that state anti-discrimination laws appear to help reduce these wage gaps.
   d) Federal data sources do not effectively capture rates of LGBT employment or rates of LGBT employment discrimination.

2. **Anti-Discrimination Laws**

   a) An inconsistent and irreconcilable patchwork of state laws against anti-LGBT workplace discrimination and federal court decisions interpreting existing federal law render LGBT employees insufficiently protected from workplace discrimination.
   b) Currently, only 20 states and the District of Columbia prohibit employment discrimination on the basis of sexual orientation and gender identity.
   c) Seventeen states offer no employment protections on the basis of sexual orientation or gender identity, but cities and local municipalities may offer their own protections.
   d) Twenty states and the District of Columbia currently have laws that explicitly prohibit employment discrimination based upon gender identity or expression, and two other states have laws prohibiting sexual orientation discrimination, but exclude transgender protections.

e) Some federal courts have concluded that the existing federal statutory protection against discrimination based on sex, under Title VII of the Civil Rights Act of 1964, includes within its protection discrimination based on sexual orientation and gender identity. Other federal courts have disagreed. These inconsistent interpretations result in different protections available to individuals based on their jurisdiction, and it is not clear when the Supreme Court will resolve the dispute.

f) Public opinion supports Congress enacting a non-discrimination bill to protect against workplace discrimination against LGBT people.

g) In the past Administration, federal agencies including the EEOC and Departments of Justice and Labor interpreted existing federal law to protect LGBT persons against employment discrimination. Under the current administration the Department of Justice has changed its position, while other agencies, including the EEOC, have not yet taken different positions on the issue.

h) In July 2017, the Department of Justice filed an amicus brief arguing that the prohibition against discrimination based on sex found in Title VII of the Civil Rights Act does not include claims based on sexual orientation. In October 2017, Attorney General Jeff Sessions withdrew guidance issued by Attorney General Eric Holder in 2014 and stated that going forward the Department of Justice would take the position that Title VII's prohibition on sex discrimination does not include discrimination based on gender identity. In addition, the current Administration has interpreted related federal civil rights laws, such as Title IX, in ways that depart from an interpretation that nondiscrimination protection on the basis of sex necessarily includes protection on the basis of sexual orientation and/or gender identity.

i) As evidenced by the Department of Justice's change in position with respect to the interpretation of "sex" in Title VII, federal agency policies and positions can be changed depending on the Administration and do not provide the same weight of protection as federal legislation.

j) The lack of binding and enumerated federal employment protections for LGBT workers remains a central vulnerability for LGBT people.

k) It has not been difficult for some private companies to adopt and implement workplace policies or practices that prohibit discrimination on the basis of sexual orientation and/or gender identity. As of 2016, 92 percent of Fortune 500 companies included sexual orientation and 82 percent included gender identity in their equal employment opportunity policies. Businesses that support these policies note such practices are beneficial to their businesses by attracting the most qualified workforce and increasing productivity.

l) There has not been a flood of litigation in response to the passage of LGBT workplace anti-discrimination laws in the states that have adopted them. To the extent litigation does occur, evidentiary requirements limit baseless claims.

RECOMMENDATIONS

a) In order to effectively and consistently protect LGBT employees from workplace discrimination, Congress should immediately enact a federal law explicitly banning discrimination in the workplace based on sexual orientation and gender identity.
b) In addition to Congressional action, federal agencies including the Departments of Justice and Labor, the Equal Employment Opportunity Commission, and the Office of Personnel Management should issue and—where relevant—reaffirm specific guidance for federal and private employers outlining protections for LGBT individuals in the workforce, including specifically enumerating protections for transgender persons.
c) Congress should authorize the necessary appropriations to ensure that all current and future non-discrimination protections are fully enforced by agencies including, but not limited to, the Departments of Justice and Labor and the Equal Employment Opportunity Commission.
d) The Commission strongly supports religious freedom and nondiscrimination on the basis of religion. Title VII offers a workable model for protecting religious freedom in the context of federal statutory nondiscrimination protections in the workplace. In *Hosanna-Tabor Evangelical Lutheran Church and School v. Equal Employment Opportunity Commission the Supreme Court* also unanimously endorsed the common law ministerial exemption, which recognizes the right of religious groups to select their own ministers and clergy. No further expansion of exceptions to nondiscrimination protections in the workplace are necessary or warranted to balance the rights to freedom of religion and to nondiscrimination on the bases either of religion or LGBT status.
e) Workplace discrimination data should be collected through the inclusion of sexual orientation and gender identity questions in population-based surveys of the workforce such as the Census, American Community Survey, and surveys fielded by the Bureau of Labor Statistics and other agencies.

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COMMISSIONERS' STATEMENTS, REBUTTALS, AND SURREBUTTALS

Statement of Chair Catherine E. Lhamon, in which Vice-Chair Patricia Timmons-Goodson concurs

Firing a person because of who the person is, rather than for nonperformance of job requirements, offends the concept of equity and ought to be unequivocally unlawful. For lesbian, gay, bisexual, and transgender (LGBT) Americans in too many parts of this country right now, it is not.

Our report notes that public opinion, untethered to political affiliation, supports fair workplace treatment for LGBT individuals.[1] While I appreciate the popular support for equity, in fact our national ideals have always sounded in equity and our federal civil rights laws have, for the past six decades, otherwise strongly protected equity. Failure to include formal federal civil rights protection for LGBT persons, regarding employment among other aspects of life, marks a distinct and unjustifiable outlying gap in the fabric of our laws.

In fact, its absence has led to tortured discussions in federal cases,[2] analyzing whether and how much sex discrimination protection applies to sexual orientation and gender identity. Together with diametrically opposing views on these questions expressed and enforced in the Trump and Obama Administrations, they underscore the need for Congress to act unequivocally to protect all workers from employment discrimination based on who they are.[3]

Congress does not fail to act on a blank slate: it has and has had concrete information about the harms LGBT Americans experience in workplace harassment and discrimination as well as about the degree of uncertainty about federal civil rights coverage applicable to LGBT employees. Over

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[1] U.S. Commission on Civil Rights, Working for Inclusion: Time for Congress to Enact Federal Legislation to Address Workplace Discrimination Against Lesbian, Gay, Bisexual, and Transgender Americans, 2017 [*hereinafter* Report] at p. 1.

[2] *See, e.g., Evans v. Georgia Reg'l Hosp.*, 850 F.3d 1248, 1266–67 (11th Cir. 2017) (Rosenbaum, J., concurring and dissenting) (arguing that the decision attempted to create "an artificial line between discrimination because an employee has not behaved in a way that the employer thinks a person of that gender should, on the one hand, and discrimination because an employee is not the way that the employer thinks a person of that gender should be, on the other. . . [which] makes no sense from a practical, textual, or doctrinal point of view."); *Videckis v. Pepperdine Univ.*, 150 *F. Supp.* 3d 1151, 1159 (C.D. Cal. 2015) (collecting cases and concluding that "the line between sex discrimination and sexual orientation discrimination is 'difficult to draw' because that line does not exist, save as a lingering and faulty judicial construct").

[3] At the time of this writing, the United States Supreme Court has pending a petition seeking its review of the question whether Title VII sex discrimination protection covers sexual orientation. *Evans v. Georgia Reg'l Hosp.*, No. 17-370, Petition for Writ of Certiorari (U.S. Sept. 7, 2017). A Supreme Court answer to that question could—or could not—render federal legislation partially duplicative, depending both on whether the Court takes the case and on what it rules if it does. The petitioners have not asked the Court to take up the question of whether Title VII sex discrimination protection covers gender identity, and so there will be a gap of protection regardless of how the Supreme Court acts in this particular case. Because we cannot know in advance whether the Court will review the question or how it will rule, Congress should act now to ensure workplace protection for LGBT Americans.

the four decades during which Congress has considered but not enacted specific workplace protective laws covering LGBT Americans, it has considered workplace vulnerability of LGBT employees as well as the reality that states and cities have specifically enacted laws excluding LGBT persons from coverage. In 1996, when the Supreme Court ruled one such law from Colorado unconstitutional, it concluded that the law, "in making a general announcement that gays and lesbians shall not have any particular protections from the law, inflicts on them immediate, continuing, and real injuries that outrun and belie any legitimate justifications that may be claimed for it."[4] Whereas Congress has not announced that LGBT Americans may not be protected in law, its inaction—in the face of evidence that some courts view existing federal law as inapplicable to these employees—nonetheless leaves these persons notably vulnerable.[5]

Before that Colorado case reached the U.S. Supreme Court, Burke Marshall—who wrote the 1964 Civil Rights Act that included Title VII, was Assistant Attorney General for Civil Rights in the Kennedy Administration, and taught me constitutional law the year of this testimony—testified as an expert in the case in trial court.[6] Marshall testified that "civil rights protections bring those discriminated against 'safely into the mainstream of American society' and enable them 'to participate fully in the life of the United States, including its economic life.'"[7] He further testified that "the purpose of anti-discrimination laws is to upset a social norm of discrimination and 'to create a society that respects and complies by the value of equality . . . which is made a constitutional norm by the . . . 14th amendment and is part of the American tradition of fairness.'"[8] I know, because when I was a third-year law student writing a paper about Title VII coverage of transgender employees, we discussed the questions, that Burke Marshall believed without question that the law he wrote—Title VII—protected transgender persons and lesbian, gay, and bisexual persons, from discrimination. And I know still, all these years later, that LGBT Americans, like all Americans, deserve the legal protection that, in Burke Marshall's expert terms, "respects and complies by the value of equality" in the "American tradition of fairness."[9]

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[4] *Romer v. Evans*, 517 U.S. 620, 635 (1996).

[5] Cementing this point, in 2003, the Court ruled that criminalization of intimate acts between same-sex couples was tantamount to "an invitation to subject homosexual persons to discrimination both in the public and in the private spheres." *Lawrence v. Texas*, 539 U.S. 558, 575 (2003). In 2013, it declared the Defense of Marriage Act unconstitutional as it "impose[d] a disadvantage, a separate status, and so a stigma upon all who enter into same-sex marriages." *United States v. Windsor*, 570 U.S. __, __, 133 S. Ct. 2675, 2693 (2013). In 2015, the Court recognized that "the right to marry is a fundamental right inherent in the liberty of the person, and under the Due Process and Equal Protection Clauses of the Fourteenth Amendment couples of the same-sex may not be deprived of that right and that liberty." *Obergefell v. Hodges*, 576 U.S. __, __, 135 S. Ct. 2584, 2604 (2015).

[6] *Evans v. Romer*, No. CIV. A. 92 CV 7223, 1993 WL 518586, at *11 (Colo. Dist. Ct. Dec. 14, 1993), aff'd, 882 P.2d 1335 (Colo. 1994), aff'd, 517 U.S. 620 (1996) (*hereinafter Evans II*).

[7] Suzanne B. Goldberg, *Gay Rights Through the Looking Glass: Politics, Morality, and the Trial of Colorado's Amendment 2*, 21 Fordham Urb. L. J. 1057, 1069 (1994) (quoting deposition transcript of Professor Burke Marshall, *Evans II*, at 13), *available at* http://ir.lawnet.fordham.edu/cgi/viewcontent.cgi?article=2581&context=ulj.

[8] *Id.* at 1069-70 (*quoting* deposition transcript of Professor Burke Marshall, *Evans III*, at 24-26).

[9] *Id.*

I urge Congress to act to put an end to decades of questions about whether some among us may—finally, today—be equal to all among us.

Resistance to formal federal protection from discrimination for LGBT employees often purports to rely on a putative conflict between religious freedom and nondiscrimination. My own experience of faith, in addition to my love of our Constitution, animates my every action—and I am offended by the notion that our existing constitutional and federal statutory protections for religious freedom prevent like protection for nondiscrimination for lesbian, gay, bisexual, and transgender Americans. I saw the fallacy of that putative conflict play out painfully some thirteen years ago, when I represented students in a south Los Angeles high school whose teachers and administrators discriminated against them because they were gay and lesbian students. Their school staff defended standing by while, among other actions, a student physically attacked another student in class, because the teacher believed the attacked student needed to be taught to be more "manly"; telling a deeply religious Catholic student she would go to hell because she dated another girl; and outing two boys to their parents in the course of disciplining the boys because the boys had been caught kissing in a school building where opposite sex couples were also kissing at the same time but were not disciplined for their behavior. These school staff reported that their religious faith dictated their actions to harm these students, because the students were gay or lesbian. A teacher's decision to tell a devout Catholic girl she would go to hell for dating another girl lowlights the error in the assumption that LGBT persons are not simultaneously persons of faith—and underscores the distinct (and in our system of laws profoundly unconstitutional) harm that privileging one understanding of faith over another can visit on people. The teachers and administrators at that school were and are free to disapprove of same sex relationships, and even of the status of being LGBT, on religious or other bases; they were and are not, however, free to act on that disapproval in ways that harmed the students as people or as learners. Likewise in an employment context, our laws should protect LGBT employees from discrimination while also protecting all of our religious freedom.

Congress and our courts have, many times in our history, reconciled religious objections to civil rights protections without denigrating the rights of Americans to be who they are. In one stark example, the United States Supreme Court quoted the federal trial court judge who sanctioned criminalization of interracial marriage justifying his decision because "'Almighty God created the races white, black, yellow, malay and red, and he placed them on separate continents. . . The fact that he separated the races shows that he did not intend for the races to mix.'"[10] Despite the invocation of a religious basis for upholding a racially discriminatory law, the Court ruled Virginia's laws against interracial marriage unconstitutional because "classifications so directly

[10] *Loving v. Virginia*, 388 U.S. 1, 3 (1967) (quoting *Loving v. Virginia* (Circuit Court of Caroline County, Virginia, 1959)).

subversive of the principle of equality at the heart of the Fourteenth Amendment . . . deprive all the State's citizens of liberty without due process of law."[11] Just as religious objection to interracial marriage or interracial association has not and as a matter of course should not have prevented federal nondiscrimination protection on the basis of race, so religious objection, where it exists, is no impediment to federal nondiscrimination protection for LGBT Americans.

The possibility that questions could arise regarding how to reconcile sincerely held religious views with nondiscrimination protections for LGBT persons does not lead logically to a conclusion that LGBT persons should lack legal protection. We already have strong religious freedom protections both in the Constitution and in federal law. The First Amendment protects against discrimination on the basis of religion, and particular additional protections are included in the Religious Freedom Restoration Act[12] as well as exemptions detailed in our longstanding federal civil rights laws.[13] What we do not have now in federal law is explicit protection for LGBT persons; that gap should be filled while simultaneously ensuring respect for faith in all its forms as well as sexual orientation and gender identity in all of theirs.

It is the Commission's core function to advise Congress, the President, and the American public about federal civil rights policy. I wholeheartedly support the Commission's recommendations including that Congress enact federal legislation as soon as possible to correct the harms we have already borne witness to, guard against future such harms, and fulfill the "American tradition of fairness."[14]

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[11] *Id.* at 12; *see also Bob Jones Univ. v. United States*, 461 U.S. 574, 603 (1983) (holding that religious objection does not justify race discrimination with respect to interracial marriage or association).
[12] Religious Freedom Restoration Act of 1993, PL 103–141, November 16, 1993, 107 Stat 1488, codified at 42 U.S.C. § 2000bb et seq.
[13] *See e.g.*, 42 U.S.C. § 2000e-2(2) (regarding Title VII's religious exemption) and 20 U.S.C. § 1681(a)(3) (regarding Title IX's religious exemption).
[14] Goldberg, *supra* note 7, at 1070.

Statement of Commissioner David Kladney

This report raises an inevitable question: why would an employer seek to fire, harass, or otherwise reduce the productivity of a successful employee merely because of that person's sexual orientation or gender identity? It makes no sense. Business leaders in many industries continually band together to say LGBT employment discrimination is bad for business. It is better to accept that every person has their own idea of how to express gender and form (or not form) a family.

Business plans for inclusion are encouraging. A representative of Northup Grumman described the way they not only accept LGBT people, but embrace them in office culture.[1] This is exactly what companies should be doing, for their own competitive advantage and because it is right. As business representatives testified they value every employee and cannot afford to turn away well-qualified people who can help them succeed.[2] Many companies make clear they welcome and value LGBT employees.

As business is growing more accepting by the day, why are employment discrimination protections necessary? As this report explains, with all the progress made in this area, employment discrimination still occurs for no valid reason. It is prevalent. As I see it, even if discrimination were rare, we should still have a federal law prohibiting it because it is wrong each and every time it happens.

Business initiative is not enough. The speed at which LGBT rights have advanced belies the progress still needed. Hundreds of companies have come out in support of a law requiring them to do what they have done voluntarily: create a work environment where people can succeed without discrimination.[3] Equal protection requires that LGBT citizens are not left to the whim of their employers. Most of these employers are corporations, large and small, who take advantage of the legal protections and shields the government affords them. As such, they should be required to not discriminate against any qualified United States citizen in employment. To do so is not consistent with the American values.

Relying on companies to do the right thing voluntarily also presumes the progress only moves one direction. It assumes that there can be no backlash to the advancements LGBT people have

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[1] Testimony of Sylvester Mendoza, Briefing Transcript, p. 166-170, *available at* http://www.usccr.gov/calendar/trnscrpt/Discrimination_LGBT_03-16-2015.pdf (stating, "Our LGBT community is mission critical to our advancement, innovation and to being a responsible global corporate citizen and global security company.")

[2] *See* Briefing Transcript, p. 166-202 (testimony on economic impacts of non-discrimination protections).

[3] *See, e.g.*, Charles E. Ramirez, *More than 100 companies join Equality Act coalition*, The Detroit News, September 25, 2017, http://www.detroitnews.com/story/news/local/detroit-city/2017/09/25/more-than-100-companies-join-equality-act-coalition/699224001/; Human Rights Campaign, *Business Coalition for Workplace Fairness, Members*, https://www.hrc.org/resources/business-coalition-for-workplace-fairness-members.

achieved. This is not the case. As we see with President Trump's unilateral ban of transgender people from serving in the military, decision makers can act in a willy-nilly fashion without any regard to the best interests of the objective—success of the mission.[4] The varying interpretations of Title VII depending on which presidential administration is interpreting it demonstrate the shifting sands beneath what should be bedrock principles of non-discrimination.[5]

The bottom line is this: people should have the right to work to support themselves and succeed for their families and our country. When people have requisite skills, they should not have to fear that their right to work is contingent on their ability to successfully hide a fundamental aspect of themselves. The purges of people from the federal government because of sexual orientation are not so far in the past.[6] Transgender people in particular still lack basic acknowledgment by the federal government that they deserve protections from discrimination.[7] People in the LGBT community are our friends and members of our families. They are in every community in the world. In this country, where we value equality and fairness, they should be able to live and work freely.

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[4] Reporting indicated the Joint Chiefs of Staff were not consulted prior to the policy change, and as of this writing the Department of Defense has delayed implementation of the ban for troops currently serving, citing the need for more study. *See* Barbara Starr, Zachary Cohen and Jim Sciutto, US Joint Chiefs blindsided by Trump's transgender ban, CNN, July 27, 2017, http://www.cnn.com/2017/07/27/politics/trump-military-transgender-ban-joint-chiefs/index.html; Dan Lamothe, Transgender ban frozen as Mattis moves forward with new review of options, Washington Post, August 29, 2017, https://www.washingtonpost.com/news/checkpoint/wp/2017/08/29/pentagon-chief-mattis-freezes-trumps-ban-on-transgender-troops-calls-for-more-study.
Numerous retired generals have stated they believe the ban, if implemented, would degrade military readiness. The Palm Center, Fifty-Six Retired Generals and Admirals Warn That President Trump's Anti-Transgender Tweets, If Implemented, Would Degrade Military Readiness, August 1, 2017, http://www.palmcenter.org/fifty-six-retired-generals-admirals-warn-president-trumps-anti-transgender-tweets-implemented-degrade-military-readiness.

[5] *See* Attorney General Jeff Sessions, Memorandum re Revised Treatment of Transgender Employment Discrimination Claims Under Title VII of the Civil Rights Act of 1964, Oct. 4, 2017, *available at* https://www.documentcloud.org/documents/4067437-Sessions-memo-reversing-gender-identity-civil.html

[6] *See, e.g.*, Judith Adkins, Congressional Investigations and the Lavender Scare, National Archives, Prologue Magazine, Summer 2016, https://www.archives.gov/publications/prologue/2016/summer/lavender.html.

[7] *See* Revised Treatment of Transgender Employment Discrimination Claims, *supra* note 5.

Statement of Commissioner Karen K. Narasaki, in which Vice-Chair Patricia Timmons-Goodson concurs

Fundamental to the founding of our nation is the principle that every person has a universal and inalienable right to "life, liberty, and the pursuit of happiness."[1] In *Obergefell v Hodges*, Justice Kennedy explained that liberty includes the right of individuals "to define and express their identity."[2] Sexual orientation and gender identity are characteristics that are fundamental and essential to one's identity.[3] To deny a person equal protection under the law due to these characteristics—whether in the workplace or elsewhere—violates not only one of our country's most sacred tenets, but the basic dignity and humanity that all people inherently deserve.

Freedom from discrimination based on sexual orientation or gender identity also naturally incorporates many other rights recognized under the Constitution, including the right to privacy[4] and freedom of expression and association. Moreover, international human rights laws complement and reinforce our nation's laws by recognizing that "all human beings are born free and equal in dignity and rights" and therefore LGBT people are entitled to the numerous protections afforded by human rights laws, including the right to be free from discrimination.[5]

Some opponents to legislation protecting LGBT workers and their families from discrimination mistakenly contend sexual orientation and gender identity are unlike other protected categories such as race and sex, which in their view are protected because they are considered immutable.[6]

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[1] The Declaration of Independence para.2 (U.S. 1776); U.S. Const. amend XIV (no State shall "deprive any person of life, liberty, or property, without due process of law").

[2] *Obergefell v. Hodges*, 135 *S. Ct.* 2584, 2593 (2015); *Lawrence v. Texas*, 539 U.S. 558, 562 (2003) (private sexual conduct included in right to liberty under Due Process Clause) ("Liberty presumes an autonomy of self that includes freedom of thought, belief, expression, and certain intimate conduct.").

[3] *See* Brief for American Psychological Ass'n *et al.* as Amici Curiae in Support of Petitioners 10, *Obergefell*, 135 *S. Ct.* 2584 (No. 14-556), 2015 WL 1004713 ("[S]exual orientation is integrally linked to the intimate personal relationships that human beings form with others to meet their deeply felt needs for love, attachment, and intimacy. It defines the universe of persons with whom one is likely to find the satisfying and fulfilling relationships that, for many individuals, comprise an essential component of personal identity.").

[4] *Lawrence*, 539 U.S. 558.

[5] *See* UN Office for the High Commissioner for Human Rights, Discriminatory Laws and Practices and Acts of Violence Against Individuals Based on Their Sexual Orientation and Gender Identity 4 (2011), http://www2.ohchr.org/english/bodies/hrcouncil/docs/19session/A.HRC.19.41_English.pdf ("The application of international human rights law is guided by the principles of universality and non-discrimination enshrined in Article 1 of the Universal Declaration of Human Rights, which states that "all human beings are born free and equal in dignity and rights." All people, including lesbian, gay, bisexual and transgender (LGBT) persons, are entitled to enjoy the protections provided for by international human rights law, including in respect of rights to life, security of person and privacy, the right to be free from torture, arbitrary arrest and detention, the right to be free from discrimination and the right to freedom of expression, association and peaceful assembly.").

[6] *See* Report at 45 (citing Family Research Council, "The Employment Non-Discrimination Act (ENDA): A Threat to Free Markets and Freedom of Conscience and Religion," Issue Brief, October 2013, *available at* http://downloads.frc.org/EF/EF13J68.pdf ("[The Civil Rights Act of 1964 bars discrimination based on "race, color, national origin, sex, and religion." The first four of these are included largely because they are inborn, involuntary

Whether a person's sexual orientation or gender identity is changeable is not the appropriate inquiry. Rather, as Ninth Circuit Court Judge Norris describes it, it is whether such "traits [] are so central to a person's identity that it would be abhorrent for government to penalize a person for refusing to change them, regardless of how easy that change might be physically."[7] Religion, for example, is not immutable in the classic sense but is central to the identity of many people,[8] which is why the First Amendment protects the right to practice religion[9] and why we have laws prohibiting employment discrimination based on religion.

Our understanding of sexual orientation and gender identity continues to evolve. Because of that, significant progress for LGBT equality has been made in recent decades, but as our report reveals much work remains.[10] As Senior Judge Davis concluded when he sided with transgender youth Gavin Grimm's efforts to use the bathroom that corresponds with his gender identity, it is now up to the resolve of our leaders and our nation to stand for equality and human dignity:

> [S]ome entities will not protect the rights of others unless compelled to do so. Today, hatred, intolerance, and discrimination persist—and are sometimes even

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and immutable. (Religion, while voluntary, is explicitly protected by the First Amendment to the U.S. Constitution.)."). However, Columbia University sociologist Shamus Khan argues sexual identity, like race, is a social construction. Shamus Khan, Not Born This Way, Aeon (July 23, 2015), https://aeon.co/essays/why-should-gay-rights-depend-on-being-born-this-way ("True, many gay and lesbian people will note that they 'always felt different' or that they knew about their homosexuality for as long as they've been aware of themselves as sexual beings. Is this not evidence of a powerful biological drive? Not necessarily, because it is also consistent with the idea of sexuality as co-determined by biology and environment. Race is a social construct, and its experience is felt from the moment we begin our lives."); *see also G.G. v. Gloucester County Sch. Bd.*, 853 F.3d 729, 730 (4th Cir. 2017) (Davis, J., concurring) ("[Gavin Grimm's] plight has shown us the inequities that arise when the government organizes society by outdated constructs like biological sex and gender.")

[7] *Watkins v. U.S. Army*, 875 *F.2d* 699, 726 (9th Cir. 1988) (Norris, J., concurring). Or as the district court in *Obergefell* stated, "To the extent that "immutability" is relevant to the inquiry of whether to apply heightened scrutiny, the question is not whether a characteristic is strictly unchangeable, but whether the characteristic is a core trait or condition that one cannot or should not be required to abandon." *Obergefell v. Wymyslo*, 962 *F. Supp.* 2d 968, 990 (S.D. Ohio 2013), *rev'd sub nom. DeBoer v. Snyder*, 772 F.3d 388 (6th Cir. 2014), *rev'd sub nom. Obergefell*, 135 *S. Ct.* 2584; Report at 49 (discussing dignity); *see also* Jessica A. Clarke, *Against Immutability*, 125 Yale L.J. 2, 6 n.7 (2015) (citing numerous comments in support of "new" immutability based on human dignity and moving away from traditional equal protection jurisprudence).

[8] Steward Harrison Oppong, *Religion and Identity*, Am. Int'l J. Contemporary Research, July 2013, at 10, http://www.aijcrnet.com/journals/Vol_3_No_6_June_2013/2.pdf (exploring link between religion and identity).

[9] Michael W. McConnell, *The Origins and Historical Understanding of Free Exercise of Religion*, 103 Harv. L. Rev. 1409, 1491-92 ("Religion is understood to be a product of individual choice, and protected as such."). In fact, the first "free exercise" clause on the continent was passed by Maryland in 1649 and guaranteed that "no[] person . . . professing to believe in Jesus Christ, shall . . . be compelled to the belief[] or exercise of any other Religion against his or her consent." *Id.* at 1425. Scholars have also argued religion should be treated as immutable because of "fundamental interests in not changing them." *See* Clarke, *supra* note 7, at 24 n. 111 (citing Douglas Laycock, *Taking Constitutions Seriously: A Theory of Judicial Review*, 59 Tex. L. Rev. 343, 383 (1981)); Testimony of Mara Kiesling at 251-52 ("[W]e believe that people should be able to select their religion. In fact, that's the beauty of religion. You have to really come to it. You really have to make the decision. It is not born to you. You may be born into a religion. But we still want to protect people's religions. We still want to respect people. We still want them to be able to have jobs, and it does not matter that . . . you're not born with your religion. But you know what? You just are born with your gender identity and you are born with your sexual orientation and saying not doesn't make it not.").

[10] *See e.g.* Testimony of Mara Kiesling at 108-09.

promoted—but by challenging unjust policies rooted in invidious discrimination, . . . one day, equality will prevail, and [ ] the core dignity of every one of our brothers and sisters is respected by lawmakers and others who wield power over their lives.[11]

[11] *Gloucester County Sch. Bd.*, 853 F.3d 729, 731 (4th Cir. 2017).

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Statement of Commissioner Michael Yaki

The concept of what constitutes "rights" has been fluid throughout time. At the time of the Founders, the notion of liberty was viewed through a lens of a land-owning white male. Freedom of speech, of religion, the freedom to assemble and speak were all, to be true, radical notions in the day. There was, in fact much debate whether these "rights" should be enshrined at all—these rights being the first ten amendments to the Constitution. Some argued government had no right to put these into the Constitution. Others, perhaps more presciently, were concerned that listing enumerated rights meant *expressio unius est exclusio alterius*—the mention of one thing amounts to the exclusion of others, and thus, nothing else could be considered now or in the future.

As we know now, a Constitution that once counted black Americans as three-fifths the worth a white American for the purposes of apportionment has been changed, through the adoption of the Thirteenth and Fourteenth Amendments, to mean something entirely different. While the Equal Protection Clause of the Fourteenth Amendment does not enumerate to whom those protections extend, jurisprudence over a century has sought to define it to mean the "suspect classes" of race, religion, and national origin. Thus, even now, *expressio unius est exclusio alterius* continues to vex constitutional scholars, Supreme Court justices, and policymakers in terms of who is entitled to equal protection.

For members of the lesbian, gay, bisexual and transgender community, the struggle to receive recognition, to be given the same rights and treatment as other Americans, has been difficult. As an elected official, I voted for the first domestic partnership registry in America, and was proud to officiate at the first ceremonies in San Francisco City Hall. From those first domestic partnerships to the U.S. Supreme Court's recognition of the right to marry[1] less than twenty years later, the strides made by the LGBT community have been significant. The fundamental right to marry, however, has not been met by equal strides in other areas of civil rights—to the point of this report, in the area of employment discrimination. Yet even today, they fight to not be excluded from the broad protections afforded other oppressed groups under the Constitution and our laws.

I. A Seminal Report at a Critical Time

As a prefatory comment, the Commission has been in existence for sixty years. This year, its' sixtieth, marks the first instance in which the Commission has undertaken and published an investigation focused solely upon the civil rights burdens suffered by lesbian, gay, bisexual, and transgender ("LGBT") people.[2] I thank my esteemed colleague, the Honorable Roberta

[1] *Obergefell v. Hodges*, 576 US ___ (2015).
[2] In its 2011 statutory enforcement report, the Commission addressed problems faced by LGBT youth alongside an examination of youth targeted due to sex, race and national origin, disability, and religion. *See* U.S. Commission on

Achtenberg, for bringing this inquiry before the Commission. The Commission's briefing was powerful.[3] Our report[4] is very thoroughly researched and written. It is comprehensive and explains the often-painful, real-life implications of federal, state, and private sector employment discrimination against LGBT people in great detail. The findings and recommendations are clear, succinct, well-grounded, and powerful. This project deservedly takes its place among our finest work.[5]

Our nation's LGBT population has a vulnerability unique among all those whom the Commission is mandated to protect: it is the only class under our jurisdiction which lacks the shelter of at least one powerful, civilian, federal statutory protection. The right to marry does not have transitive properties, at least in terms of the qualities that, to date, the Courts have looked at for protection under the Civil Rights Act of 1964. Yet, it is undisputed that LGBT Americans have faced and still face invidious discrimination at the hands of the government and private sectors. Therefore, the Commission has a special duty to be mindful of civil rights deprivations faced by LGBT Americans, to investigate and publicize those abridgements, and to recommend loudly and clearly to the Congress and the President actions which the federal government must take to remediate and prevent such abuses. With regard to our LGBT community, the Commission has a special obligation to fulfill its role as the conscience of the nation, and sound alarms as current and future developments may dictate.

The Commission's far-reaching report comes at a critical juncture of the incremental march toward full legal equality and social inclusion for LGBT people in this country. The obstacles have been many, as homophobia and transphobia have long permeated the American worldview. Until 1973, the American Psychiatric Association classified a homosexual orientation as a mental disorder[6]—and it considered a transgender identity in the same category until 2012.[7] States had the ability to—and did—criminalize intimate same-sex conduct between consenting adults and imprison "offenders" until the U.S. Supreme Court put an end to so-called "sodomy laws" a mere fourteen

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Civil Rights, "Peer to Peer Violence + Bullying: Examining the Federal Response," September 2011, *available at* http://usccr.gov/pubs/2011statutory.pdf.

[3] In particular, thanks are due to panelists Mara Keisling, Kylar Broadus, Gina Duncan, and Ilona Turner for their briefing statements regarding transgender issues.

[4] U.S. Commission on Civil Rights, "Working for Inclusion: Time for Congress To Enact Federal Legislation to Address Workplace Discrimination Against Lesbian, Gay, Bisexual, and Transgender Americans," September 2017, *available at* http://www.usccr.gov/pubs/LGBT_Employment_Discrimination2017.pdf ("USCCR Report").

[5] Thanks are due to all staff members, past and present, who worked diligently on this investigation and report.

[6] *See, e.g.,* Jack Drescher, "Out of DSM: Depathologizing Homosexuality," *Behavioral Sciences*, December 4, 2015, *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4695779/pdf/behavsci-05-00565.pdf; *and* Carla Moleiro and Nuno Pinto, "Sexual Orientation and Gender Identity: Review of Concepts, Controversies and Their Relation to Psychopathology Classification Systems," Frontiers in Psychology, U.S. National Library of Medicine, National Institutes of Health, October 2015, *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4589638/.

[7] Moleiro and Pinto, n. 6 *supra.*

years ago in 2003.[8] The challenges remain intense, as many powerful fundamentalist Christian and other conservative groups vociferously oppose legal and social equality for LGBT people.

It is in this context, therefore, that sexual orientation was hardly mentioned, let alone even considered for inclusion, when courts began naming those characteristics that required greater scrutiny as they began to interpret the breadth of the Equal Protection Clause. And by omission—by *exclusion alterius*—the issue of sexual orientation remained in the closet of jurisprudence for much of the 20th century.

Since the final quarter of the 20th century, many sectors of American society have been moving, inch by inch, toward the end of marginalization and demonization of LGBT people in society.[9] We can only hope that these changes in social attitudes will erode the pervasive discrimination which LGBT people face in the employment sector. And where changes in social attitude move deliberately, the swifter enactment of laws to protect LGBT people, as this report recommends, becomes more important.

II. The Federal Government's (Forgotten?) History of Perpetuating Employment Discrimination Against LGBT People: 1940s through the 1970s

From the 1940s into the 1970s, the federal government was no mere bystander in the societal discrimination against the LGBT community. To the contrary, it was an overt proponent of employment discrimination against LGBT people. Many "homosexuals and other sex perverts" lost their federal jobs during the "Lavender Scare" that began in the Truman Administration.[10] This purge was fueled when:

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[8] *Lawrence v. Texas*, 539 U.S. 558 (2003). *See also* William N. Eskridge, Jr., Dishonorable Passions: Sodomy Laws in America 1861-2003, Viking, 2008.

[9] *See, e.g.*, GALLUP News, "Gay and Lesbian Rights," 2017, *available at* http://news.gallup.com/poll/1651/gay-lesbian-rights.aspx; Pew Research Center, Religion and Public Life, "Changing Attitudes on Gay Marriage," June 26, 2017, *available at* http://www.pewforum.org/fact-sheet/changing-attitudes-on-gay-marriage/; and Andrew R. Flores, "National Trends in Public Opinion on LGBT Rights in the United States," The Williams Institute, November 2014, *available at* https://williamsinstitute.law.ucla.edu/wp-content/uploads/POP-natl-trends-nov-2014.pdf.

For information on "acceptance" of homosexuality across the globe, with better statistics coming in general from more affluent and less religious nations, *see, e.g.*, Pew Research Center, Global Attitudes and Trends, "The Global Divide on Homosexuality," June 4, 2013, *available at* http://www.pewglobal.org/2013/06/04/the-global-divide-on-homosexuality/. Of note is this Commissioner's objection to the notion of the terminology and concept of "acceptance" of homosexuality or any status on the LGBTQ (lesbian, gay, bisexual, transgender, and queer) spectrum, while recognizing its widespread use in social discourse and academic parlance. These human conditions simply exist. "Accepting" them is not the core issue, as people do not have the right to "accept" people—or not—based upon race, color, sex, national origin, age, disability status, gender identity, sexual orientation, or any other inherent characteristic. People simply are who they are. Merely recognizing their existence and valuing the equality of all individuals, regardless of sexual orientation or gender identity, is at the center of a compassionate value system.

[10] *See, e.g.*, David K. Johnson, The Lavender Scare: The Cold War Persecution of Gays and Lesbians in the Federal Government, The University of Chicago Press, 2004; U.S. Merit Systems Protection Board, "Sexual Orientation and the Federal Workplace: Policy and Perception: A Report to the President and Congress of the United States," May

> the U.S. Senate created a subcommittee, chaired by North Carolina Senator Clyde Hoey, to evaluate the threat homosexuals presented to public civil service and national security. [fn. 10: *See generally* JOHNSON, *supra* note 1, at 101-18 (providing a thorough account of the subcommittee's investigation, the evidence it ignored, and its report).] In December 1950, the Hoey Subcommittee issued its report, entitled *Employment of Homosexuals and Other Sex Perverts in Government*, unanimously concluding that those who engage in acts of homosexuality and other perverted sex activities are unsuitable for employment in the Federal Government. In the committee's view, homosexuals and other sex perverts should be barred from civil service positions, those who were already employed should be fired, and the government should expend resources to aggressively ferret them out. [fn. 11: S. COMM. ON EXPENDITURES IN THE EXEC. DEP'T, SUBCOMM. ON INVESTIGATIONS, 81ST CONG. 2ND SESS., EMPLOYMENT OF HOMOSEXUALS AND OTHER SEX PERVERTS IN GOVERNMENT 4527-4528 (Cong. Rec. Vol. 96 1950). The report stated "It is the opinion of this subcommittee that those who engage in acts of homosexuality and other perverted sex activities are unsuitable for employment in the Federal Government. This conclusion is based upon the fact that persons who indulge in such degraded activity are committing not only illegal and immoral acts, but they also constitute security risks in positions of public trust."][11]

In 1953, President Eisenhower issued Executive Order 10450, "Security Requirements for Government Employment," which effectively prohibited the United States government from retaining or employing in the first instance anyone who engaged in "sexual perversion."[12] Thousands of LGBT federal employees were fired simply due to their sexual orientation, and thousands of applicants were denied jobs.[13] "Although we will never know the exact number of individuals who were denied employment or who had their employment terminated based on their

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2014, *available at* https://www.mspb.gov/mspbsearch/viewdocs.aspx?docnumber=1026379&version=1030388&application=ACROBAT; and Brad Sears, Nan D. Hunter, Christy Mallory, "Documenting Discrimination on the Basis of Sexual Orientation and Gender Identity in State Employment," The Williams Institute, September 2009, *available at* https://williamsinstitute.law.ucla.edu/research/discrimination/documenting-discrimination-on-the-basis-of-sexual-orientation-and-gender-identity-in-state-employment/.

[11] Sears, Hunter, and Mallory, "Documenting Discrimination on the Basis of Sexual Orientation and Gender Identity in State Employment," p. 5–4, n. 7 *supra*, *available at* https://williamsinstitute.law.ucla.edu/wp-content/uploads/5_History.pdf.

[12] Executive Order 10450, "Security Requirements for Government Employment," Sec. 8(a)(1)(iii), 3 CFR, 1949-1953 Comp., p. 396, April 27, 1953, *available at* https://www.archives.gov/federal-register/codification/executive-order/10450.html.

Ironically, President Eisenhower advocated for the creation of this United States Commission on Civil Rights as part of the Civil Rights Act of 1957 (Pub.L. 85-315, 71 Stat. 634). The juxtaposition of these two actions of his demonstrates just how far removed from the civil rights domain any consideration of LGBT rights remained.

[13] *See, e.g.*, Capehart, Jonathan, "Frank Kameny: American Hero," The Washington Post, October 21, 2011, *available at* https://www.washingtonpost.com/blogs/post-partisan/post/frank-kameny-american-hero/2011/03/04/gIQAH2DRfL_blog.html; and Sears, Hunter, and Mallory, n. 8 *supra*.

actual or assumed sexual orientation, one estimate places this number between 7,000 and 10,000 in the 1950s alone."[14] State and local employment purges were common as well.[15]

The ban remained in full effect for twenty years. In 1973, the U.S. District Court for the District of Columbia ruled, upon motion from two gay men denied continued federal employment, that "the [Civil Service] Commission *is* prohibited from excluding plaintiffs from federal employment unless *particular* circumstances are enumerated which may justify dismissal on charges relating to homosexual conduct."[16]

However,

> [i]t was not until July 1975 that the CSC announced a new approach to determining the suitability of homosexual applicants for Federal employment. The CSC stated that the new guidelines were a significant change from past policies and were a result of court decisions requiring that persons not be disqualified from Federal employment based solely on homosexual conduct. The new guidelines applied the same standards to evaluating sexual conduct, whether heterosexual or homosexual. Although applicants could no longer "be found unsuitable based on unsubstantiated conclusions concerning possible embarrassment for the Federal service, a person may be dismissed or found unsuitable where the evidence exists that sexual conduct affects job fitness." [orig. fn. 86: "Homosexual Hiring is Revised by U.S.," The New York Times, July 4, 1975, p. 45.]
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> This change in policy was not absolute, however—the CIA and FBI were exempted from its requirements.[17]

LGBT people's access to security clearances may have been negatively impacted by vague, hold-ever rules until as late as 1991[18] or even 1995.[19] No President put forth any openly LGBT candidate for a position requiring Senate confirmation until President Bill Clinton nominated our recent Commissioner Roberta Achtenberg for Assistant Secretary of Fair Housing and Equal Opportunity at Housing and Urban Development in 1993, who prevailed after a deeply homophobic effort to deny her confirmation.[20] We did not have an openly LGBT U.S. Ambassador until James Hormel

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[14] U.S. Merit Systems Protection Board, p. i, n. 10 *supra*.
[15] Sears, Hunter, and Mallory, pp. 5—18, n. 11 *supra*.
[16] *Baker v. Hampton*, U.S. District Court for the District of Columbia, No. 2525-71, decided December 21, 1973, 1973 WL 274 (not reported in F.Supp.).
[17] U.S. Merit Systems Protection Board, p. 18, n. 10 *supra*.
[18] *See, e.g.*, U.S. General Accounting Office, "GAO Report: Security Clearances: Consideration of Sexual Orientation in the Clearance Process," March 1995, p. 2, *available at* http://www.gao.gov/assets/230/220962.pdf.
[19] Executive Order 12968, "Access to Classified Information," Sec. 3.1, August 2, 1995, 60 CFR 40245, August 7, 1995, *available at* https://fas.org/sgp/clinton/eo12968.html. *See also* Todd S. Purdum, "Clinton Ends Ban on Security Clearance for Gay Workers," The New York Times, August 5, 1995, *available at* http://www.nytimes.com/1995/08/05/us/clinton-ends-ban-on-security-clearance-for-gay-workers.html.
[20] "Nomination: Roberta Achtenberg, of California, to be an Assistant Secretary of Housing and Urban Development, . . . 05/24/1993: Confirmed by the Senate," Action PN154—103rd Congress (1993-1994), *available*

was put in place by virtue of President Clinton's recess appointment in 1999,[21] an appointment held up by a vicious and bigoted smear campaign launched by extremist groups. Until the 2011 implementation of the Don't Ask, Don't Tell Repeal Act of 2010, lesbians, gay men, and bisexuals could not serve openly in our military.[22] The U.S. Supreme Court finally capped decades of social and political debate, legislation, and litigation by recognizing that the fundamental right to marriage extends to same-sex couples as recently as 2015.[23]

III. Selected Historical Efforts by LGBT Americans to Foster Inclusivity

The recent progress, of course, has been no accident. It is fueled by the decades of momentum created by brave LGBT Americans who risked prosecution, careers, and families to come together, to stand up publicly against condemnation and criminalization, and to demand their rights to full equality.

Activist Harry Hay and others co-founded the Mattachine Society in 1951 for purposes of furthering societal equality and also personal growth. The Mattachine Society . . . began sponsoring discussion groups in 1951, providing lesbians and gay men an opportunity to share openly, often for the first time, their feelings and experiences. The meetings were frequently emotional and cathartic.[24]

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at https://www.congress.gov/nomination/103rd-congress/154. An elected member of the San Francisco Board of Supervisors from 1990 to 1993, Assistant Secretary Achtenberg was the highest-ranking openly LGBT official in the Clinton administration. *See also* Michael Ross, "Gay Activist OKd for Fair Housing Post: Government: Roberta Achtenberg of San Francisco is the First Openly Declared Lesbian to Serve in High Federal Office, Senate Approval on 58-31 Vote Follows Impassioned Debate on Gay Rights," The Los Angeles Times, *available at* http://articles.latimes.com/1993-05-25/news/mn-39579_1_gay-rights. President Barack Obama appointed Assistant Secretary Achtenberg to the U.S. Commission on Civil Rights in January 2011, a seat she held until her term expired in December 2016. *See, e.g.,* Nick Wing, "Obama Announces Three High-Profile LGBT Appointments," The Huffington Post, January 28, 2011, *available at* https://www.huffingtonpost.com/2011/01/28/obama-announces-lgbt-appointments_n_814852.html.

[21] *See, e.g.*, Claude Summers, "Obama's 6 Gay U.S. Ambassadors are Leading the Global Fight for LGBT Rights," The New Civil Rights Movement, August 21, 2016, *available at* http://www.thenewcivilrightsmovement.com/claude_summers/america_s_openly_gay_ambassadors. *See also* Colby Itkowitz, "The Six Openly Gay U.S. Ambassadors Were in One Room Together," The Washington Post, March 25, 2015, *available at* https://www.washingtonpost.com/blogs/in-the-loop/wp/2015/03/25/the-six-openly-gay-u-s-ambassadors-were-together-in-one-room/.

[22] H.R. 2965, S. 4023 (2011); *see also* Elisabeth Bumiller, "Obama Ends 'Don't Ask, Don't Tell' Policy," The New York Times, July 22, 2011, *available at* http://www.nytimes.com/2011/07/23/us/23military.html.

It was 2016 before we had our first openly LGBT Service Secretary, Eric Fanning, Secretary of the Army. *See. e.g.*, Aaron Mehta and Joe Gould, "Senate Confirms Eric Fanning, First Openly Gay Service Secretary," Defense News, May 17, 2016, *available at* https://www.defensenews.com/interviews/2016/05/17/senate-confirms-eric-fanning-first-openly-gay-service-secretary/.

[23] *Obergefell v. Hodges*, n. 1 *supra.*

[24] Craig Kacaorowski, "Mattachine Society," glbtq, Inc., 2004, *available at* http://www.glbtqarchive.com/ssh/mattachine_society_S.pdf. A friend and fellow activist of Mr. Hay's, Phyllis Lyon, said, "He was marvelous. "He was one of the first to remind us we need to stop, to consolidate our efforts," said Lyon, who with her partner Del Martin, founded the nation's first lesbian rights organization, the Daughters of Bilitis in 1955. "He was really the originator of the concept of gays, lesbians, bisexuals and transgender people as a minority to be reckoned with."

The Mattachine Society's visionary Statement of Purpose, which set forth the road map on which the movement for full LGBT inclusion and equality yet travels, states

> It is the purpose of this organization to act by any lawful means:
>
> (a) To secure for homosexuals the right to life, liberty, and the pursuit of happiness, as proclaimed for all men by the Declaration of Independence; and to secure for homosexuals the basic rights and liberties established by the word and the spirit of the Constitution of the United States;
>
> (b) To equalize the status and position of the homosexual with those of the heterosexual by achieving equality under law, equality of opportunity, equality in the society of his fellow men, and be eliminating adverse prejudice, both private and official;
>
> (c) To secure for the homosexual the right, as a human being, to develop and achieve his full potential and dignity, and the right, as a citizen, to make his maximum contribution to the society in which he lives.[25]

This succinct credo has shaped, both by design and by virtue of common sense, the LGBT civil rights movement.

Life-long couple Phyllis Lyon and Del Martin co-founded the Daughters of Bilitis in 1955 for women. They offered private and public meetings regarding homosexuality.[26] Their iconic newsletter, "The Ladder," reached isolated women and offered hope and empowerment for many years.[27] Del Martin and Phyllis Lyon were the first couple married when San Francisco, CA offered same-sex marriage certificates in 2004, and again in 2008 when the state of California recognized marriage equality. Unfortunately, Del Martin did not live to see marriage equality become the law of the land.[28]

Christopher Heredia, "Henry 'Harry" Hay—Gay Rights Pioneer / He Started Mattachine Society," (obituary), San Francisco Chronicle Gate, October 25, 2002, *available at* http://www.sfgate.com/bayarea/article/Henry-Harry-Hay-gay-rights-pioneer-He-2779360.php.

[25] Mattachine Society of Washington, "Mattachine Society of Washington Statement of Purpose," undated, digitized archival copy, accessed September 15, 2017, *available at* https://rainbowhistory.omeka.net/items/show/4937957.

[26] Teresa Theophano, "Daughters of Bilitis," glbtq, Inc., 2004, *available at* http://www.glbtqarchive.com/ssh/daughters_bilitis_S.pdf.

William Grimes, "Del Martin, Lesbian Activist, Dies at 87," The New York Times, August 27, 2008, *available at* http://www.nytimes.com/2008/08/28/us/28martin.html.

[27] Stuart Hinds, "The Ladder: the Voice of A Lesbian Generation," The Phoenix Newsletter, Winter 2014, *available at* https://library2.umkc.edu/spec-col/glama/pdfs/history/phoenix-2014-01-winter.pdf. *See also* Diana Lee Johnson, "A Narrative Life Story of Activist Phyllis Lyon and Her Reflections on a Life with Del Martin," Masters Thesis, Grand Valley State University, (2012), *available at* http://scholarworks.gvsu.edu/cgi/viewcontent.cgi?article=1021&context=theses.

[28] William Grimes, "Del Martin, Lesbian Activist, Dies at 87," The New York Times, August 27, 2008, *available at* http://www.nytimes.com/2008/08/28/us/28martin.html.

The Daughters of Bilitis also rallied the community against abusive police raids on neighborhood LGBT bars.[29] Transgender people, including Marsha P. Johnson and Sylvia Rivera, took their place alongside lesbians and gay men in the public fight for equality at the Stonewall Riots in New York City which ushered in a new era in the march for LGBT equality.[30]

When the Stonewall Riots began in Greenwich Village on June 28, 1969, neighborhood bars where LGBT people gathered across the country were no strangers to police raids. These raids were carried out to, often under the pretext of stopping illegal liquor and cigarette sales, to harass, intimidate and subjugate the LGBT community because they had to create their own public places in which to congregate.[31] When police conducted a raid at the Stonewall Inn on that fateful night,

> [a] crowd had gathered outside the tavern by the time the police were ready to load up their wagons with contraband alcohol, Stonewall employees, and unhappy bar goers. When the cops started to manhandle their unruly prisoners, the onlookers became enraged, throwing coins, stones, and bottles at the officers. The police, a few prisoners, and a writer from the Village Voice who had noticed the fracas from his nearby office, were forced to retreat into the bar, which the mob then tried to set on fire. The cops were eventually rescued with the intervention of the fire department and the riot squad, which dispersed the crowd. But low-level protests lasted for four more days, flaring up for a final time on Wednesday, when the Voice published an inflammatory account of the uprising. Why did the gays of Christopher Street suddenly fight back after decades of persecution? Witness Morty Manford likened the melee to "a slight lancing of the festering wound of anger at this kind of unfair harassment and prejudice." He said, "We had just been kicked and punched around symbolically by the police. They weren't doing this at heterosexual bars. And it's not my fault that the local bar is run by organized crime and is taking payoffs and doesn't have a liquor license."[32]

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[29] *See, e.g.,* Zoe Sonnenberg, "Daughters of Bilitis: Historical Essay," FoundSF, 2015, *available at* http://www.foundsf.org/index.php?title=Daughters_of_Bilitis.

[30] *See, e.g.,* Jamilah King, "Meet the Trans Women of Color Who Helped Put Stonewall on the Map," Mic, June 25, 2015, *available at* https://mic.com/articles/121256/meet-marsha-p-johnson-and-sylvia-rivera-transgender-stonewall-veterans#.3RBDc3H9O.

[31] *See, e.g.*, June Thomas, "The Gay Bar: Why the Gay Rights Movement Was Born in One," Slate, June 2011, *available at http://www.slate.com/articles/life/the_gay_bar/2011/06/the_gay_bar_4.html.*

[32] *Id.*

There were at least two known instances prior to the Stonewall Riots when gay patrons of gathering places resisted arrest.

In May 1959, a skirmish broke out around Cooper's Doughnuts, a shabby all-night Los Angeles coffee shop frequented by hustlers and their customers, when gays threw coffee cups and paper plates at police officers rather than submit to arbitrary arrests. This "was perhaps the first homosexual uprising in the world," according to Gay L.A. . . . Similarly, in the summer of 1966, transvestite patrons of Compton's Cafeteria in San Francisco's Tenderloin district fought with cops who were trying to detain them. Again, the incident failed to generate attention.

Id.

Perhaps buoyed by the energy of post-Stonewall community activism—and understanding that changing the laws that oppressed them could only be done through the political process—LGBT people began to openly enter the world of elected public service in the mid-1970s. In 1974, 21-year old Kathy Kozachenko become the nation's first openly LGBT elected official when she won a seat on the Ann Arbor, MI City Council.[33]

Harvey Milk, a child of Lithuanian Jewish immigrants,[34] a Navy veteran,[35] and the "Mayor of Castro Street,"[36] became California's first openly LGBT public official upon his election to the San Francisco Board of Supervisors in 1977.[37] He was quickly able to garner more than enough votes needed to pass a landmark gay rights ordinance, with ten out of the eleven Supervisors voting in support.[38] His brief eleven months in office came to a tragic end as former Supervisor Dan White—the only Supervisor who voted against the gay rights ordinance—gunned him down, along with Mayor George Moscone, in San Francisco City Hall on November 27, 1978.[39]

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[33] Steve Friess, "The First Openly Gay Person to Win an Election in America Was Not Harvey Milk," Bloomberg Politics, December 11, 2015, *available at* https://www.bloomberg.com/news/features/2015-12-11/the-first-openly-gay-person-to-win-an-election-in-america-was-not-harvey-milk.

[33] Rebecca Spence, "Harvey Milk, in Life and on Film, Typified the Proud Jew as Outsider," Forward, December 2008, *available at* http://forward.com/news/14715/harvey-milk-in-life-and-on-film-typified-the-pro-02973/.

[34] Sam LeGrone, "Navy to Name Ship After Gay Rights Activist Harvey Milk," U.S. Naval Institute News, July 28, 2016, *available at* https://news.usni.org/2016/07/28/navy-name-ship-gay-rights-activist-harvey-milk.

The United States Navy announced plans to name a ship after Harvey Milk on July 14, 2016.

Id.

[36] *See, e.g.,* Randy Shilts, The Mayor of Castro Street: The Life and Times of Harvey Milk, Stonewall Editions, 1988.

[37] *See, e.g.,* Darby West, "Harvey Milk, the First Openly Gay Elected Official in California: Not Your Typical Candidate," FoundSF, accessed September 15, 2017, *available at* http://www.foundsf.org/index.php?title=Harvey_Milk,_the_First_Openly_Gay_Elected_Official_in_California:_Not_Your_Typical_Candidate.

[38] *See, e.g.,* Natalie Jones, "The Life of Harvey Milk," American Civil Liberties Union, accessed September 15, 2017, available at https://www.aclu.org/files/pdfs/lgbt/schoolsandyouth/ramona_milk_presentation.pdf.

[39] Tim O'Rourke, "Chronicle Covers: The Assassinations of Moscone and Milk," November 2016, *available at* http://www.sfchronicle.com/news/article/Chronicle-Covers-The-assassinations-of-Moscone-10629367.php.

Sen. Dianne Feinstein, then the president of the Board of Supervisors who would become mayor upon Moscone's death, was in City Hall when the killings occurred and found Milk's body. "I put my finger to see if there was any pulse, and it went in a bullet hole in his chest," Feinstein told The Chronicle's Carl Nolte in 2003. "I think of it as if it were yesterday. I remember Harvey's body, his blood on me. I see it all." Both Moscone and Milk died instantly.

Id.

Before his brutal end at age forty-eight, Supervisor Milk was aware of death threats. He hoped, unfortunately prophetically, that "[i]f a bullet should enter my brain, let that bullet shatter every closet door."

Jamie McGonnigal, "In Memoriam: 'If a bullet should enter my brain, let that bullet shatter every closet door,'" LGBTQ Nation, November 2011, *available at* https://www.lgbtqnation.com/2011/11/if-a-bullet-should-enter-my-brain-let-that-bullet-shatter-every-closet-door/.

Given the seminal nature of his San Francisco gay rights ordinance banning discrimination in public accommodations, housing, and employment, and the impact of the "White Night Riots"—which erupted in San Francisco on Mary 21, 1979, the night that his killer was given a light sentence for manslaughter—it is safe to say that Dan White's bullets helped to shatter closet doors for generations yet to come.

See, e.g., Martin Stezano, "What Were the White Night Riots?," History, June 2017, *available at* http://www.history.com/news/ask-history/what-were-the-white-night-riots.

Milk's assassination galvanized a generation of LGBT leadership that continue to this day. In 1987, Barney Frank (D-MA) became the first sitting Member of Congress to publicly identify as LGBT.[40] Rep. Frank served in Congress from 1981 to 2013, and "was the primary sponsor of 31 bills that were enacted," including the 2010 Dodd-Frank Act which precipitated an overhaul of the American finance industry.[41] A powerful and outspoken leader, Rep. Frank was Chair of the House Financial Services Committee.[42] In 2012, Rep. Frank became the first sitting Member of Congress to marry a same-sex spouse.[43]

Today, a record six openly LGBT members serve in the U.S. House of Representatives: Reps. David Cicilline (D-RI), Sean Patrick Maloney (D-NY), Mark Pocan (D-WI), Jared Polis (D-CO), Kyrsten Sinema (D-AZ), and Mark Takano (D-CA).[44] November 2012 saw the election of the country's first openly LGBT Senator, the former Representative Tammy Baldwin (D-WI).[45] At the state level, Oregon elected our country's first openly LGBT Governor, Kate Brown, in 2016.[46] That these public officials display integrity and commitment to serving all constituents during this difficult era in progressive politics is more than laudable.

IV. The White House Fuels A Rising Tide of Inequality

Despite this Report's recommendations, and despite the progress made by the LGBT community, it is clear that in today's climate, no gains are safe. No one who values LGBT equality can rest easily, despite decades' worth of advancements. In stark contrast to the time of the Commission's 2015 briefing on these issues, the American political landscape is at an inflection point that can

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[40] Barney Frank, "My Life as a Gay Congressman," Politico Magazine, March 2015, *available at* http://www.politico.com/magazine/story/2015/03/barney-frank-life-as-gay-congressman-116027?o=0. *See also* Stuart Weisberg, Barney Frank: The Story of America's Only Left-Handed, Gay, Jewish Congressman, Sheridan Books, 2009.

[41] "Rep. Barney Frank," govtrack, accessed September 15, 2017, *available at* https://www.govtrack.us/congress/members/barney_frank/400140.

[42] *See, e.g.*, CNBC News Releases, "House Financial-Services Committee Chairman, Rep. Barney Frank (D) Massachusetts on 'Kudlow & Company' with Larry Kudlow (Transcript Included)," September 10, 2010, *available at* https://www.cnbc.com/id/20720084.

[43] Justin Sink, "Barney Frank to Marry Longtime Partner," The Hill, January 2012, *available at* http://thehill.com/blogs/blog-briefing-room/news/206799-report-barney-frank-to-marry; *and* Amanda Cedrone, "Barney Frank Marries Longtime Partner Jim Ready," The Boston Globe, July 8, 2012, *available at* https://www.bostonglobe.com/metro/2012/07/08/frank/J1ebJWjTAq2MgRUt2opQSM/story.html.

[44] Congressional Equality Caucus, "About the Caucus," accessed September 15, 2017, *available at* https://lgbt-polis.house.gov/about. (Note: This leadership list refers to members of the 114th Congress, but all members remain in office during the 115th Congress. In addition to its six openly LGBT Co-Chairs, the Caucus benefits from the membership of many other Representatives as well.)

[45] Emanuella Grinberg, "Wisconsin's Tammy Baldwin is First Openly Gay Person Elected to Senate," CNN, November 7, 2012, *available at* http://www.cnn.com/2012/11/07/politics/wisconsin-tammy-baldwin-senate/index.html.

[46] Camila Domonoske, "For First Time, Openly LGBT Governor Elected: Oregon's Kate Brown," National Public Radio, November 9, 2016, *available at* http://www.npr.org/sections/thetwo-way/2016/11/09/501338927/for-first-time-openly-lgbt-governor-elected-oregons-kate-brown.

move our nation forward, or send it backwards in a reactionary reflex to a time prior to the creation of the Commission. Recent progress is being actively and speedily undone.

Actions taken by President Trump and his administration, some of which are highlighted below, underscore the importance and timeliness of the Commission's report, including its Findings and Recommendations. Executive Branch documents on which the proverbial—or literal—ink is barely dry increase the urgency of the Commission's recommendations and decrease the likelihood that they will be honored in the near term. It is vitally important that Congress enact the Commission's recommendation to explicitly ban discrimination in the workplace based on sexual orientation and gender identity."[47] As this Administration revels in the cultural wars that it has created, Congress must act to even out an incomplete and contradictory patchwork of state and local laws, and to acknowledge that nothing akin to the federal government's reprehensible "Lavender Scare"[48] could be repeated.

During the 2016 Presidential campaign, then-candidate Trump worked hard to project the image of a devoted supporter of LGBT people.[49] However, the early record of his administration is replete with actions demonstrating that he is anything but interested in protecting LGBT Americans. This President is quickly building a legacy of transphobic and homophobic public policies.[50] Whether

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[47] USCCR Report, p. 73, n. 4 *supra*.

[48] *See, e.g.*, Johnson, The Lavender Scare: The Cold War Persecution of Gays and Lesbians in the Federal Government; U.S. Merit Systems Protection Board May 2014 report; and Sears, Hunter, and Mallory, Williams Institute report, n. 10 *supra*.

[49] During the campaign, then-candidate Trump made the following statements:

"'People are people to me, and everyone should be protected,' he told The Washington Post in a May 2016 interview." Anne Gearan, "White House Spokeswoman Says Trump and Alabama's Roy Moore 'Don't Agree' on Gay Rights," The Washington Post, September 28, 2017, *available at* https://www.washingtonpost.com/news/post-politics/wp/2017/09/28/white-house-spokeswoman-says-trump-and-alabamas-roy-moore-dont-agree-on-gay-rights/

"Ask yourself who is really the friend of women and the L.G.B.T. community, Donald Trump with actions or Hillary Clinton with her words?", he said. "I will tell you who the better friend is, and someday I believe that will be proven out, big-league." Haberman, Maggie, "Furious Gay Rights Advocates See Trump's 'True Colors,'" The New York Times, July 26, 2017, *available at* https://www.nytimes.com/2017/07/26/us/politics/furious-gay-rights-advocates-see-trumps-true-colors.html. "I will do everything in my power to protect our L.G.T.B.Q. citizens from the violence and oppression of a hateful foreign ideology." *Id.*

Commentators note that

Trump is only a few months into his presidency, and we've already seen a quiet but steady chipping away of protections for LGBT Americans. This president may have said he would be great for the LGBT community, but actions speak louder than words. And it's clear his veneer of inclusion can't hide the intent of his administration to make the lives of LGBT people, young and old, more difficult.

Lanae Erickson Hatalsky and Nathan Kasai, "Trump's Quiet War Against LGBT Americans," Newsweek, April 24, 2017, *available at* https://www.usnews.com/opinion/civil-wars/articles/2017-04-24/donald-trumps-guerrilla-war-against-against-lgbt-americans. *See also* Emanuella Grinberg, "The First 100 Days in LGBT Rights," CNN, April 28, 2017., *available at* http://www.cnn.com/2017/04/28/politics/first-100-days-lgbt-rights-trnd/index.html.

Depending upon the actions of the judicial nominees whom he may be successful in placing on the federal bench, including, of course, the U.S. Supreme Court, this legacy will likely live long past 2020 or 2024. *See, e.g.*, Mark Joseph Stern, "Obergefell is Already Under Attack," *Slate*, September 20, 2017, *available at* http://www.slate.com/articles/news_and_politics/jurisprudence/2017/09/trump_is_laying_the_groundwork_to_overturn_marriage_equality.html.

or not a specific action which negatively impacts upon LGBT people directly affects workplace discrimination is not germane to this overarching inquiry; all pieces of this puzzle are interconnected, and the removal of one threatens the stability of all.

If Trump meant any word of his pre-election pronouncements, then he should waste little time in using one of his many Executive Orders to implement our specific recommendation that "federal agencies including the Departments of Justice and Labor, the Equal Employment Opportunity Commission, and the Office of Personnel Management should issue and—where relevant—reaffirm specific guidance for federal and private employers outlining protections for LGBT individuals in the workforce, including specifically enumerating protections for transgender persons."[51] Yet it is evident that the difference between candidate Trump and President Trump on the issue of LGBT rights and protections is stark. Already, some federal agencies have already taken actions which contravene the Commission's specific call for protection, changing the terms of engagement and likely rendering the enforcement issues moot.

It is particularly sad and disturbing that the new Administration's first public anti-LGBT action was aimed at children and youth. In February 2017, Attorney General Jeff Sessions and Education Secretary Betsy DeVos, at the direction of the President, rolled back protections of Title IX of the Civil Rights Act of 1964 which the Obama Administration had interpreted as allowing transgender youth to use the school bathrooms that aligned with their gender identities.[52] For an Administration which has trumpeted, through its First Lady, an anti-bullying manifesto, this action seems particularly cruel and hypocritical.

Also sadly, but predictably, the President struck a blow against LGBT workplace protections in March 2017 (and as discussed in the report) when he made it easier for federal contractors to discriminate against LGBT employees or prospective workers. Executive Order 13673 required federal contractors to demonstrate compliance with the antidiscrimination requirements of Executive Order 13672 and other Executive Orders and federal laws.

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[51] USCCR Report, p. 73, n. 4 *supra.*
Further, recognizing that a right without a remedy is not a right at all, the Commission recommends that "Congress should authorize the necessary appropriations to ensure that all current and future non-discrimination protections are fully enforced by agencies including, but not limited to, the Departments of Justice and Labor and the Equal Employment Opportunity Commission."
Id. at p. 73.

[52] "'As President Trump has clearly stated, he believes policy regarding transgender bathrooms should be decided at the state level," the White House said in a statement . . . .'" Erin Dooley, Geneva Sands, Justin Fishel, Katherine Faulders, and Veronica Stracqualursi, "Trump Reverses Transgender Bathroom Guidance," ABC News, February 22, 2017, *available at* http://abcnews.go.com/Politics/trump-administration-issue-guidance-transgender-bathrooms/story?id=45663275. *See also* Jeremy W. Peters, Jo Becker, and Julie Hischfeld Davis, "Trump Rescinds Rules on Bathrooms for Transgender Students," The New York Times, February 22, 2017, *available at* https://www.nytimes.com/2017/02/22/us/politics/devos-sessions-transgender-students-rights.html.

The U.S. military has historically been a battleground for recognition of LGBT rights. From the first tentative steps of "don't ask, don't tell" of the Clinton Administration to the full integration of LGBT servicepersons during the Obama administration, the rights of LGBT to serve our country has been, unfortunately, a continuing flashpoint of controversy. Yet, until recently, the issue had been swiftly and surely receding. However, the President broadcasted a series of morning tweets on July 26, 2017,[53] apparently issued to the surprise of military leadership—despite the fact that he claimed consultation with them[54]—announcing that transgender people would no longer be allowed to serve in the U.S. military. He cited the "tremendous medical costs" associated with their care and the "disruption" they create as justification.[55] The President's reasoning for reversing existing policy is specious at best and transphobic at worst.

The two leading studies on the question of the military's medical costs associated with transgender service members to be anything but "tremendous." A better word, in the context of the military's astronomical budget, might be "miniscule." The RAND Corporation estimates the annual costs to be in the range of $2.4 to $8 million dollars.[56] The New England Journal of Medicine estimates $5.6 million annually.[57]

These numbers are the size of a speck of dust in the military's annual budget of $496 billion. They still pale in comparison to the military's reported annual expenditure of $64.4 million for Viagra and Cialis.[58] "Tremendous?" No. Taking this to scale, the annual costs projected for transgender

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[53] "After consultation with my Generals and military experts, please be advised that the United States Government will not accept or allow . . . ." Trump, Donald J. (@realDonaldTrump), Tweet, July 26, 2017, *available at* https://twitter.com/realDonaldTrump/status/890193981585444864.

" . . . Transgender individuals to serve in any capacity in the U.S. Military. Our military must be focused on decisive and overwhelming . . . ." Trump, Donald J. (@realDonaldTrump), Tweet, July 26, 2017, *available at* https://twitter.com/realDonaldTrump/status/890196164313833472.

" . . . victory and cannot be burdened with the tremendous medical costs and disruption that transgender [people] in the military would entail. Thank you[.]" Trump, Donald J. (@realDonaldTrump), Tweet, July 26, 2017, *available at* https://twitter.com/realDonaldTrump/status/890197095151546369.

[54] Scott Maucione, "Congress Wants Answers on Who Advised Trump on Transgender Military Ban," Federal News Radio, October 10, 2017, *available at* https://federalnewsradio.com/defense-main/2017/10/congress-wants-answers-on-who-advised-trump-on-transgender-military-ban/. *See also* Nick Visser, "Letter From 1114 House Democrats Challenges Trump's Decision to Ban Transgender Troops," The Huffington Post, October 11, 2017, *available at* https://www.huffingtonpost.com/entry/trump-transgender-troop-ban_us_59dd9756e4b04fc4e1e9cfa9.

[55] Trump, n. 53 *supra*. *See also* Julie Hirschfeld Davis and Helene Cooper, "Trump Says Transgender People Will Not be Allowed in the Military," The New York Times, July 26, 2017, *available at* https://www.nytimes.com/2017/07/26/us/politics/trump-transgender-military.html.

[56] Agnes Gereben Schaefer, Radha Iyengar, Srikanth Kadiyala, Jennifer Kavanagh, Charles C. Engel, Kayla M. Williams, and Amii M. Kress, "Assessing the Implications of Allowing Transgender Personnel to Serve Openly," RAND Corporation, 2016, p. 33, 37, *available at* https://www.rand.org/content/dam/rand/pubs/research_reports/RR1500/RR1530/RAND_RR1530.pdf.

[57] Aaron Belkin, "Caring for Our Transgender Troops—the Negligible Cost of Transition-Related Care," The New England Journal of Medicine, September 17, 2015, p. 1089, 1090, *available at* http://www.nejm.org/doi/pdf/10.1056/NEJMp1509230.

[58] Paul Szoldra and Skye Gould, "The Pentagon Spends 5 Times More on Viagra Than Transgender Services," Business Insider, July 26, 2017, *available at* http://www.businessinsider.com/pentagon-transgender-medical-comparison-2017-7.

service members is akin to a federal budget rounding error. Further, discharging transgender service members is estimated to cost $960 million—more than the equivalent of over a decade's worth of their medical care.[59] In other words, notwithstanding whether there can even be an economic justification for the transgression of civil rights, the lie behind the President's statements is laid bare by even the most cursory of analysis.

The President cited the "disruption" which, by their very presence in the military, he apparently believes that transgender people create. Again, evidence that transgender people create disruption in the military is lacking. To the contrary, based on analysis of other nations which permit military service by transgender people, the RAND Corporation found that disruption was not inherent and that straightforward policy changes could minimize any impact upon unit cohesion.[60] At least eighteen of our sister nations across the globe allow transgender service members to serve openly.[61]

On the same day on which the President tweeted that transgender service members would be removed, his Department of Justice inserted itself into federal litigation involving civilian workplace protections for LGBT people. The Department, as an uninvited participant, is using the private litigation between a fired gay worker and his former employee as a forum in which to argue that Title IX of the Civil Rights Act of 1964 does not protect LGBT people from employment discrimination. This is starkly and sadly in opposition to a 2015 decision by the Equal Employment Opportunity Commission.[62]

The Commission has recommended that "[w]orkplace discrimination data should be collected through the inclusion of sexual orientation and gender identity questions in population-based surveys of the workforce such as the Census, American Community Survey, and surveys fielded by the Bureau of Labor Statistics and other agencies."[63] This worthy recommendation is likely to be ignored as well. The Census Bureau has already removed planned questions involving gender

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[59] The Palm Center reports that "[t]he upshot of our analysis is that implementing President Trump's transgender service ban would cost $75,000 per person in order to accrue an annual savings of $656 per person. For the military as a whole, fully implementing President Trump's ban would cost $960 million in pursuit of saving $8.4 million per year." Aaron Belkin, Frank J. Barrett, Mark J. Eitelberg, and Marc J. Ventresca, "Discharging Transgender Troops Would Cost $960 Million," Palm Center, August 2017, p. 1, *available* at http://www.palmcenter.org/wp-content/uploads/2017/08/cost-of-firing-trans-troops-3.pdf.

[60] Schaefer, et al., n. 56 *supra.*

[61] Paul LeBlanc, "The Countries That Allow Transgender Troops to Serve in Their Armed Forces," CNN, July 27, 2017, *available at* http://www.cnn.com/2017/07/27/us/world-transgender-ban-facts/index.html.

[62] Alan Feuer, "Justice Department Says Rights Law Doesn't Protect Gays," The New York Times, July 27, 2017, *available at* https://www.nytimes.com/2017/07/27/nyregion/justice-department-gays-workplace.html.

[63] USCCR Report, p. 73, n. 4 *supra.*

identity and sexual orientation from the 2020 Census.[64] Further, federal survey questions regarding use of services by homeless and elderly LGBT people are on the chopping block. Sadly,

> [c]ombined with the withdrawal of another planned survey evaluating the effectiveness of a homelessness project for lesbian, gay, bisexual and transgender youth, the moves have alarmed watchdogs who worry they may point to a manipulation of government data collection to serve the ideology of a government they view as hostile to their causes.[65]

Even as the approved text of the Commission's report was being prepared for release, the President and his administration took additional actions against LGBT people's right to employment protection.

First, on October 4, 2017, the Department of Justice dismantled a powerful tool for the protection of transgender people in the workplace. It rescinded the Obama-era interpretation of the Civil Rights Act of 1964 Title VII as providing protection for transgender workers.[66] This Administration believes that Title VII "only prohibits discrimination on the basis of a worker's biological sex, and not their gender identity."[67]

Second, on October 6, 2017, the Administration took aim at employment protections for all LGBT people under the guise of "religious liberty." The Commission addressed this critical and highly-charged issue:

> Title VII offers a workable model for protecting religious freedom in the context of federal statutory nondiscrimination protections in the workplace. In *Hosanna-Tabor Evangelical Lutheran Church and School v. Equal Employment Opportunity Commission* the Supreme Court also unanimously endorsed the common law ministerial exemption, which recognizes the right of religious groups to select their own ministers and clergy. No further expansion of exceptions to nondiscrimination protections in the workplace are necessary or warranted to balance the rights to

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[64] Stephen Dinan, "President Trump Cancels Sexual Orientation Questions on 2020 Census," The Washington Times, March 28, 2017, *availalable at* http://www.washingtontimes.com/news/2017/mar/28/trump-cancels-census-sexual-orientation-questions-/.

[65] Matt Sedensky, "Federal Surveys Trim LGBT Questions, Alarming Advocates," US News, March 20, 2017, *available at* "https://www.usnews.com/news/us/articles/2017-03-20/federal-surveys-trim-lgbt-questions-alarming-advocates.

[66] Laura Jarrett, "Sessions Says Civil Rights Law Doesn't Protect Transgender Workers," CNN, October 5, 2017, *available at* http://www.cnn.com/2017/10/05/politics/jeff-sessions-transgender-title-vii/index.html. (Note: The Department of Justice memo is embedded in this article.)

[67] Daniel Wiessner and Sarah N. Lynch, "U.S. Anti-Bias Law Does Not Protect Transgender Workers: Justice Dept.," Reuters, October 5, 2017, *available at* http://www.reuters.com/article/us-usa-lgbt/u-s-anti-bias-law-does-not-protect-transgender-workers-justice-dept-idUSKBN1CA1Z9?il=0.

> freedom of religion and to nondiscrimination on the bases either of religion or LGBT status.[68]

To the contrary, however, the Department of Justice published guidance directing the "interpreting religious liberty protections in federal law" in accordance with the President's May 2016 Executive Order 13798.[69] After setting forth the precept that stating that "individuals and organizations do not give up their religious-liberty [sic] protections by . . . seeking to earn or earning a living; [or] by employing others to do the same"[70] this guidance implicitly allows religious businesses—which openly agitated for this interpretation—to decline to hire LGBT people if the religion holds anti-LGBT beliefs.

Even more alarmingly, the guidance implicitly seeks to expand dramatically the reach of the Religious Freedom Restoration Act ("RFRA"), which, on its face, protects only the First Amendment Free Exercise rights of a "person."[71] The U.S. Supreme Court expanded that reach, holding in *Burwell v. Hobby Lobby*[72] that the federal RFRA prevents the government from dictating the religiously-motivated behavior of "a closely held, for-profit corporation."[73] The guidance rides the *Hobby Lobby* toboggan as it boldly careens down a slippery slope, declaring—in the apparent absence of statutory or judicial authority—"RFRA protects the exercise of religion by individuals and by *corporations, companies, associations, firms, partnerships, societies, and joint stock companies*."[74] It is unclear whether the Attorney General's twisted interpretation has, in fact, any legal authority. But many will take the guidance at face value.

V. Conclusion

As this statement was being written, the President became the first sitting President to address [an] anti-LGBTQ event.[75] He boasted about his new "religious freedom" guidance (as discussed above)

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[68] Commission Report, p. 73, n. 4 *supra*.

[69] Executive Order 13798, "Promoting Free Speech and Religious Liberty," May 4, 2017, 82 CFR 21675, *available at* https://www.federalregister.gov/documents/2017/05/09/2017-09574/promoting-free-speech-and-religious-liberty.

[70] U.S. Department of Justice, "Memorandum for All Executive Departments and Agencies: Federal Law Protections for Religious Liberty," Paragraph 4, p. 2, October 6, 2017, *available at* https://www.justice.gov/opa/press-release/file/1001891/download. *See also* David Crary and Ricardo Alonso-Zaldivar, "Trump's One-Two Punch Hits Birth Control, LGBT Rights," Chicago Tribune October 7, 2017, *available at* http://www.chicagotribune.com/business/sns-bc-us--trump-religious-rules-20171006-story.html#article.

[71] The Religious Freedom Restoration Act, 42 U.S.C. sec. 2000bb—2000bb4, Pub.L. No. 103-141, 107 Stat. 1488, Sec. 3(a) November 16, 1993.

[72] *Burwell v. Hobby Lobby*, 573 U.S. ____, 2014.

[73] U.S. Department of Justice Memorandum, Paragraph 11, p. 4, n. 70 *supra*.

[74] *Id.*, italics added. *See also* Julie Moreau, "Justice Department 'Religious Liberty' Guidance: A 'License to Discriminate'?," NBC News, October 9, 2017, *available at* https://www.nbcnews.com/feature/nbc-out/justice-dept-religious-liberty-guidance-license-discriminate-n808836.

[75] Paige Lavender, "Trump Becomes First Sitting President to Address Anti-LGBTQ Event," The Huffington Post, October 13, 2017, *available at* https://www.huffingtonpost.com/entry/donald-trump-values-voter-summit_us_59e0b596e4b03a7be57fe666?ncid=inblnkushpmg00000009.

to the annual "Values Voter Summit" [76]organized by Family Research Council.[77] He spoke in full view of an audience that had been given pamphlets containing excerpts from "The Health Hazards of Homosexuality" and advertising the website www.HealthHazardsOfHomosexuality.info.[78] The pamphlet included statements that claimed that same-sex marriage "made sodomy a right" and that homosexuality was a mental disorder.[79] In the context of an event hosted by an organization that considers anyone in the LGTB community to be "unnatural"[80] and that the Bible punishes homosexuality[81] is it any wonder that many LGTB Americans would be alarmed when he said that his Administration was "returning moral clarity to our view of the world" and "stopping cold the attacks on Judeo-Christian values."[82]

So this President, who campaigned as a self-professed "friend . . . of the L.G.B.T. community,"[83] who compared himself to Secretary Hillary Clinton by averring, "I will tell you who the better friend is, and someday I believe that will be proven out, big-league,"[84] spoke proudly to an organization labelled an anti-LGBT hate group by the Southern Poverty Law Center.[85] It is in this context that the actions of the Administration become clear.

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[76] *Id.*

[77] The Southern Poverty Law center states that "[t]he FRC often makes false claims about the LGBT community based on discredited research and junk science. The intention is to denigrate LGBT people as the organization battles against same-sex marriage, hate crime laws, anti-bullying programs and the repeal of the military's "Don't Ask, Don't Tell" policy." Southern Poverty Law Center, *available at* https://www.splcenter.org/fighting-hate/extremist-files/group/family-research-council

[78] Aris Foley, "Anti_LGBT Pamphlets Handed Out at Values Voter Summit Trump Spoke At," AOL News, October 13, 2017, *available at* https://www.aol.com/article/news/2017/10/13/anti-lgbt-pamphlets-handed-out-at-values-voter-summit-trump-spoke-at-hate-groups/23242678/. "The Health Hazards of Homosexuality" is written by Mass Resistance, which the Southern Poverty Law Center recognizes as a hate group. *See, e.g.,* Southern Poverty Law Center, "Texas Chapter of Anti-LGBT Hate Group Mass Resistance Launches, Helmed by Robert Oscar Lopez," March 29, 2017, *available at* https://www.splcenter.org/hatewatch/2017/03/29/texas-chapter-anti-lgbt-hate-group-mass-resistance-launches-helmed-robert-oscar-lópez.

[79] https://www.nbcnews.com/feature/nbc-out/hazards-homosexuality-flier-distributed-values-voter-summit-n810471.

[80] From the Family Research Council website: "Family Research Council believes that homosexual conduct is harmful to the persons who engage in it and to society at large, and can never be affirmed. It is by definition unnatural, and as such is associated with negative physical and psychological health effects." *Available at* http://www.frc.org/homosexuality.

[81] The Family Research Council has a publication entitled "The Bible's Teachings on Marriage and Family" which states that "[i]n recent years, homosexual advocates have argued that the Bible, rightly interpreted, does not forbid homosexual relationships, only perverse expressions of such. For example, they have argued that God's judgment on Sodom on Gomorrah (Genesis 18:17-19:29) was merely for these cities' inhospitality, not for the sin of homosexuality. However, while Sodom and Gomorrah did in fact show a lack of hospitality, *it is hardly conceivable that God would punish these cities by utter annihilation for this comparatively minor offense*. Also, the Epistle of Jude clearly states that the people of Sodom and Gomorrah "indulged in sexual immorality and pursued unnatural desire" (*i.e.* homosexuality; Jude 7; cf. Romans 1:26-27), emphasis added, *available at* http://www.frc.org/brochure/the-bibles-teaching-on-marriage-and-family.

[82] Lavender, n. 54 *supra;* and Dan Merica, "Trump: We Are Stopping Cold the Attacks on Judeo-Christian Values," CNN, October 13, 2017, *available at* http://www.cnn.com/2017/10/13/politics/trump-values-voters-summit/index.html.

[83] Haberman, n. 49 *supra.*

[84] *Id.*

[85] Southern Poverty Law Center, "Hate Groups," accessed September 15, 2017, *available at* https://www.splcenter.org/hate-map.

This incident underscores the fact that the Commission's report, especially when read in the context of all anti-LGBT actions by the current President and his Administration, is a call to action. The progress has been halted, the roll-backs are in motion, the need for immediate action is real. LGBT people, their allies (long including this Commissioner), and all who care about social justice and true equality for all must exercise vigilance in tracking new developments and participate in all non-violent and legal forms of activism to oppose setbacks. Without the pre-existing benefit of deeply-embedded federal and judicial protections, LGBT people are a fair target for discrimination by the government and private actors alike. It is apparently open season.

Despite the assurances from the candidate in 2016, the President and his Administration have taken actions in 2017 in contravention to the Commission's recommendations before the Commission could even get its report out the door or before this Commissioner could hit save on the final version of this Statement. For many in the LGTB community, it is dismaying that the President and this Administration have taken actions that appear to be committed to targeting LGBT people for the denial of hard-won basic rights and protections as minority members of our society. This behavior is decidedly un-American. It is vicious, spiteful, exclusionary, and—at its most basic—needless. The LGBT civil rights quest has never been about the dreaded boogeyman of "special rights." It is a search for mere equality, not supremacy. It is the oft-repeated story of disqualifying the qualified because of fear, jealous, and hatred.

The breadth and pace of this Administration's actions underscore the need for all fair-minded Americans to practice vigilance and activism. Part of that activism must be work to try to prevent future dangers. Just how far will this President and his Administration go in trying to force LGBT people back into the proverbial closet and reduce their abilities to participate fully and openly in American life—to interfere with their pursuit of happiness? The federal actions since Inauguration Day, and the specter of what may yet be in the offing, especially in appointments to the judiciary, only emphasize the need for federal legislation barring employment discrimination which the Commission recommends. Most telling, a chilling harbinger of what is yet to come, is the President's open embrace of the possible election of a United States Senator[86] with a long history of virulently homophobic beliefs.[87]

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[86] The President has articulated enthusiastic support for Roy Moore. "'Spoke to Roy Moore of Alabama last night for the first time. Sounds like a really great guy who ran a fantastic race. He will help to #MAGA!' the president tweeted, referring to his own "Make America Great Again" campaign slogan."
Julia Manchester, "Trump: Roy Moore 'Sounds Like a Really Great Guy,'" The Hill, September 27, 2017, *available at* http://thehill.com/homenews/administration/352616-trump-speaks-to-roy-moore-after-primary-victory-tweets-support.

[87] Roy Moore has likened homosexuality to bestiality. *See, e.g.*. Eugene Scott, "How Roy Moore's Rhetoric on Gays, Muslims Harks Back to Alabama's Past," The Washington Post, September 27, 2017, *available at* https://www.washingtonpost.com/news/the-fix/wp/2017/09/27/roy-moores-values-could-take-alabama-back-to-a-place-many-of-its-residents-have-tried-to-get-past/?utm_term=.3e245740a6f9.

It is more apparent than it has been in decades that LGBT people require even farther-reaching, more comprehensive, federal legal protections than just in the workplace. Such safeguards in the arenas of employment, public accommodation, housing, credit, and federally funded programs are feasible via amendments to the Civil Rights Act of 1964, the Fair Housing Act, and other federal laws. Such amendments would place sexual orientation and gender identity under the Acts' umbrellas as protected classes. The bipartisan Equality Act of 2017 seeks to do just that.[88] This is not fringe legislation; there are 197 co-sponsors in the House[89] and 45 co-sponsors in the Senate.[90] The Commission's next step in executing its duty to safeguard the civil rights of LGBT people should be to explore the broader issues which underlie the Equality Act and the remedies which it offers.

If there is any lesson from the recent events in Charlottesville, it is that the ugliness of racism, bigotry, homophobia, and transphobia still resides within a deep dark crevasse of the American soul. It is the duty of leaders in our government, especially the President, to denounce and deny these groups and individuals in the strongest possible terms. It is the duty of leaders in our government, especially the President, to take strong action to dismantle and disarm the leaders and the organizations that give bigotry, hatred, homophobia, and transphobia a voice. And it is the duty of our leaders in government, especially the President, to show that our government will enact laws to protect people from bigotry, hatred, homophobia, and transphobia.

This Commission has a duty to be the federal government's watchdog on civil rights, a mandate placed on it 60 years ago, a charge that requires us to give voice to the oppressed. It has been the Commission's voice that has spoken loudest when the civil rights laws of this country were required to be extended to other groups not named in the testimony surrounding the Civil Rights Act of 1964, as we did for women, as we did for the disabled, and as we do today for the LGBT community. It is a terrible day when the Oval Office chooses not just to ignore what we say on behalf of the American people, but to deliberately, and callously, act in opposition to the extension of these those hard-won civil rights to a group that is deserving and in need of their protection.

While Chief Justice of Alabama, Moore opined that "[h]omosexual conduct by its very nature is immoral, and its consequences are inherently destructive to the natural order of society." In *re D.H. v. H.H.*, Supreme Court of Alabama, Docket No. 1002045, decided February 15, 2002, *available at* http://caselaw.findlaw.com/al-supreme-court/1303306.html.

[88] H.R. 2282: Equality Act, 115th Congress, 1st Session, introduced May 2, 2017, *available at* https://www.gpo.gov/fdsys/pkg/BILLS-115hr2282ih/pdf/BILLS-115hr2282ih.pdf. *See also* S. 1006: Equality Act, 115th Congress (2015-2017), introduced May 2, 2017, *available at* https://www.congress.gov/115/bills/s1006/BILLS-115s1006is.pdf.

[89] "All Information (Except Text) for H.R.2282—Equality Act," Congress.gov, accessed September 15, 2017, *available at* https://www.congress.gov/bill/115th-congress/house-bill/2282/all-info.

[90] "S.106—Equality Act," Congress.gov, accessed September 15, 2017, *available at* https://www.congress.gov/bill/115th-congress/senate-bill/1006/cosponsors .

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Dissenting Statement of Commissioner Gail Heriot

I have sympathy for some of the goals of the basic legislative proposal discussed in this Report. In a different world, I might have been able to support at least a more modest version of it. I continue to support Title VII of the Civil Rights Act of 1964's provisions prohibiting discrimination in employment on the basis of race, color, religion, sex and national origin. But, alas, given the ways in which that legislation has been misapplied over the years, I worry about the wisdom of expanding it further unless the expansion comes packaged with general Title VII reform.

For example, under current interpretations of Title VII, employers must endeavor to prevent their employees from engaging in the sexual harassment of their colleagues. That is a worthwhile goal. But the concept of sexual harassment has been given such a broad and vague construction that its effect has been to force employers to squelch not just sexual harassment, but free expression at the workplace.[1] By extending the reach of anti-discrimination laws to sexual orientation and gender identity, the proposed legislation would only compound this problem.

Quite apart from my concerns over the proposed legislation, I have concerns over this report's usefulness as a guide to Congress.[2] The data are not always presented fairly and in context. For example, by focusing on employee *perceptions* of discrimination, it almost certainly overstates the

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[1] A good example of this is the recent firing of Google software engineer James Damore, which I discuss infra at Part IB(2).

[2] The report is unsatisfying in part because of an unbalanced record. Given that I had no fixed view on this particular issue—that is, I am not categorically against all anti-discrimination laws of this kind— I was looking forward to a balanced panel that could help me clarify my thinking. A balanced briefing on this topic should have had about the same number of witnesses who are generally for, as well as generally against, federal prohibitions on sexual orientation and gender identity discrimination in employment. Yet this briefing had 15 panelists generally in favor of such prohibitions and two generally against them. The Commission secured one of the two witnesses against—Ryan Anderson—at the very last minute, only after Commissioner Kirsanow and I complained vociferously about panel imbalance.

Although I was told that staff made a good-faith effort to secure a balanced panel and that the panel was imbalanced only because too many opponents declined to testify, that appears to be untrue. At a Commission business meeting on February 20, 2015, about three weeks before the briefing, the then-head of the Commission's Office for Civil Rights Research and Evaluation ("OCRE") happily said that she had already confirmed 13 witnesses and was looking to fill only two more slots.

See United States Commission on Civil Rights, Transcript of Business Meeting, February 20, 2015, 19-21, *available at* http://www.usccr.gov/calendar/trnscrpt/UNEDITEDCommissionMeetingTranscript_02-20-15.pdf.

After that meeting, OCRE agreed to provide us with a list of witnesses who had already been invited.

That list showed that only two critics of sexual orientation discrimination laws had been invited as of then. OCRE then tried to argue that the briefing was balanced because some potential panelists from the Human Rights Campaign and the Center for American Progress criticized the proposed federal Employment Non-Discrimination Act for not going far enough. These organizations are nonetheless strong supporters of ENDA's core prohibition on sexual orientation discrimination; the Human Rights Campaign at the time had a large banner on its website that said "Pass ENDA Now," and the proposed witness Gene Robinson of the Center for American Progress has gone so far as to assert that Christian opposition to ENDA would embarrass Jesus. *See* http://www.huffingtonpost.com/bishop-gene-robinson/enda-vote-jesus_b_4234440.html.

The notion that these panelists were interchangeable with conservatives and libertarians or made the panels more balanced was risible. I am forced to conclude that there never was a plan in place for a balanced briefing.

extent of discrimination based on sexual orientation. It states, for example, that "[s]tudies have found that anywhere from 21[3] to 47[4] percent of LGBT adults faced employment discrimination because they were gay or transgender." Rep. at 10. But the cited studies were all based on the *perceptions* of job applicants/employees (and the latter figure was for transgender/gender-nonconforming persons only). When one looks at the Equal Employment Opportunity Commission's statistics on the matter, one learns that "charges" of discrimination are not the same as actual discrimination. The vast majority of charges filed by job applicants/employees with the EEOC are found to be without merit. For Fiscal Year 2016, the EEOC found ***"No Reasonable Cause" for 67.6% of all LGBT-based charges.*** It found ***"Reasonable Cause" for only a tiny number—3.7% of LGBT-based charges.*** An additional 17.1% of charges were not pursued by the charging party.[5]

To be sure, this problem is not unique to LGBT-based charges of discrimination. EEOC data for Fiscal Year 2016 are similar for race-based charges (No Reasonable Cause 73.7%, Reasonable Cause 2.1%), religion-based charges (No Reasonable Cause 70.7%, Reasonable Cause 3.2%), and sex-based charges (No Reasonable Cause 64.2%, Reasonable Cause 3.2%).[6] Dealing with non-meritorious charges is part of the price we pay for our protections against employment discrimination, and it is a price we should be willing to pay in a well-functioning system that seeks to root out non-meritorious claims quickly and efficiently.[7] But in deciding whether to extend Title

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[3] The 21 percent figure appears to be taken from a Pew Research Survey: http://www.pewresearch.org/fact-tank/2013/11/04/as-congress-considers-action-again-21-of-lgbt-adults-say-they-faced-workplace-discrimination/. The actual question was whether the respondent had been "treated unfairly by an employer because of their sexual orientation or gender identity (5% say this happened within the past year and 16% report that this happened but not within the past year)." Note that some of what respondents consider unfair treatment may not violate employment discrimination laws.

[4] *See* Jaime M. Grant, Lisa A. Mottet & Justin Tanis, Injustice at Every Turn: A Report of the National Transgender Discrimination Survey 51 (2011)("Forty-seven percent (47%) said they had experienced an adverse job outcome, such as being fired, not hired or denied a promotion because of being transgender/gender non-conforming"), *available at* http://www.thetaskforce.org/static_html/downloads/reports/reports/ntds_full.pdf. For a criticism of the methodology in this survey, see *infra* at 107.

[5] The rest of the cases were as follows: In 7.2%, some sort of settlement was arrived at without a finding of reasonable cause on the part of the EEOC. An additional 4.5% were classified as "withdrawals with benefits" in the sense that, while no official findings were ever arrived at, the employer gave the employee at least something in return for the withdrawal. Rep. at 13.

[6] Race-Based Charges, https://www.eeoc.gov/eeoc/statistics/enforcement/race.cfm; Religion-Based Charges, https://www.eeoc.gov/eeoc/statistics/enforcement/religion.cfm; Sex-Based Charges, https://www.eeoc.gov/eeoc/statistics/enforcement/sex.cfm.

[7] Note that as discrimination becomes more rare, the ratio of non-meritorious cases to meritorious cases likely gets higher. Since our system of rooting out non-meritorious cases leaves something to be desired, the downside of having a law against discrimination becomes more prominent. Commissioner Kladney argues that "even if discrimination were rare, we should still have a federal law prohibiting it because it is wrong each and every time it happens." Kladney Statement at 79. I wonder if he really means that. There are all sorts of ways in which an employer can act arbitrarily. Suppose, for example, I refuse to hire Commissioner Kladney because his given name is "David" and my ex-husband's name is David. Or I refuse to hire him because he rooted for the Indians instead of my beloved Cubs in the 2016 World Series . . . or because his wristwatch keeps better time than mine. All are bad reasons to deny someone a job. But the obvious solution for each would be for him to go onto the next opportunity. Since my hypothetical reasons for declining to hire him are so idiosyncratic, he is unlikely to be worse off. Just as there are a lot of fish in the sea, there are a lot of employers out there. If discrimination on the basis of sexual

VII's coverage, it is important that we understand that perceptions of discriminations on the part of job applicants/employees are just that—perceptions. To get a real estimate of the size of the problem of discrimination, one must try to dig deeper.

The misidentified statistics concerning "perceptions" of discrimination are not the only example. Parts of the Report positively bristle with statistics about various aspects of life in the LGBT community. But rather than take those statistics at face value, I would urge the reader to drill down to the material in the footnotes and to approach that material with a critical eye. Gathering statistics on the LGBT community requires researchers to find a broad, representative sample. That isn't as easy as it sounds, particularly for the transgender subset of the population, given its extremely small size. Some of the surveys cited in the report try to get around the difficulty by using problematic methodologies.

One survey cited in this report—*The National Transgender Discrimination Survey*—"decided to pay stipends to workers in homeless shelters, legal aid clinics, mobile health clinics and other service settings to host 'survey parties' to encourage respondents whose economic vulnerability, housing insecurity, or literacy level might pose particular barriers to participation."[8] While I respect the researchers' efforts to try to find hard-to-reach persons, it should not have been surprising that looking in these places tended to uncover lots of respondents with low incomes, spotty employment histories, and other personal difficulties. Would a different approach have yielded a brighter picture of what it is like to be transgender? That question cannot be answered with certainty, though it seems likely. But the Report makes no effort to grapple with these

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orientation were rare to the point of being idiosyncratic, it's hard to see how Kladney could support its being outlawed, unless he would favor laws that employers can't make stupid decisions.

Commissioner Kladney makes another point in his Statement that deserves comment: He writes that most employers "are corporations, large and small, who take advantage of the legal protections and shields the government affords them" and that "[a]s such, they should be required to not discriminate against any qualified United States citizen in employment. To do so is not consistent with . . . American values." *Id.* This is another one that I have a hard time believing an easy-going guy like Commissioner Kladney really means. I can't imagine anything more inconsistent with American values than to demand that every employer who uses the corporate form (*i.e.* practically all private employers) act consistently with American values. A tolerant, plural society does not impose the values of the majority on everyone. That's what liberalism is supposed to be about (and what I thought it was about back in the days when I was a liberal).

[8] Approximately 500 out of a total of about 7,500 responses came from such efforts. The rest came through an online survey, which was evidently brought to the attention of potential respondents "through direct contacts with more than 800 transgender-led or transgender-serving community based organizations in the U.S." and "through 150 active online community listserves." See Jaime M. Grant, Lisa A. Mottet, & Justin Tanis, Injustice at Every Turn: A Report of the National Transgender Discrimination Survey at 12 (2011), *available at* http://www.thetaskforce.org/static_html/downloads/reports/reports/ntds_full.pdf. This methodology, of course, has its own problems.

The Report cites this survey for a variety of purposes. For example, it cites the survey in stating that "90 percent of transgender employees report experiencing some form of harassment or mistreatment on the job"—a figure it terms "staggering." Report at 11, n.54.

methodological issues, instead accepting at face value these surveys' assertions about the problems faced by transgender persons.[9]

A second example is the U.S. Transgender Survey, which is the largest survey of transgender persons taken to date, conducted in 2015.[10] The researchers responsible for it relied heavily on transgender advocacy organizations to disseminate the survey. That, of course, can lead to problems. We have no way of knowing whether transgender persons who have suffered from discrimination are more likely to respond to such surveys than those who have had no problems. But intuitively it certainly seems likely. The study's authors therefore cautioned readers:

> Although the intention was to recruit a sample that was as representative as possible of transgender people in the U.S., it is important to note that respondents in this study were not randomly sampled and the actual population characteristics of transgender people in the U.S. are not known. Therefore, it is not appropriate to generalize the findings in this study to all transgender people.[11]

This warning about the survey's limitations didn't make it into this Report. For this and other reasons, some of which I will have the opportunity to detail below, many of the factual assertions in this Report need to be taken with a grain of salt.

I. THE CASE FOR ANTI-DISCRIMINATION LEGISLATION FOR SEXUAL ORIENTATION IS SOMEWHAT WEAKER THAN THAT FOR RACE, COLOR, RELIGION, SEX AND NATIONAL ORIGIN IN 1964 AND HAS BEEN MADE WEAKER STILL BY SUBSEQUENT EVENTS. THE CASE FOR ANTI-DISCRIMINATION LEGISLATION FOR GENDER IDENTITY HAS BEEN RENDERED EVEN WEAKER ON ACCOUNT OF OVER-BROAD DRAFTING.

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[9] The methodological problem with the use of the General Social Survey ("GSS") in this Report is less dramatic, but nonetheless serious. The GSS surveys a large random sample of the country, and its findings concerning the views of Americans in general can usually be considered methodologically sound. But the Williams Institute chose to rely on its data to look at the employment experiences of sexual minorities in particular. Unfortunately, the number of GSS respondents who qualify as members of sexual minorities is tiny—57 self-identified as lesbian, gay or bisexual. In addition, 23 did not identify as lesbian, gay or bisexual, but nonetheless disclosed that they had had same-sex sexual partners. This is out of a total of 3,559 respondents. Even if one can assume that 3,359 respondents can be broadly representative of the American population as a whole, it is not at all clear that 80 can represent lesbian, gay and bisexual Americans.

[10] Rep. at n. 96 and 98.

[11] Sandy E. James, Jody L. Herman, Susan Rankin, Mara Keisling, Lisa Mottet & Ma'ayan Anafi, The Report of the 2015 U.S. Transgender Survey, National Center for Transgender Equality at 26 (2016) *available at* https://www.transequality.org/sites/default/files/docs/usts/USTS%20Full%20Report%20-%20FINAL%201.6.17.pdf. This Report cited the 2015 U.S. Transgender Survey for the proposition that "Transgender individuals are three times as likely to be unemployed and are more than twice as likely to live in poverty compared to the rate in the U.S." Rep. at 15, n.71.

A. A Presumption in Favor of Freedom of Association Should Always Be Applied When Anti-Discrimination Legislation Is Proposed; While that Presumption Can Be (and Has Been) Overcome in the Right Cases, It Takes A Convincing Argument to Do So.

The report quotes Professor Andrew Koppelman for this: "The general principle governing transactions between private parties should be freedom of association, for reasons of both liberty and efficiency. Any departure from that rule, such as a prohibition of discrimination, has the burden of proof."[12]

Koppelman is no conservative. But nearly all conservatives as well as most moderates and liberals would likely agree: If one is going to depart from the ordinary rule that in a free society private parties get to decide for themselves how to order their activities, including how to hire employees for their businesses,[13] one must have a good reason.[14]

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[12] Report at 49, *quoting* Andrew Koppelman, "Richard Epstein's Imperfect Understanding of Antidiscrimination Law, Library of Law and Liberty," January 2016, *available at* http://www.libertylawsite.org/liberty-forum/richard-epsteins-imperfect-understanding-of-antidiscrimination-law/.

[13] Interestingly, despite widespread agreement that race and sex discrimination are wrong, no one argues that prospective employees (as opposed to employers) should be prohibited from considering the race or sex of a prospective employer in deciding whether to apply for or accept an offer of employment.

[14] One person who seems not to agree is Commissioner Narasaki. Her statement seems to be premised on the notion that the freedom at stake in this area of the law is "freedom *from* discrimination" rather than freedom *of* association. Narasaki Statement at 81. As much as I respect Commissioner Narasaki, our views on the meaning of the word "freedom" and hence on the principles she identifies as fundamental to the founding of our nation could not be more different. Sometimes it is appropriate for the federal or state governments to coerce cooperation from private individuals (*i.e.* limit their freedom of association). But it is important not to lose sight of the fact that we are engaging in coercion, and dressing up coercion as providing "freedom *from*" this or that for others promotes unclear thinking. A free society must be ever vigilant before it encroaches on the freedom of private individuals (including employers) to choose the persons with whom they are willing to associate. As Koppelman put it, the "burden of proof" must always be on the advocates of departures from the basic rule of freedom of association.

As an American, I enjoy the Constitutional right to the free exercise of my religion. But I have no Constitutional right to require particular churches to accept me as one of their own. I have a right of free speech, but that does not include the power to coerce private individuals into buying my book.

Commissioner Narasaki uses *Obergefell v. Hodges*, 576 U.S. ___ (1976), as the starting point for her argument in favor of the proposed Employment Non-Discrimination Act. Since discrimination against same-sex marriage was prohibited in that case, it should be prohibited in employment as well—or so her argument goes. But *Obergefell* was not about the coercion of private individuals. It establishes a right of same-sex couples to marry, but it does not establish a right for individuals to marry someone who doesn't wish to marry them for reasons deemed arbitrary by the state.

For a law coercing individuals to marry someone they don't wish to marry, even if the reason given is arbitrary and capricious, would (I hope) take one heck of a reason. Coercing private employers to hire someone they don't wish to hire, even if their reason is rock stupid, presumably requires a lesser showing of necessity, but the presumption is still against it. In 1964, in passing Title VII to the Civil Rights Act, Congress decided that the problem of race, sex, religion, and national origin discrimination was so serious that the usual presumption in favor of freedom of association was overcome. But note that Congress did not decide that all wrongheaded decisions not to hire should be outlawed. It is still perfectly legal for an employer to be stupid. An employer can choose not to hire a job applicant because the applicant's hairstyle is too old-fashioned, the applicant used to date the employer's weird Cousin Cedric, the applicant is a Republican, the applicant is active in the Sierra Club, or the applicant is a devoted Star Trek fan.

How strong the presumption in favor of freedom of association should be is a question upon which reasonable minds will disagree. I'm not always sure myself. Reasonable individuals are on both sides of the question of whether

The reason for departing from that rule cannot be just that private parties are making bad decisions not to associate (or not to hire). If individuals are free only to make "good" decisions (*i.e.* decisions approved by the government), then they are not free at all. Nor can the reason be that by declining to associate with someone, private individuals have somehow "harmed" that person. While no one is free to physically attack another or to take, destroy, or otherwise injure another's property, declining to confer a benefit on someone (including the benefit of one's association) cannot be equated with imposing a harm. If it could be, the concept of freedom of association would evaporate. Something more is needed to overcome the presumption of freedom.[15]

So under what circumstances is the presumption in favor of free association overcome? A traditional example might be the common law rule that common carriers and public utilities must provide service to all who could pay. These entities were considered special because they tended toward monopoly. If a natural gas utility refuses service to anyone for a reason other than failure to pay, that individual has no practical alternative. If he relies on the free market to provide him with natural gas, he will be waiting a long time, since the town where he resides will likely have only one natural gas provider.

Anti-discrimination laws are a more recent addition to the list of exceptions. Because Title VII applied broadly to the conduct of private employers, it was by far the most controversial part of the Civil Rights Act of 1964. But there was nevertheless a strong argument for Congressional action—especially in the case of discrimination against African Americans. In the view of members of Congress, irrational race discrimination had become so pervasive, it could only be corrected through national legislation: Sometimes extraordinary steps are necessary.

It wasn't just that *some* employers in the South were discriminating on the basis of race: Essentially, all employers of any size were. The complex web of Jim Crow laws made it difficult for Southern employers to employ African-American workers on an equal basis even if they wanted to. If employers had to provide separate bathrooms, shower facilities and even pay

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sexual orientation should join race, color, religion, sex and national origin as prohibited classifications for Title VII purposes. My only point is that we ought to be able to agree that the presumption should always be in favor of freedom of association (and hence of employer choice) and not coercion. The proponents of legislation thus have the burden of persuading us why sexual orientation should be made part of Title VII, rather than opponents of the legislation having the burden to prove it why it should not. This is why I object to Commissioner Narasaki's quotation at the end of her Statement, which attempts to associate opposition to coercive laws—even well-intentioned coercive laws—with "hatred" and "intolerance." There is massively less hatred in the world than social justice warriors who toss the word "hatred" around carelessly think. As for "intolerance," it is a much more complicated phenomenon than they seem to understand. It is not always the ones the crowd is accusing of intolerance who are the most intolerant.

[15] As Koppelman recognizes, it is not just the value of freedom that drives the presumption in favor of freedom of association. What he calls "efficiency," too, is at stake. It is sometimes tempting for governments to believe that they can make better decisions on behalf of individuals. But it often doesn't turn out the way they thought it would. Sometimes the individuals know more about their particular situation than the government does. What may look to outsiders like invidious discrimination may turn out to be something else entirely.

windows for each race, it is not remarkable that many employers didn't hire African Americans at all or did so only on a limited basis. [16]

That was the intent of those laws—to ensure that whites were hired first into the best jobs. This is what happens when an entire segment of the population is effectively disfranchised. Those who can vote pass laws designed to benefit themselves; those who cannot will be on the losing end of the deal. Discrimination was so pervasive that help wanted ads in newspapers customarily were divided into "Help Wanted—White" and "Help Wanted—Colored." This wasn't subtle stuff.

And it wasn't just employers. Formally or informally, unions were frequently whites only, not just in the South, but also in the North. And employers were obliged to play by union rules. This angle of the discrimination problem was compounded by the Davis-Bacon Act, Pub. L. 71-798,40 Stat. 1494, 40 U.S.C. §§ 3141-48, which requires the federal contractors on public works projects to pay the "prevailing wage" in a given locality. Prevailing wage in practice meant (and continues to mean) union-scale wage. Since union members would ordinarily be more experienced than non-union members, if one had to pay union-scale wages, one might as well hire union members. When these unions were whites only, the system worked to the detriment of African-American workers. [17]

In the view of many members of Congress at the time, the case for protection against sex discrimination may have been somewhat weaker, but it was nevertheless strong. Like race discrimination, sex discrimination was so pervasive it was the norm for help wanted advertisements to separate "Help Wanted—Male" from "Help Wanted—Female."

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[16] This point tracks an observation made by C. Vann Woodward in The Strange Career of Jim Crow (1955)—the book Martin Luther King called "the bible" of the civil rights movement. Many people argued at the time that Southern culture had always and would always favor racial separation. It didn't matter whether the law required segregation or not; it would have happened without the law.

Woodward disputed this. He showed there was lots of early opposition to Jim Crow laws and without the power of the State to *require* segregation, it would likely not have become as ingrained in Southern culture as it did. To use Woodward's vocabulary, folkways did not dictate stateways. Instead, stateways—that is state laws—profoundly shaped Southern folkways—that is Southern culture. And as long as those laws remained unaltered, southern culture would be frozen in place. The Civil Rights Act of 1964, including Title VII, was a way of uprooting them. While it would be difficult to say that it was the perfect solution to the country's complex race problems, it did manage to accomplish the task of displacing those laws.

[17] Note that to supporters of the Davis-Bacon Act, this was a feature, not a bug. Rep. Robert Bacon, who represented a Long Island House District and for whom the law was named, was motivated in large part by race. In 1927, a contractor from Alabama won a bid to build a Veteran's Bureau in Long Island and brought an African American construction crew with him up from Alabama. Bacon was appalled and began his push to outlaw such competition. *See* David Bernstein, Roots of the Underclass: The Decline of Laissez-Faire Jurisprudence and the Rise of Racist Labor Legislation, 43 Am. U. L. Rev. 85, 115 (1993).

He was not alone. In supporting the proposed legislation, Rep. John J. Cochran of Missouri stated in connection with the proposal that he had "received numerous complaints in recent months about southern contractors employing low-paid colored mechanics getting work and bringing the employees from the South." Hearings on H.R. 7995 and H.R. 9232 Before the House Committee on Labor, 71t Cong. 2d Sess. 17 (26-27). Rep. Clayton Allgood agreed, complaining of "cheap colored labor" that "is in competition with white labor throughout the country." 74 Cong. Rec. 6513 (1931).

Some of this tendency was frozen in place by the law. Progressive Era state legislation often purported to make distinctions between men and women in order to protect the health of the supposedly weaker sex, but at least some of the motivation behind such laws was the desire to exclude women from the most desirable jobs. And while the hey-day of such laws was the early part of the 20th century (at a time when many women could not vote), many remained in place at the time Title VII was passed.[18]

In *Muller v. Oregon*, 208 U.S. 412 (1908), the Supreme Court had unanimously upheld the constitutionality of an Oregon statute restricting women from working for more than 10 hours a day. Justice Josiah Brewer's opinion for the Court stated:

> That woman's physical structure and the performance of maternal functions place her at a disadvantage in the struggle for subsistence is obvious. This is especially true when the burdens of motherhood are upon her. Even when they are not, by abundant testimony of the medical fraternity continuance for a long time on her feet at work, repeating this from day to day, tends to injurious effects upon the body, and as healthy mothers are essential to vigorous offspring, the physical well-being of woman becomes an object of public interest and care in order to preserve the strength and vigor of the race.

208 U.S. at 412.

As such laws multiplied during the Progressive Era and beyond, some feminists, like Suzanne LaFollette, voiced their objections:

> [I]f discriminative laws and customs are to continue to restrict the opportunities of women and hamper them in their undertakings, it makes little difference for whose benefit those laws and customs are supposed to operate, whether for the benefit of men, of the home, of the race, or of women themselves; their effect on the mind of woman and her opportunities will be the same. While society discriminates against her sex, for whatever reason, she can not be free as an individual.
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> . . . Laws which fix fewer hours of work for women than for men may result . . . in the substitution of men—or children—for women in factories where but few have been employed. Laws prohibiting night-work may reduce the chances of women to get much-needed employment, and may sometimes shut them out of work which would offer higher returns on their labor than anything they might get to do during the day . . .

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[18] The EEOC took the position that Title VII overruled all discriminatory statutes of this kind unless sex is a *bona fide* occupational qualification. But it took some work to uproot them. In *Megelkoch v. Industrial Welfare Commission*, 442 *F.2d* 1119 (9th Cir. 1971), a woman employee had to challenge California's maximum hour statute for women when her employer refused to promote her on the ground that she couldn't work the same hours as her male colleagues. She won. In *Weeks v. Southern Bell*, 408 *F.2d* 228 (5th Cir. 1969), the court held that a Georgia law imposing weightlifting limits of 30 pounds on women was void under Title VII. *Rosenfeld v. Southern Pacific Co.*, 293 *F. Supp.* 1219, 1223 (C.D. Cal. 1968), aff'd 444 *F.2d* 1219 (9th Cir. 1971), was similar.

Suzanne LaFollette, Concerning Women 19-20 (1926).

Sexual orientation provides an interesting comparison to race and sex. There is no doubt that racial minorities, sexual-orientation minorities, and women (as well as others) have suffered significant discrimination in employment. But there are interesting differences too, and these differences sometimes cut in different directions. For example, members of sexual orientation minorities have traditionally mitigated the effects of discrimination by declining to disclose their membership in a minority to their employer. For most women and members of racial minorities, that was never an option. On the other hand, the stigma associated with membership in a sexual orientation minority has in some ways been greater than the stigma associated with being female or with being a member of a racial minority.

Another interesting contrast: Unlike women and racial minorities, sexual orientation minorities have never been disfranchised on the ground of their sexual orientation. On the other hand, sexual orientation minorities tend to be very small and except in a small number of localities their voting power has been small.

This may be the most significant contrast: Few actual state laws have discriminated on the basis of sexual orientation in employment. Those that have existed have disappeared. This is in contrast to the situation with regard to race and even sex in 1964 when Title VII was promulgated. This is not to say that no government policies ever existed that hampered LGBT individuals from getting desired employment. As the Report indicates, for a time, the federal government took the position that the social stigma suffered by LGBT individuals made them vulnerable to blackmail and hence security risks. Rep. at 61. LGBT individuals applying for some federal jobs therefore had to hide their sexual orientation. If they were hired, their troubles were not over. If their sexual orientation became known, they would be fired.[19] To be fair, however, one must point out that this policy was abandoned decades ago.[20]

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[19] For a more detailed discussion of the federal policy, see Yaki Statement at 87-96. At this point in time it is unclear how many LGBT individuals were discouraged from applying for, were screened out from, or were fired from a federal job on account of their sexual orientation. But my own mother, who was working for the Department of Defense in the 1950s, remembers a colleague of hers being unceremoniously removed from his job when his sexual orientation was apparently discovered for the first time. She is 92 years old today and has not forgotten the unfairness of it.

[20] The relationship of military serviceman or servicewomen to the federal government is not one of employment. The various legislative proposals discussed in this Report therefore do not apply. But it should be pointed out that it was not until the 1990s that the policy of "Don't Ask, Don't Tell" was implemented, thus allowing closeted gays, lesbians and bisexuals to join the military. Department of Defense Directive 1304.26 (December 21, 1993). It was not until 2011 that openly gay, lesbian and bisexual individuals were permitted to join the military. See Pub. L. 111-321, 124 Stat. 3515, 10 U.S.C. § 654 (2010)(policy went into effect September 20, 2011).

Policies that gave better benefits to married rather than unmarried discriminate on the basis of marital status, not sexual orientation. Most of those who end up with the short end of the stick are not LGBT. But nevertheless at a time that same-sex marriage was unrecognized in most states, LGBT individuals were disproportionately affected. Since *Obergefell v. Hodges*, 576 U.S. ___ (2015), however, all states have recognized same-sex marriage.

The bottom line, as far as I can see, is that the case for an anti-discrimination law for sexual orientation is weaker than the case for race or sex.[21] But, given the history of stigma associated with LGBT status, it is not insubstantial. That makes it a tough decision. What makes it somewhat easier to decide is the fact that Title VII has been misapplied so much over the years, it may be unwise to expand it before reforms are put into place.[22] Will it be possible to draft legislation that will make some version of the proposed Employment Non-Discrimination Act a good idea? I think so. Indeed, it is clear that some members of Congress have been working on the problem. But, in my view, we are not there yet.

On the other hand, the case for "gender identity" coverage is weak—not on the ground that transgender persons have not been historically discriminated against (they have been), but on the ground that the treatment of gender identity in the legislative proposals in this area to date have been overbroad to the point of incoherence.

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[21] Some have argued that only immutable characteristics should form the basis of anti-discrimination laws. In response those who support the proposed legislation have argued that sexual orientation *is* an immutable characteristic. I have no need to resolve that dispute, since I do not believe that only immutable characteristics should form the basis of anti-discrimination laws (although immutability might well be a factor to consider in determining whether the argument for banning discrimination on that basis is strong enough to overcome the presumption against coercing private parties to associate). From the beginning, Title VII contained a provision banning discrimination based on religion, and yet religion is not an immutable characteristic. Religion and sexual orientation also have something in common in the sense that some employers may have religious or moral objections to working with persons of religious persuasions or sexual orientations they consider to be sinful or otherwise problematic. That raises important and interesting questions that need careful consideration. Rather than attempt to address them here, I refer the reader to my Commission Statement in Peaceful Co-Existence: Reconciling Nondiscrimination Principles with Civil Liberties at (September 2016)(Statement of Gail Heriot), *available at* http://www.usccr.gov/pubs/Peaceful-Coexistence-09-07-16.PDF. The Statement is also *available at* https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2897849.

Commissioner Narasaki makes a different argument—that a characteristic's immutability should not drive whether anti-discrimination laws are appropriate for it (I agree with this part), but that whether the characteristic is "central to a person's identity" should. Narasaki Statement at 81-2. But that dog won't hunt. That notion that "characteristics that are fundamental and essential to one's identity," *id.* at 1, should be made the subject of anti-discrimination laws, without any further justification, runs into the problem of human complexity.

Some people consider their race fundamental to their identities; others regard their race as literally skin deep. Indeed, up until fairly recently, it was the fashion among right-thinking liberals to believe exactly that—that race was unimportant. A few days ago I overheard a young man say to an elderly woman that he had no idea about the origins of his surname and didn't know his ethnicity. On the other hand, I've known individuals who regard their astrological sign, their musical ability, their sense of humor, their extremist political ideology, their artistic ability, their entrepreneurial spirit, their Myers-Briggs personality type, and their facility with the written word to be central to their identities. One could always argue with them about what is fundamental to *their* identities. But usually, if persons say that something is fundamental to their identity, it's best to just accept that it is.

Do individuals regard sexual orientation as central to their identity? The answer is almost certainly that some do and some don't. In some surveys, some individuals acknowledge frequent consensual same-sex activity, but nonetheless do not identify themselves as lesbian, gay or bisexual.

[22] I have expressed no opinion on the extent to which Title VII, through the Supreme Court's decision in *Price Waterhouse v. Hopkins*, 490 U.S. 228 (1989), already offers protection to those who have been discriminated against on the basis of sexual orientation or gender identity. This issue became more of a front-burner issue for the Commission after this Report was approved. At the point of this writing, the Commission is preparing to address the Department of Justice's conclusion that Title VII does not cover sexual orientation and gender identity. Since I have not yet had time to consider the Commission's proposed amendments, I have not addressed them in this Statement.

Prior to 2007, the various versions of the proposed Employment Non-Discrimination Act applied only to sexual orientation and not to gender identity. Since then, however, a number of versions have been introduced that do cover gender identity. Typical of these proposed Employment Non-Discrimination Act of 2013 (S. 815),[23] which defines "gender identity" thusly:

> (7) GENDER IDENTITY.—The term "gender identity" means the gender-related identity, appearance, or mannerisms or other gender-related characteristics of an individual, with or without regard to the individual's designated sex at birth.

The proposed Act goes on to declare it to be "an unlawful employment practice for an employer" "to fail or refuse to hire or to discharge any individual, or otherwise discriminate against any individual . . . because of such individual's actual or perceived . . . gender identity."

That won't work. Race, sex, and sexual orientation (at least where sexual orientation is defined narrowly)[24] are statuses that for the most part are unrelated to how one does a particular job. Gender identity, however, at least as it is defined here, is not a single thing, but a whole range of things. Any "gender-related" "mannerisms" or "characteristics" constitute "gender identity."

The problem is that huge numbers of mannerisms and characteristics are gender-related, and some of them are commonly job-related. In general, we regard aggressiveness to be more characteristic of males than females. That was the whole point of *Price Waterhouse v. Hopkins*, 490 U.S. 228 (1989). The plaintiff in that case alleged that she was not promoted because she was thought to have an aggressive and hence "unladylike" personality, but that she would have been promoted if she had been a male with the same kind of personality. The Court agreed that if she would have been promoted if she had been male, she was discriminated against on the basis of sex within the meaning of Title VII.

By making gender-related characteristics (rather than sex itself) the subject of anti-discrimination laws, the proposed law would radically change the law. Right now it is a violation to fail to promote a woman with an aggressive personality if a man with the same personality would have been promoted. Under the proposed law, it would be a violation to fail to promote someone with a passive personality, if someone with an aggressive personality would have gotten the job.

But there are lots of jobs for which an aggressive personality is a legitimate job qualification, just as there are lots of jobs where a more passive, but nurturing, personality is the right fit. If the federal government prohibits employers from making hiring decisions on the basis of "gender-related characteristics," it will be prohibiting a lot of rational behavior.

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[23] https://www.congress.gov/bill/113th-congress/senate-bill/815/text.

[24] In the proposed Employment Non-Discrimination Act of 2013 (S. 815), "sexual orientation" was defined this way: "(10) SEXUAL ORIENTATION.—The term "sexual orientation" means homosexuality, heterosexuality, or bisexuality." It does not include such things as pedophilia, necrophilia, or sexual sadism.

I rather suspect this is not what the drafters of the proposed Employment Non-Discrimination Act had in mind. But it is what they wrote. Its supporters may not have thought this out very well. One version actually passed the Senate in 2013. What were they thinking?

B. Expansions of Title VII and Why They Have Made It Risky to Add Sexual Orientation to the Already-Existing List of Race, Color, Religion, Sex and National Origin.

(1) Preferential Treatment

If there is one thing you can depend on it's that the 88th Congress banned both discrimination against women and minorities and discrimination in favor of them. It's not just that the text of Title VII makes this clear (though it does):

> It shall be an unlawful employment practice for an employer—to fail or refuse to hire or to discharge any individual, or otherwise to discriminate against any individual with respect to his compensation, terms, conditions, or privileges of employment, because of such individual's race, color, religion, sex, or national origin; or to limit, segregate, or classify his employees or applicants for employment in any way which would deprive or tend to deprive any individual of employment opportunities or otherwise adversely affect his status as an employee, because of such individual's race, color, religion, sex, or national origin.

42 U.S.C. § 2000e-2(a).

Title VII easily could have been drafted to ban "discrimination against women" or "discrimination against racial minorities." But if it had been, it almost certainly wouldn't have passed. Instead the text proudly declares that discrimination on the basis of race, color, religion, sex, or national origin is prohibited.

If the text hadn't been crystal clear, then the legislative history would have easily clarified matters. For example, when H.R. 7152 reached the floor of the House of Representatives, the very first speech in support of it was delivered by the bill's chief sponsor, Committee on the Judiciary Chairman Emanuel Celler. Part of his speech responded to arguments against the bill, one of which was that it would lead to discrimination against whites. He responded that these arguments were "entirely wrong" and stated:

> Even [a] court could not order that any preference be given to any particular race, religion or other group, but would be limited to ordering an end of discrimination. The statement that a Federal inspector could order the employment only of members of a specific racial or religious group is therefore patently erroneous.
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> . . . The Bill would do no more than prevent . . . employers from discriminating against *or in favor* of workers because of their race, religion, or national origin.

110 Cong. Rec. 1518 (emphasis added).

Celler's sentiments were echoed repeatedly in the Senate. In their well-known interpretative memorandum on Title VII, Senators Joseph Clark and Clifford Case, bipartisan floor managers for the bill, wrote:

> Title VII would have no effect on established seniority rights. Its effect is prospective, and not retrospective. Thus, for example, if a business has been discriminating in the past and, as a result, has an all-white working force, when the title comes into effect, the employer's obligation would be simply to fill future vacancies on a nondiscriminatory basis. He would not be obliged—*or indeed permitted*—to fire whites in order to hire Negroes, or to prefer Negroes for future vacancies, or, once Negroes are hired, to give them special seniority rights at the expense of the white workers hired earlier.

110 Cong. Rec. at 7213 (emphasis added).

This is why the 5-4 decision in *United Steelworkers v. Weber*, 443 U.S. 193 (1979), was shocking to many. In *Weber*, the Court decided that, despite all this, it was permissible for Kaiser Aluminum and Chemical Corp. and the United Steelworkers to enter into a collective bargaining agreement that permitted whites to enter into their training program *only* on a one-to-one basis with African Americans (regardless of the applicants' comparative credentials and despite the fact that white applicants were more numerous).

The majority decision in Weber triggered one of the most devastating dissents in Supreme Court history:

> [B]y a tour de force reminiscent not of jurists such as Hale, Holmes and Hughes, but of escape artists such as Houdini, the Court eludes clear statutory language, "uncontradicted" legislative history and uniform precedent in concluding that employers are, after all, permitted to consider race in making employment decisions.

United Steelworkers v. Weber, 443 U.S. 193, 219, 222 (1979)(Rehnquist, J., dissenting).

Justice Rehnquist's take-no-prisoners prose showed step by step how Title VII could not fairly be construed to allow racial preferences of any kind, including those practiced by Kaiser and the United Steelworkers. *See also* Bernard D. Meltzer, *The* Weber *Case: The Judicial Abrogation of the Antidiscrimination Standard in Employment*, 47 U. Chi. L. Rev. 423 (1980).

What does *Weber* have to do with the legislative proposals that would prohibit discrimination on the basis of sexual orientation? Perhaps a lot. Americans have learned that when they pass laws that forbid discrimination, what they sometimes get are laws that give preferential treatment to the group that is perceived by those in power as the underdog. For those who oppose preferential treatment, that obviously seems bad. For those who support it, it may seem good. But that may be only at a superficial level. When executive agencies and courts interpret laws to go far beyond

what was originally intended by a statute, no one should be surprised that moderate legislators become gun shy. Further legislative action becomes more difficult.[25]

At least one version of the legislative proposal appears to specifically eschew the use of affirmative action preferential treatment. But after *Weber*, such efforts would need to be ironclad. This one doesn't seem to be.

The proposed Employment Non-Discrimination Act of 2013 (S. 815) states:

> (f) NO PREFERENTIAL TREATMENT OR QUOTAS.—Nothing in this Act shall be construed or interpreted to require or permit . . .
>
> (1) any covered entity to grant preferential treatment to any individual or to any group because of the actual or perceived sexual orientation or gender identity of such individual or group on account of an imbalance which may exist with respect to the total number or percentage of persons of any actual or perceived sexual orientation or gender identity employed by any employer, referred or classified for employment by any employment agency or labor organization, admitted to membership or classified by any labor organization, or admitted to, or employed in, any apprenticeship or other training program, in comparison with the total number of percentage of persons of such actual or perceived sexual orientation or gender identity in any community, State, section, or other area, or in the available work force in any community, State, section, or other area; or
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> (2) the adoption of implementation by a covered entity of a quota on the basis of actual or perceived sexual orientation or gender identity.

But note that this prohibits preferential treatment only in the context of efforts to match the proportions of those hired or promoted to the proportions found in some outside "community, State, section or other area." Aggressive lawyers might claim that preferential treatment designed to reap the unspecified benefits of diversity rather than to mimic the demographics of any particular "community, State, section or other area" are permissible.

On a blank slate, I would regard this as a weak argument. But in *Regents of the University of California v. Bakke*, 438 U.S. 265 (1978), a Title VI case, Justice Powell drew exactly this distinction. In his controlling opinion, he rejected the idea that the University of California could grant preferential treatment on the basis of race to medical school applicants in order to better match the student body to the racial composition of California. But he upheld the authority of the

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[25] *See* Daniel B. Rodriguez & Barry R. Weingast, The Positive Political Theory of Legislative History: New Perspectives on the 1964 Civil Rights Act and Its Interpretation, 151 U. Penn. L. Rev. 1417, 1535 (2003) (arguing that, after the judicial expansions of Title VII, some Members of Congress "were likely nervous about agreeing [with Members who supported those expansions] on legislative bargains, which, when they came before the courts, would be rewritten").

University of California to grant preferential treatment on the basis of race in order to reap the pedagogical benefits of diversity.

Justice Rehnquist was right. For the majority in *Weber* to come out as they did required the skills of escape artists like Houdini. Given *Bakke*, however, getting around the proposed Employment Non-Discrimination Act of 2013's ban on preferential treatment or quotas would not be nearly as difficult.

(2) Harassment

It is difficult to defend *Weber* as a matter of statutory interpretation no matter what one thinks of it as a matter of policy. The interpretation was just plain wrong, and painfully so. It would not be fair to put *Meritor Savings Bank v. Vinson*, 477 U.S. 57 (1986), in the same category. For reasons I hope to write about elsewhere, I believe the basic thrust of *Meritor Saving Bank* decision—that at least in some circumstances sexual harassment can be actionable under Title VII—is surely defensible.

The origins of the problems with current doctrine on sexual harassment are more subtle. Five years after *Meritor Savings Bank*, when the ill-conceived Civil Rights Act of 1991 made ordinary monetary damages available under Title VII, sexual harassment lawsuits became much more common, and employers became more fearful of them.

Their fear was mainly of "hostile environment" cases.[26] Employers could be liable for the *cumulative* effect of a series of many rude remarks, slights, and inconveniences, each of which might have come from a different employee (or even a customer). The only way to be sure of not being sued was (and is) to prevent as many as possible of them.

If an employee is upset at the photo of her colleague's bikini-clad wife on his desk, it is in the employer's interest to make him get rid of it.[27] If another employee doesn't like to be told by her

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[26] The "quid pro quo" kind of sexual harassment case was easier for employers to deal with. These are the cases in which an employee is told that she (or he) must engage in sexual relations if she (or he) wishes to be hired, get a promotion, or avoid dismissal. So long as the employee can demonstrate that a similarly-situated employee of the opposite sex would not have had to submit to this, one can see why such a deal amounts to discrimination on the basis of sex. Note that the shoe can be on the other foot here as well. An employee whose sexual favors are not desired may also have a Title VII complaint, because he (or she) was not given a similar opportunity to be hired, promoted, or avoid dismissal.

To deal with the "quid pro quo" cases, employers need to make it crystal clear to their supervisory personnel that such deals will not be tolerated. As a secondary precaution, they need to make sure that employees know the rules and have someone other than their supervisor to report to if their supervisor breaks those rules.

[27] Bonnie Miller Rubin & Judy Peres, Workplace on Edge Over Harassment, Chicago Tribune (April 3, 1998)("In 1993, a University of Nebraska graduate student was forced to remove a photo of his bikini-clad wife from his desk when two fellow students complained that it offended their sensibilities").

boss that her hair looks nice today, the employer has every incentive to order him to stop.[28] And if a copy of Goya's Naked Maja hanging in the building upsets an employee, the employer's instinct is unlikely to leave it there for others to enjoy. Rather, the picture is likely to be taken down.[29] If the other employees start to complain, the safe solution is to tell them to shut up and arrange for them to take a course in sexual harassment once a year.

"'We advise employers not to focus on the legal definition of harassment, but to have zero tolerance for any behavior extraneous to the workplace. There shouldn't be any touching or sexual joking. Period,'" an employment lawyer told the *Chicago Tribune* in 1998.[30]

When these kinds of actions started to become commonplace, many Americans—indeed a majority—began to wonder if we weren't going down the wrong road. In a 1997 CNN poll, 57% of men and 52% of women agreed that "we have gone too far in making common interactions between employees into cases of sexual harassment."

Since then, the pressure to avoid saying anything that might be construed as offensive has only increased. Sometimes it had served to suppress serious discussions.[31] A recent example is the firing of software engineer James Damore at Google.

Damore wrote what was intended to be an internal discussion memorandum entitled "Google's Ideological Echo Chamber." Contrary to what some media outlets claimed, it was not an anti-diversity or misogynistic screed. In fact, it went out of its way to suggest helpful ways to make employment at Google more attractive to women.

But it dared to question whether women's underrepresentation in software engineering and in leadership positions at Google is wholly due to bias against them. It argued—alluding to a large body of scientific evidence—that fewer women than men may aspire to be software engineers. Damore was careful to acknowledge that there is plenty of variation among men and among women, but as a group, women tend to be more interested in people-oriented jobs. And while Damore's statement says nothing about particular women or particular men, especially those who already work at Google, it happens to be a true statement at the general level. It's certainly worth talking about whether that might account for some of the under-representation of women at Google.[32]

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[28] *See Ellison v. Brady*, 924 *F.2d* 872 (9th Cir. 1991)("Well-intentioned compliments by co-workers or supervisors can form the basis of a sexual harassment cause of action . . . .").
[29] Nat Hentoff, Sexual Harassment by Francisco Goya, Washington Post (December 27, 1991).
[30] Bonnie Miller Rubin & Judy Peres, Workplace on Edge Over Harassment, Chicago Tribune (April 3, 1998).
[31] *See* David Bernstein, You Can't Say That!: The Growing Threat to Civil Liberties from Antidiscrimination Laws (2004).
[32] *See, e.g.*, Peter Singer, Why Google Was Wrong: Did James Damore Really Deserve to be Fired for What He Wrote? N.Y. Daily News (August 10, 2017).

But instead the author of the memo was fired. And one of the arguments made for his firing was that his memo violates Title VII: He is creating a hostile atmosphere for women, some observers argued; if he isn't fired, Google may be sued. *See e.g.*, Dan Eaton, Here's Why Google Had the Right to Fire that Employee over his Diversity Memo, cnbc.com (August 8, 2017)("Google Vice President of Diversity, Inclusion & Governance Danielle Brown is correct that an employee has no right to engage in workplace discourse that offends anti-discrimination laws; employees may not engage in unlawful harassment under the guise of protected concerted activity or political grievances."), *available at* https://www.cnbc.com/2017/08/08/heres-why-google-had-the-right-to-fire-that-employee-over-his-diversity-memo-commentary.html.

Some people at Google might have wanted Damore fired even if they had believed Google didn't need to worry about Title VII liability. But the culture—an intolerance of serious discussions about issues relating to sex—has been created in part because cautious people err on the side avoiding litigation. All too often that means appeasing extremists.

Google, of course, is a private entity and is not required to honor Damore's First Amendment rights. But Congress is. Insofar as Title VII liability was what drove Google's decision, Title VII (as interpreted) itself is unconstitutional.

Expanding Title VII's reach to other areas, whether it's to sexual orientation, gender identity or something else, can only compound the problem. Future discussions like that Damore tried to initiate would be squelched.

Consider the following situation: Even ten years ago, if someone had argued that New York City would pass a law requiring landlords to address tenants by the pronouns of the tenant's choice (rather than the pronouns of the landlord's choice or the pronouns that correspond to the tenant's actual anatomical sex), they would have been laughed at. But that has become a reality.[33] Would expanding Title VII cause such a rule to be applied to the workplace around the country? It isn't clear to me why it wouldn't.

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[33] New York City Commission on Human Rights Legal Enforcement Guidance on Discrimination on the Basis of Gender Identity or Expression: Local Law No. 3 (2002); N.Y.C. Admin. Code § 8-102(23). Eugene Volokh, You Can Be Fined for Not Calling People "Ze" or "Hir," if That's the Pronoun that They Demand You Use, The Volokh Conspiracy, May 17, 2016, *available at* https://www.washingtonpost.com/news/volokh-conspiracy/wp/2016/05/17/you-can-be-fined-for-not-calling-people-ze-or-hir-if-thats-the-pronoun-they-demand-that-you-use/; Richard Thomson, Transgender Individuals and Free Speech in New York City, The Federalist Society Blog, May 16, 2016, *available at* https://www.fed-soc.org/blog/detail/?dbid=459. See also Naveed Ahsan, The Silencing of Jordan Peterson, Fair Observer (August 30, 2017)(discussing the practices of the Ontario Human Rights Commission under which "it is now punishable if individuals refuse to use non-gender pronouns such as 'ze' or 'zir' to refer to transgender people"), *available at* https://www.fairobserver.com/region/north_america/jordan-peterson-canada-transgender-rights-debate-news-51321/; Lindsey Bever, Students Were Told to Select Gender Pronouns; One Chose "Your Majesty" to Protest "Absurdity," Washington Post (October 7, 2016).

Unlike the problem of preferential treatment, the problem of harassment overreach is not treated at all in any version of the legislative proposals considered in this Report.

(3) Disparate Impact

This is another one where the Supreme Court has misapplied Title VII, transforming it from a statute that requires equal treatment into one that presumptively requires equal results. See *Griggs v. Duke Power Co.*, 401 U.S. 424 (1971). The various iterations of the proposed Employment Non-Discrimination Act have attempted to deal with this problem.[34] But for reasons I will discuss more fully below, at least the version that passed the Senate in 2013 ultimately failed in its attempt to do so. In addition, the proposed Equality Act does allow for disparate impact claims.

To explain how all this fits together, one must start at the beginning:

While the passage of Title VII was important and historic, it was not intended to assert federal control over every aspect of the workplace. Its carefully limited purpose was to prohibit employment discrimination based on race, color, religion, sex and national origin. As Representative William M. McCulloch et al. put it:

> [M]anagement prerogatives and union freedoms are to be left undisturbed to the greatest extent possible. Internal affairs of employers and labor organizations must not be interfered with except to the limited extent that correction is required in discrimination practices.[35]

At the time, this was likely seen as an obvious, but important, point. Free enterprise had always been the engine that drove the nation's prosperity. For that and other reasons, the best way for the federal government to promote the general welfare, including the welfare of women and minorities, had usually been to allow peaceable and honest individuals the freedom to run their own business affairs. When exceptions become necessary (as they did in 1964), they were understood by most as precisely that—exceptions. They were not intended to swallow the rule.

Congressional leaders assured their colleagues that Title VII would not interfere with employer discretion to set job qualifications—so long as race, color, religion, sex and national origin were not among them. Senators Clifford Case (R-N.J.) and Joseph Clark (D-Pa.), the bill's co-managers on the Senate floor, emphasized this in an interpretative memorandum:

> There is no requirement in Title VII that employers abandon *bona fide* qualification tests where, because of differences in background and education, members of some

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[34] The proposed Employment Non-Discrimination Act of 2013 (S. 815), *available at* https://www.congress.gov/bill/113th-congress/senate-bill/815/text. It states: "(g) NO DISPARATE IMPACT CLAIMS.—Only disparate treatment claims may be brought under this Act." For reasons why this language fails to cover disparate impact claims brought under the "gender identity" provisions of the proposal, see infra at 127.

[35] Statement of William M. McCulloch, et al., H.R. Rep. No. 914, 88th Cong., 2d Sess. (1964). McCulloch was the House Judiciary Committee's ranking member and was considered by many to have been indispensable in passing the Act.

> groups are able to perform better on these tests than members of other groups. An employer may set his qualifications as high as he likes, he may test to determine which applicants have these qualifications, and he may hire, assign, and promote on the basis of test performance.

Case & Clark Memorandum, 110 Cong. Rec. 7213.

Note that Case and Clark used the term "*bona fide* qualification tests," meaning qualification tests adopted in good faith, and not "necessary" or "scientifically valid" qualification tests. To Case and Clark the issue was whether the employer chose a particular job qualification *because* he believed it would bring him better employees or *because* he believed it would help him exclude applicants based on their race, color, religion, sex or national origin. *See also* Case & Clark Memorandum, 110 Cong. Rec. 7247 (Title VII "expressly protects the employer's right to insist that any prospective applicant, Negro or white, must meet the applicable job qualifications. Indeed, the very purpose of Title VII is to promote hiring on the basis of job qualifications, rather than on the basis of race or color.").

Congress's intention to outlaw only discriminatory treatment and not disparate impact is made clear from Title VII's central prohibition, which bans discrimination against any individual "because of such individual's race, color religion, sex, or national origin." As Richard K. Berg, one of the government lawyers who worked on Title VII's passage, wrote, to "discriminate" against an individual "because of" his "race, color, religion, sex, or national origin" always requires some level of intentionally, whether the intention is conscious or unconscious.[36]

But just in case Section 703 were to be misinterpreted, the bill was amended in the Senate at the insistence of Republican Leader Everett Dirksen—without whose support the bill likely never would have gotten past the Southern filibuster. Dirksen insisted on adding the word "intentionally" to Section 706(g), which deals with judicial power to enforce the prohibitions of Section 703. As modified, Section 706(g)(1) read:

> (1) If the court finds that the respondent has intentionally engaged in or is intentionally engaging in an unlawful employment practice charged in the complaint, the court may enjoin the respondent from engaging in such unlawful employment practice, and order such affirmative action as may be appropriate, which may include, but is not limited to, reinstatement or hiring of employees, with or without back pay . . . , or any other equitable relief as the court deems appropriate. . . .

42 U.S.C. sec. 2000e-5(g)(1).

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[36] *See* Richard K. Berg, Equal Employment Opportunity Under the Civil Rights Act of 1964, 31 Brook. L. Rev. 62, 71 (1964) ("Discrimination is by its nature intentional. It involves both an action and a reason for the action. To discriminate 'unintentionally' on grounds of race . . . appears a contradiction in terms").

In explaining why the term "intentionally" was added here, Senator Hubert Humphrey said, "Section 706(g) is amended to require a showing of intentional violation of the title in order to obtain relief. . . . The expressed requirement of intent is designed to make it wholly clear that inadvertent or accidental discrimination will not violate the title or result in entry of court orders." 110 Cong. Rec. 12,723-28 (1964).[37]

In addition, by denying the newly-created EEOC both substantive rulemaking authority and to issue cease and desist orders, Title VII's Congressional supporters attempted to ensure Title VII's reach could not be expanded. The power to issue regulations might be interpreted to authorize limited prophylactic measures, and Congress evidently wished to make it clear that Title VII was already as broad as they intended it to be. The EEOC was to be a mediating agency *only*.

But EEOC officials soon began issuing guidances as an alternative to substantive regulations. Alfred W. Blumrosen, BLACK EMPLOYMENT AND THE LAW 52 (1971). Given most employers' eagerness to stay on the right side of the law, these guidances can be as effective (or even more effective) as regulations at influencing employer practices. An advantage from the EEOC's perspective is that they are not subject to notice and comment requirements and thus tend to receive less public scrutiny or government oversight. They are also difficult to challenge in court.[38] They are, of course, supposed to be interpretations of the Act and not extensions of it. But in practice the EEOC went much further.

Blumrosen, the EEOC's first "Chief of Conciliations" and disparate impact liability's primary architect, was unabashed in describing the extent to which the EEOC was (and in his view should be) aggressive in its interpretation of Title VII:

> Creative administration converted a powerless agency operating under an apparently weak statute into a major force for the elimination of employment discrimination. . . . [Legal education] rarely deals with the affirmative aspects of administration. Rather, the law schools provide elaborate intellectual equipment to *restrict* the efforts of administrators. Constitutional law and administrative law are still largely concerned with what government may not do, rather than with how it should decide what it may do. Students impatient with the negativism of present legal education would be better equipped as lawyers if they would focus sharply on the question of "how we can best fulfill the purposes which brought our agency into being" rather than on the question of "whether the courts will sustain this course of action."

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[37] Dirksen's amendment and Humphrey's explanation are not in perfect harmony, since the amendment applied only to judicial remedies, while Humphrey's explanation applies generally. Dirksen might possibly have intended to foreclose courts from intervening even in the case of unconscious disparate treatment and to leave such cases entirely to the EEOC's mediation efforts. An employer who engaged in unconscious discrimination would essentially be allowed "one free bite." If the employer continued its practices after EEOC mediation efforts, it would be difficult for the employer to maintain that its actions were unconscious.

[38] The fact that Title VII makes EEOC investigations and mediations confidential, 42 U.S.C. 2000e-8(e), adds to the degree to which EEOC policymaking has tended to escape both public scrutiny and government oversight.

Id. at 53 (emphasis in original).

Blumrosen was part of the generation of civil rights policymakers profoundly influenced by the turbulence of the late 1960s—something that is easy to forget today. He urgently pushed the EEOC to interpret Title VII with an eye toward effectuating what he perceived as a higher purpose—increasing African-American employment as quickly as possible—rather than with an eye towards what the courts would be likely to uphold as consistent with Congressional intent as well as the statute's text. In particular, he pushed a "disparate impact" approach to Title VII. Under it, employer intent didn't matter. If, given the job qualification required by an employer, proportionately fewer African Americans than whites qualify, the employer is in violation of Title VII unless it can demonstrate that it essentially had no choice.

Historian Hugh Davis Graham wrote concerning this period in the EEOC's history:

> "The EEOC legal staff was aware from the beginning that a normal, traditional, and literal interpretation of Title VII could blunt their efforts [based on disparate impact theory] against employers who used either professionally developed tests or *bona fide* seniority systems. The EEOC's own official history of these early years records with unusual candor the commission's fundamental disagreement with its founding charter, especially Title VII's literal requirement that the discrimination be intentional."

Hugh Davis Graham, THE CIVIL RIGHTS ERA: ORIGINS AND DEVELOPMENT OF NATIONAL POLICY at 248-49 (1990).

In *Griggs v. Duke Power Co.*, the Supreme Court deferred to the EEOC's disparate impact approach to Title VII liability. It held, therefore, that under Title VII, "practices, procedures, or tests neutral on their face, *and even neutral in terms of intent*, cannot be maintained if they operate to 'freeze' the status quo of prior discriminatory employment practices." *Id.* (emphasis supplied). "The touchstone is business necessity," it stated. "If an employment practice which operates to exclude Negroes cannot be shown to be related to job performance, the practice is prohibited." *Id.* at 431.[39]

As explained above, this was certainly a misinterpretation of Title VII. *See* Hugh Davis Graham, THE CIVIL RIGHTS ERA: ORIGINS AND DEVELOPMENT OF NATIONAL POLICY at 387 (1990)("Burger's interpretation in 1971 of the legislative intent of Congress in the Civil Rights Act would have been greeted with disbelief in 1964"); Daniel Rodriguez & Barry R. Weingast, *The Positive Political Theory of Legislative History: New Perspectives on the 1964 Civil Rights Act and Its Interpretation*, 151 U. Penn L. Rev. 1417 (2003) (also arguing that the 88th Congress would have been astonished at the result in *Griggs*).

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[39] The facts of Griggs may well have involved intentional discrimination. But if so, it should have been incumbent upon the plaintiffs to prove their case on that theory.

After *Griggs*, Title VII was interpreted to demand two things: (1) Employers must provide equality of opportunity to all persons regardless of race, color, sex, religion or national origin (the traditional interpretation of Title VII); and (2) In deciding upon job qualifications, employers must provide at least equal results for women and minorities unless they can prove they were driven by business necessity to do otherwise (the disparate impact interpretation). For decades, few remarked on it, but these dual requirements were at war with each other from the beginning. Equality of treatment and equality of results are very different.[40]

One problem with disparate impact theory is that all job qualifications have a disparate impact. It is no exaggeration to state that there is always some protected group that will do comparatively poorly with any particular job qualification. As a group, men are stronger than women, while women are generally more capable of fine handiwork. Chinese Americans and Korean Americans score higher on standardized math tests and other measures of mathematical ability than most other ethnic groups. Subcontinental Indian Americans are disproportionately more likely to have experience in motel management than Norwegian Americans, who more likely have experience growing durum wheat. African Americans are over-represented in many professional athletics as well as in many areas of the entertainment industry. Unitarians are more likely to have college degrees than Baptists. *See Watson v. Fort Worth Bank & Trust*, 487 U.S. 977 (1988)(recognizing that disparate impact liability applies to subjective as well as objective job qualifications).

Some of the disparities are surprising. Cambodian Americans are disproportionately likely to own or work for doughnut shops and hence are more likely to have experience in that industry when it is called for by an employer. *See* Seth Mydans, *Long Beach Journal: From Cambodia to Doughnut Shops*, N.Y. Times, May 26, 1995. The reasons behind other disparities may be more obvious: Non-Muslims are more likely than Muslims to have an interest in wine and hence develop qualifications necessary to get a job in the winemaking industry, because Muslims tend to be non-drinkers.

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[40] The problem was compounded by establishing a stringent standard of proof for "business necessity" that few employers can dream of achieving in *Albemarle Paper Co. v. Moody*, 422 U.S. 405 (1975). The employer there had hired an expert industrial psychologist to conduct a validation study to justify its use of standardized tests to hire and promote its employees. But the Court found the expert's report was not sufficiently scientifically rigorous. Among other things, the job qualifications had not been validated at the micro-level, i.e. for each of an employer's job categories. But it is nearly impossible for any but the largest employers to generate enough data for statistically significant validation studies. Under *Albemarle*, unless a bank could scientifically prove that high-school graduates make better tellers than high-school dropouts, it could not require a high-school diploma for tellers, since proportionally more whites than African Americans possess such a diploma. Indeed, its proof would have to apply specifically to its own tellers, including its minority tellers, not just to tellers in general. It was Justice Blackmun in his concurrence who tentatively sounded the alarm: "I fear that a too-rigid application of the EEOC Guidelines will leave the employer little choice, save an impossibly expensive and complex validation study, but to engage in a subjective quota system of employment selection." 422 U.S. at 449 (Blackmun, J., concurring in the judgment). While *Wards Cove Packing Co. v. Atonio*, 490 U.S. 642 (1989), appeared to overrule *Albemarle*, the Civil Rights Act of 1991 restored the law to its pre-*Wards Cove* condition.

The result is that the labor market is anything but free and flexible. At any moment, the EEOC—an agency Congress designed to have very limited power—can declare an employer's long-standing job requirements to be a violation of Title VII.[41]

The upshot of this is that hiring and firing practices must be shrouded in secrecy. Employers seldom advertise clear job qualifications for fear they will attract a lawsuit. Performance tests, indeed any kind of innovative hiring practices, are invitations to a lawsuit. Wise employers try to be on good terms with the EEOC, knowing that when everything is potentially illegal, the name of the game is to avoid antagonizing the regulator.

Passing any version of the employment discrimination legislative proposal discussed in this Report can only make the problem worse. Even the proposed Employment Non-Discrimination Act of 2013, which specifically eschews the application of disparate impact liability, has the problem. By defining "gender identity" as "the gender-related identity, appearance, or mannerisms or other gender-related characteristics of an individual, with or without regard to the individual's designated sex at birth," the proposal embeds disparate impact into the proposal's core prohibition.

There is no way to define "gender-related" mannerisms and characteristics except by disparate impact. Not all women wear make-up or skirts, but those characteristics are more commonly associated with women than with men. Not all men sing baritone, have short hair, enjoy watching sports on television, own guns, or wear boxer shorts, but these are all characteristics that are to a greater or lesser extent more common among men than among women.

If a statute prohibits employers from discriminating on the basis of characteristics that have a disparate effect on men and women, there is no need for a separate ability to bring lawsuits based on a disparate impact theory.

II. DATA ARE NOT ALWAYS ACCURATELY AND FAIRLY PRESENTED IN THIS REPORT

There is a lot that is wrong with this Report simply from the standpoint of accurately and fairly reporting the facts. Consider, for example, the very first sentence of the very first section: "American employees spend the majority of our awake hours at work." That isn't true.[42] Assuming

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[41] Note that disparate impact liability applies to promotions and terminations too. *See George v. Farmers Electric Cooperative, Inc.*, 715 *F.2d* 175 (5th Cir. 1983); *Wilmore v. Wilmington*, 699 *F.2d* 667 (3d Cir. 1983).

[42] Bureau of Labor Statistics, Department of Labor, American Time Use Survey—2016 Results (June 27, 2017), *available at* https://www.bls.gov/news.release/pdf/atus.pdf. The data in that report don't make it easy to calculate exactly how much time American employees spend at work. But it is possible to see or to calculate from Table 4 that full-time workers were 77% of all American workers. They worked just a hair over 5 days a week and an average of 8.15 hours per day on the days they worked (for a total of approximately 40.75 hours). Part-time workers were 33% of the workforce. On average they worked slightly less than 4 days per week and averaged 5.34 hours on the days that they worked.

that the typical American employee sleeps 8 hours a day, that leaves 112 waking hours per week. Assuming a 5-day, approximately 40-hour work week, that is less than half, even before one figures in holidays and vacations. Once one figures in part-time work, the sentence isn't close to true. The point is trivial . . . but it doesn't fill one with a lot of confidence to start the Report that way.[43]

Other errors are somewhat less trivial. Accurately reporting the results of the 2013 survey conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics somehow got botched. The report states that "3.4 percent of Americans identify themselves as gay or lesbian (1.6%), bisexual (0.7%) or 'something else' (1.1%)." The correct figures are that 2.5% percent of Americans identify themselves gay or lesbian (1.6%), bisexual (0.7%) or "something else" (0.2%).[44] Two additional categories were "I don't know" (0.4%) and refused to provide an answer (0.6%).

There are likely more such errors. But I have time to describe only one significant area. Perhaps the most troubling aspect of the report's use of data what looks a bit like a purposeful effort to hide the ball concerning income disparities. In the portion of the report entitled "Economic Impacts from Workplace Discrimination," the report recites, "On average gay men earn from 10 to 32 percent less than similarly qualified heterosexual males."[45] Rep. at 14.[46] By itself, that figure may

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[43] After I handed in my Statement (and apparently as a result of my criticism), this problem was corrected (along with several other corrections). It is extremely unusual to make anything other than formatting changes to reports that have already voted on by the Commission, since corrected reports need to be resubmitted to the Commission.

[44] The material in the text is as of the date the Commission approved the report. After the due date of the Commission's statements, but before the deadline for rebuttal material, I learned that the staff planned to alter the passage to read, "A 2013 survey conducted by the Center for Disease Control and Prevention's National Center for Health Statistics found that 3.4 percent of Americans identify themselves as gay or lesbian (1.6 percent), bisexual (0.7 percent) or 'other' (1.1 percent)." This is still wrong. Individuals who refuse to answer the question (0.6 percent) or who have reported that they don't know (0.4 percent) did not "identify" themselves as "other." Even those who identify themselves as "something else" may simply mean that they are celibate. Beyond all this, the staff should never make substantive changes to a report after it has been adopted by the Commission without a Commission vote to accept those changes.

[45] When the Report says these studies compare gay men to "similarly qualified heterosexual males" it means that they controlled for things like whether the individuals covered in the study had a high school diploma, some college, a college degree or advanced degree and whether they reside in a metropolitan area. The studies also attempt roughly to control for broad job categories. Only then do the numbers begin to suggest that gay men might be "underpaid" relative to heterosexual men.

But the qualifications controlled for are far too rough to be fair. Not all college degrees are equal. An electrical engineering or computer science degree will ordinarily result in a much higher starting salary than a degree in psychology or communications.

Similarly, the efforts to control for job category are rudimentary. For example, one article divided up individuals into "executive," "specialist," "low-skilled workers," and "everyone else." Nathan Berg & Donald Lien, Measuring the Effect of Sexual Orientation on Income: Evidence of Discrimination?, 20 Contemp. Econ. Pol'y 394 (2002)(Berg & Lien also controlled for race, experience, experience squared, union membership, region of the country, urban status and educational attainment). *See also* John M. Blandford, The Nexus of Sexual Orientation and Gender in the Determination of Earnings, 56 Indus. & Lab. Rel. Rev. 622, 638-39 (2003)(making the point that controls for job category are rudimentary in these studies).

[46] Curiously, the Report does not cite the actual studies it (indirectly) is referring to. Rather, it cites an article that attempts to summarize those studies. Rep. at 14, n.70 (citing M.V. Lee Badgett, Holming Lau, Brad Sears, Deborah

seem to some to indicate discrimination. But a closer examination shows that things are much more complicated.[47]

The Report's sin is one of omission. First of all, it fails to make clear that comparisons between lesbians and heterosexual women run strongly in the opposite direction: ***On average, lesbians substantially out-earn heterosexual women.*** Instead, the Report states only that several studies "*show that lesbian or bisexual women* ***do not earn less*** *than heterosexual women*." Rep. at 50 (boldface added).

For example, in *The Nexus of Sexual Orientation and Gender in the Determination of Earnings*, among full-time workers, the median income for Lesbian/Bisexual women was almost 18% more than that for married or unmarried women.[48] Similarly, *An Investigation into Sexual Orientation Discrimination as an Explanation for Wage Differences* found "women living with partners of the same sex tend to have higher earnings than otherwise similar women."[49] *The Earnings Effects of Sexual Orientation* came to a similar conclusion—that lesbian/bisexual orientation is associated with about a 20% wage premium.[50] There is no shortage of such studies.[51] In *Measuring the Effect*

Ho, Bias in the Workplace: Consistent Evidence of Sexual Orientation and Gender Identity Discrimination, Williams Institute (June 2007), *available at* https://williamsinstitute.law.ucla.edu/research/discrimination/bias-in-the-workplace-consistent-evidence-of-sexual-orientation-and-gender-identity-discrimination/.

[47] Gay men are more likely to have college and advanced degrees than heterosexual men. In addition, gay men are more likely to live in metropolitan areas, where wage scales are higher (and living expenses are also higher). *See, e.g.*, Christopher Carpenter, Samuel Eppink, Does it Get Better? Recent Estimates of Sexual Orientation and Earnings in the United States, *available at* http://onlinelibrary.wiley.com/doi/10.1002/soej.12233/full. The studies referred to by the Report attempt to control for these factors. Some early surveys found that gay men out-earn heterosexual men when such factors are not controlled for. *See, e.g.*, Steve Teichner, Results of Polls, San Francisco Examiner A-19 (June 6, 1989).

[48] John M. Blandford, The Nexus of Sexual Orientation and Gender in the Determination of Earnings, 56 Indus. & Lab. Rel. Rev. 622, 633 (2003). Comparisons are between full-time workers.

[49] Suzanne Heller Clain & Karen Leppel, An Investigation into Sexual Orientation Discrimination as an Explanation for Wage Differences, 33 Applied Econ. 37 (2001). Heller & Leppel noted that Badgett came to the opposite conclusion in 1995 (*i.e.* that lesbian and bisexual women earned less than heterosexual women). They state, however, that Badgett's "finding was not consistently statistically significant across specifications" and that "Badgett's sample included only 34 (4.9%) lesbian or bisexual women, . . . so insignificant results are not surprising." *Id.* at 37. *See* M.V. Lee Badgett, The Wage Effects of Sexual Orientation Discrimination, 48 Indus. & Lab. Rel. Rev. 726 (1995).

[50] Dan A. Black, Hoda R. Makar, Seth G. Sanders & Lowell J. Taylor, The Earnings Effects of Sexual Orientation, 56 Indus. & Lab. Rel. Rev. 449, 463 (2003)("Lesbian/bisexual orientation appears to raise earnings of women by about 20%, a result that is both economically and statistically significant"). Comparisons are between full-time workers. "While gays and lesbians had levels of education similar to those of their heterosexual counterparts, they were half as likely to be married, they were more likely to live in the West and Northeast, and they were more likely to live in large cities. Following Badgett, we use regression analysis to control for these background differences." *Id.* at 452.

[51] *See* Christopher S. Carpenter, Self-Reported Sexual Orientation and Earnings: Evidence from California, 58 Indus. & Lab. Rel. Rev. 258, 263 (2005)("[L]esbian full-time workers report higher average earnings last month ($3,816) than do female unmarried bisexuals ($3,247), married bisexuals ($3,329), unmarried heterosexuals ($3070), or married heterosexuals ($3,631)"). This California-based study had interesting results for men too: Gay men earned more than heterosexual men. The authors wrote: "Among full-time working men, married straight men report the highest average earnings last month, $5,207, followed by gay men ($4,504), bisexual married men ($4,076), unmarried straight men ($3,518), and unmarried bisexual men ($3,382)." *Id.* at 263. But if one combines the heterosexual married men (n=8,810) and heterosexual unmarried men (n=7,158) categories, one gets an average

of Sexual Orientation on Income: Evidence of Discrimination?, the authors found that lesbians, on average, earn more than 30% more than heterosexual women.[52]

Why is that important? The data on lesbian earnings put the data on gay men's earnings in an entirely different light. The Report asks us to take a leap of logic. It tries to suggest that if, once certain basic credentials are controlled for, heterosexual men earn more than gay men, then it must be because of discrimination against gay men. But if lesbians substantially out-earn heterosexual women after such rudimentary controls are put into place, ***there needs to be an explanation for why. If we are to assume adjusted wage disparities prove gay men are being discriminated against, employers discriminate against gay men, then why don't we assume that employers are discriminating in favor of lesbians?*** The most logical explanation for all this is that the initial premise is wrong and that there is a lot more going on with these numbers than discrimination. Indeed, discrimination may not be playing any role at all.

The Report paraphrases Badgett et al. for its attempt at an explanation for why lesbians, in the Report's language "do not earn less than heterosexual women":

> Badgett et al., argue that this does not imply the absence of employment discrimination. They argue that these findings suggest that since lesbians may not be constrained by the same gender expectations that result from being in relationships with men, they may make different decisions than heterosexual women (*e.g.* choosing to delay or not have children, invest more into training, go into male-dominated professions) which may hide effects of discrimination.

Report at 48.

Well, yes, of course. But the Report doesn't seem to realize it has given away the store. Just as lesbians may make different career choices, so might gay men. They may choose a career in nursing instead of a career in mechanical engineering. They may choose not to work overtime in order to earn the money necessary to put a down payment on a five-bedroom house that will fit the children. They may choose to engage in a high-risk entrepreneurial activity—like opening a new restaurant—because they don't expect to be having to support a family in the near future. Just as the fact that lesbians earn more than heterosexual women doesn't eliminate the possibility that they have been discriminated against, the fact the gay men earn less (at least after rudimentary

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income for heterosexual men of $4,450, which is less than the income for gay men (although greater than the income for the two bisexual categories).

[52] Nathan Berg & Donald Lien, Measuring the Effect of Sexual Orientation on Income: Evidence of Discrimination?, 20 Contemp. Econ. Pol'y 394 (2002). *See also* Christopher S. Carpenter & Samuel T. Eppink, Does It Get Better?: Recent Estimates of Sexual Orientation and Earnings in the United States, 84 Southern Econ. J. 426, 426 (2017)(calling the finding that self-identified lesbians earn significantly more than comparable heterosexual women "well-documented" and reproducing that finding yet again).

controls are used) doesn't prove they have been discriminated against. There can be lots of other explanations.

If we want to understand the situation, we need to be looking at the different jobs that gay and heterosexual men are undertaking. There is certainly evidence gay men are disproportionately attracted to certain jobs. "Numerous scholars have noted the disproportionately high number of gay and lesbian workers in certain occupations" and that "common to both gay men and lesbians is a propensity to concentrate in occupations that provide task independence or require social perceptiveness, or both."[53]

We also need to be looking at differences in college major choice. It is not easy to come up with solid empirical data on the differences in college major choices between gay and heterosexual men. But there is lots of data about the differences in college major choices between women and men. For example, according to the American Enterprise Institute, electrical engineering majors (82% of whom are male) can expect to earn an average of $70,000 in their first 5 years of work. By contrast, psychology majors (only 23.3% of whom are male) can expect only $42,000.[54] Given these differences, it would be surprising if gay and heterosexual men made precisely the same college major choices.[55]

In addition, we need to know which households are rearing children. Who has primary responsibility for providing monetary support for children and who doesn't? Who has primary responsibility for providing direct supervision for children?

The kind of information necessary to undertake such a study is hard to come by. But that is why President Eisenhower and the 85th Congress established the Commission in the first place—in order to conduct research on civil rights issues that otherwise might not get undertaken. Instead of conducting that research, the Commission chose to simply present other people's research on income disparities without proper context.

Here is what John Blandford had to say on the subject in *The Nexus of Sexual Orientation and Gender in the Determination of Earnings* (a study that found both that gay/bisexual men are paid

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[53] Andras Tilcsik, Michel Anteby, and Carly R. Knight, "Concealable Stigma and Occupational Segregation: Toward a Theory of Gay and Lesbian Occupations, 60 Administrative Science Quarterly 446 (2015), *available at* http://www.michelanteby.net/files/manteby/files/concealable_stigma.pdf. Although Tilcsik et al. argue that bias against gays does influence these preferences—*e.g.* people who are concerned about being discriminated against are more likely to prefer occupations where they are often able to work independently—the mechanism described in their study is more complex than simple "discrimination drives gays out of certain jobs."

[54] Mark J. Perry, Highest-Paying College Majors, Gender Composition of Students Earning Degrees in those Fields and the Gender Pay Gap, American Enterprise Institute (October 19, 2016), *available at* http://www.aei.org/publication/highest-paying-college-majors-gender-composition-of-students-earning-degrees-in-those-fields-and-the-gender-pay-gap/.

[55] I am not aware of any claims that major choices of gay and heterosexual males are identical. But most of the discussions of the issue involve at least in part informal observations. *See* Manil Suri, Why Is Science So Straight?, N.Y. Times (September 4, 2015).

less than heterosexual men and that lesbian/bisexual women are paid more than heterosexual women):

> The evidence described in this study strains the credibility of the argument that measured wage differentials between heterosexual workers and gay, lesbian, and bisexual workers are owing solely to workplace attitudes about homosexuality. Defending that explanation would require explaining how workplace attitudes could penalize non-heterosexual male workers while simultaneously awarding lesbian and bisexual female workers with a substantial premium. Certainly, workplace attitudes toward sexual orientation may have a gender component; that is, bias against homosexuality and bisexuality may be more strongly expressed against persons of one gender than of another. Nonetheless, it seems unlikely that the wage effects would differ in sign rather than merely in magnitude.
>
> A more probable explanation for the disparate earnings effects of sexual orientation across genders may be found in treating workplace bias as but one orientation-related factor influencing earnings outcomes. Workplace bias that might negatively affect the wages of lesbian and bisexual women appears to be offset by other labor market factors. Most influential among these factors are subtle occupational clustering effects not adequately captured by the two-digit controls in this study or by the one-digit controls employed elsewhere (Badgett 1995). Case-level analysis of occupational patterns associated with sexual orientation points to trends that are both highly nuanced and gender-specific, suggesting that parameter estimates may over-estimate the direct effect of orientation on earnings. Lesbian and bisexual women are revealed to be unusually successful in gaining employment in largely male-dominated—and typically better-remunerated—occupational categories. For gay and bisexual men, in contrast, over-representation in female-identified occupations likely further depresses returns to human capital attributes relative to other male workers.[56]

There are further anomalies in the literature that should give pause those who would rush to judgment about the prevalence of discrimination. For example, among heterosexual males, married men, cohabiting men, and single men have been repeatedly shown to earn very different wages, with married men far outdistancing cohabiting men who in turn do better than single men.[57] And this is true even when age (or years of work experience) and other factors are controlled for. Yet few argue that the differences are caused by discrimination.

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[56] John M. Blandford, The Nexus of Sexual Orientation and Gender in the Determination of Earnings, 56 Indus. & Lab. Rel. Rev. 622, 638-39 (2003).

[57] *See, e.g.*, Sylvia A. Allegretto & Michelle M. Arthur, An Empirical Analysis of Homosexual/Heterosexual Male Earnings Differentials: Unmarried and Unequal?, 54 Indus. & Lab. Rel. Rev. 631 (2001)(finding that gay men in unmarried partnered relationships earn on average 15.6% less than otherwise similar married heterosexual men, but the come in only 2.4% lower than otherwise similar unmarried partnered heterosexual men); Donna K. Ginther & Madeline Zavodny, Is the Male Marriage Premium Due to Selection?: The Effect of Shotgun Weddings on the Return to Marriage, 14 J. Population Econ. 313 (2001); Sander Korenman & David Neumark, Does Marriage Really Make Men More Productive?, 26 J. Human Res. 282 (1991).

The premium for married men over single or co-habiting men is comparable to the gap between gay and heterosexual men. Yet no one has ever suggested that the reason is that employers are discriminating against co-habiting men or single men. The actual reasons are likely more complex. Among them we might find the following: (1) High-income men have an easier time finding women willing to marry them; (2) The same attributes that are conducive to success in creating and maintaining stable relationships at home are also conducive to success in one's professional life and; (3) Men who have or plan to have children are more likely to seek out higher paying jobs and work long hours to support them rather than seek out the jobs they find most interesting or spend their extra time at leisure activities.

Finally, it is important to point out that the most recent empirical studies on income disparities between gay and heterosexual men have been turning out very different from the studies cited in the article that the Report cites for its conclusion that "on average gay men earn from 10 to 32 percent less than similarly qualified heterosexual males." Indeed, the most recent empirical study of which I am aware—*Does It Get Better?: Recent Estimates of Sexual Orientation and Earnings in the United States*—comes to precisely the opposite conclusion: ***Gay men employed full time on average earn almost 10% more than comparable heterosexual men***. [58]

The findings of that study—conducted by Christopher Carpenter and Samuel T. Eppink—are broadly consistent with some other recent research. For example, in *The Disappearing Gay Income Penalty*, Geoffrey Clarke and Purvi Sevak examined data from the National Health and Nutrition Examination Surveys (NHANES) from 1988 to 2007.[59] They found that while men who reported same-sex sexual activity had lower household income than otherwise similar heterosexual men during the earlier part of the time frame they examined, by the end of that time frame the situation was reversed with the average gay man's earnings topping those of similar heterosexual men. Similarly, Marieka Klawitter's meta-analysis of all published studies on sexual orientation and earnings indicated that both the lesbian premium and gay male penalty were decreasing over time.[60]

One possible explanation for the disappearing wage penalty for gay men is that the stigma associated with being gay. As Carpenter & Eppink put it:

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[58] This finding was significant at 5%. Christopher S. Carpenter & Samuel T. Eppink, Does It Get Better?: Recent Estimates of Sexual Orientation and Earnings in the United States, 84 Southern Econ. J. 426, 432, tbl. 2 (2017). The authors were working with a database in which individuals had self-identified as either gay, bisexual, other sexual orientation, do not know sexual orientation, or heterosexual, had refused the sexual orientation question, or the sexual orientation information was missing from the data. They controlled for the month of the year in which the answers were given. They also controlled for age and its square, race, Hispanic ethnicity, level of educational attainment, relationship status, young children in the household, older children in the household, region of the country, number of years on the job and its square, firm size, and sector of employment. They also used 26 industry dummies and 26 occupation dummies.

[59] Geoffrey Clarke & Purvi Sevak, The Disappearing Gay Income Penalty, 121 Econ. Letters 542 (2013).

[60] Marieka Klawitter, Meta-Analysis of the Effects of Sexual Orientation on Earnings, 54 Indus. Rel.: J Econ. & Soc'y 4 (2015)(analyzing all such studies up until 2012).

> Improved attitudes toward the lesbian, gay, bisexual, and transgender (LGBT) communities have been some of the most striking and rapid social changes in the United States in the past several decades. These improved attitudes are perhaps most evident in the well-documented shift in public attitudes regarding same-sex marriage: The proportion of adults in the United States who favored same-sex marriage increased from 35 to 55% from 2001 to 2016, the year after the U.S. Supreme Court granted nationwide legal access to same-sex marriage in *Obergefell v. Hodges* in 2015. And historical data from the General Social Survey suggest that these shifts in attitudes began in the early 1990s: while in 1991 fully 72% of adults considered homosexual behavior "always wrong," the associated share reporting this view in 2010 fell to 44%. The share of adults saying homosexual behavior was "not wrong at all" increased over this same period from 14 to 41%.[61]

Ultimately, however, Carpenter & Eppink express doubt that changing attitudes is what is behind their result. They point out that changing attitudes might be expected to decrease the "penalty" for gay men's earnings, but it is not clear why it would produce a premium or why gay men would continue to have lower employment rates than heterosexual men. In addition, changing attitudes would be expected to help lesbians too (by increasing the premium they have over heterosexual women). Yet the findings in the article are instead that the premium has continued at pretty much the same level.[62]

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[61] Carpenter & Eppink at 426.
[62] Carpenter & Eppink at 436.

Rebuttal of Commissioner Peter Kirsanow

Commissioner Yaki writes: "Our nation's LGBT population has a vulnerability unique among all those ***whom the Commission is mandated to protect***: it is the only class ***under our jurisdiction*** which lacks the shelter of at least one powerful, civilian, federal statutory protection."[1]

This is wrong. LGBT matters as such are not within the Commission's jurisdiction, which is one reason the Commission had not examined this issue before. The Commission's authorizing statute provides, "The Commission shall investigate allegations in writing under oath or affirmation relating to deprivations—because of color, race, religion, sex, age, disability, or national origin; or as a result of any pattern or practice of fraud; of the right of citizens of the United States to vote and have votes counted".[2] Sexual orientation or gender identity are nowhere mentioned. I understand that my colleagues think this is an important issue that needs to be addressed.[3] Fair enough. But it is not within our jurisdiction.[4]

Constitutional and Secular Concerns Regarding ENDA

It is indisputable that some individuals hold positions regarding LGBT issues out of pure animus. It is also indisputable that there is no system equivalent to Jim Crow that is designed to prevent LGBT people from participating in society. The Commission majority's findings testify to this fact:

> It has not been difficult for some private companies to adopt and implement workplace policies or practices that prohibit discrimination on the basis of sexual orientation and/or gender identity. As of 2016, 92 percent of Fortune 500 companies included sexual orientation and 82 percent included gender identity in their equal employment opportunity policies. Businesses that support these policies note such practices are beneficial to their businesses by attracting the most qualified workforce and increasing productivity.[5]

Had such an overwhelming majority of companies voluntarily adopted similar policies regarding race in 1964, passage of Title VII of the 1964 Civil Rights Act would have been far less

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[1] Statement of Commissioner Yaki at 90.

[2] 42 U.S.C. § 1975a.

[3] Statement of Commissioner Karen Narasaki at851 ("international human rights laws complement and reinforce our nation's laws by recognizing that 'all human beings are born free and equal in dignity and rights' and therefore LGBT people are entitled to the numerous protections afforded by human rights laws, including the right to be free from discrimination."). It doesn't really matter what international human rights laws say. We are the *Civil* Rights Commission, not the *Human* Rights Commission, and our jurisdiction extends only to the *civilly*-recognized rights listed in our originating statute.

[4] Before Commissioner Yaki cites *Pricewaterhouse* and "sexual orientation discrimination as sex-stereotyping discrimination" to me, *see* discussion of *Pricewaterhouse*, *infra* at 141-43.

[5] Commission Findings at 76; *see also* Statement of Commissioner David Kladney at 83-84.

consequential. Indeed, if EEO policies had so abounded in the early Sixties, passage of Title VII may not have been a legislative imperative. As Roger Clegg from the Center for Equal Opportunity stated in his testimony, it actually is unclear whether Congress has the constitutional authority to prohibit discrimination on the basis of sexual orientation or gender identity. But then, constitutionality seems an increasingly trivial impediment to government action. Congress had the authority to enact the 1964 Civil Rights Act because discrimination against African-Americans was pervasive and, in significant parts of the country, inescapable.[6] LGBT discrimination is not comparable to the pervasive racial discrimination that prompted and gave constitutional authority to passage of the 1964 Civil Rights Act.

My colleagues appear to hold that Title VII ought to evolve into a "general civility code," which the Supreme Court sought to avoid in its decision in *Oncale v. Sundowner*.[7] The Supreme Court cautioned in *Oncale* that any sex-discrimination claims brought under Title VII must be ***because of*** sex, and that "We have never held that workplace harassment, even harassment between men and women, is automatically discrimination because of sex merely because the words used have sexual content or connotations."[8] The report approvingly cites an EEOC decision that a transgender individual was discriminated against on the basis of her sex because coworkers continued to address her using masculine pronouns.[9] The problem with determining that this is discrimination on the basis of sex is the person's sex is *literally* male. It may be a breach of decorum, sensibility, civility, and good manners to refer to the person using masculine pronouns, but it is not *sex* discrimination.

The EEOC and some courts have claimed that discrimination against transgender individuals is sex discrimination prohibited by the "sex stereotyping" interpretation of Title VII, because "A person is defined as transgender precisely because of the perception that his or her behavior transgresses gender stereotypes."[10] If a person is protected by the sex stereotyping theory, it is because he or she supposedly is not conforming to gender stereotypes. For example, a man wearing makeup and a dress or a woman taking testosterone to grow a beard do not conform to gender stereotypes. But a woman would not be transgressing gender stereotypes by wearing a dress, and a man would not be transgressing gender stereotypes by growing a beard.[11] So it cannot perforce

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[6] Written Statement of Roger Clegg at 2-3.

[7] *Oncale v. Sundowner Offshore Services, Inc.*, 523 U.S. 75 (1998).

[8] *Id.* at 80. This is also strong evidence that my colleagues are wrong in interpreting our jurisdiction over sex discrimination as encompassing discrimination on the basis of sexual orientation and gender identity.

[9] *Bost v. Sam's East, Inc.*, Charge No. 430-2014-01900 (E.E.O.C. 2017), at http://transgenderlegal.org/media/uploads/doc_729.pdf.

[10] *Macy v. Holder*, 2012 WL 1435995 (E.E.O.C. 2012), at 9, *quoting Glenn v. Brumby*, 663 F.3d 1312 (11th Cir. 2011).

[11] *See E.E.O.C. v. R.G. & G.R. Funeral Homes, Inc.*, 201 F.Supp.3d 837, 840 (E.D.Mich. 2016).

(a) The EEOC claims the Funeral Home fired Stephens for failing to conform to the masculine gender stereotypes expected as to work clothing and that Stephens has a Title

be discrimination on the basis of sex to refer to a transgender person by the name or pronouns of his or her birth sex, when the only reason this person purportedly is protected by Title VII is because the person is not conforming to gender stereotypes.[12] We are in a wilderness of mirrors.

All of this reveals that it would be helpful for the Supreme Court to revisit *Pricewaterhouse v. Hopkins*, and possibly *Oncale v. Sundowner*. In recent years, *Pricewaterhouse* has been used by the EEOC and some courts to attempt to transform sexual orientation and gender identity into protected classes.[13] Abuses of authority by federal agencies are by this time unremarkable, as is judicial activism. The fact that some courts are now discovering that transgenderism is encompassed within Title VII and Title IX[14] should alert everyone that they are legislating from the bench.[15]

> VII right *not to be subject to gender stereotypes* in the workplace. Yet the EEOC has not challenged the Funeral Home's sex-specific dress code, that requires female employees to wear a skirt-suit and requires males to wear a pants-suit with a neck tie. Rather, the EEOC takes the position that Stephens has a Title VII right to "dress as a woman" (*i.e.*, dress in a stereotypical feminine manner) while working at the Funeral Home, in order to express Stephens's gender identity. If the compelling interest is truly in eliminating gender stereotypes, the Court fails to see why the EEOC couldn't propose a gender-neutral dress code as a reasonable accommodation that would be a *less restrictive* means of furthering that goal under the facts presented here. But the EEOC has not even discussed such an option, maintaining that Stephens must be allowed to wear a skirt-suit in order to *express* Stephens's gender identity. If the compelling governmental interest is truly in *removing or eliminating* gender stereotypes in the workplace in terms of clothing (*i.e.*, making gender "irrelevant"), the EEOC's chosen manner of enforcement in this action does not accomplish that goal.

[12] As the Eastern District of Michigan has noted, this is because "As a practical matter, the EEOC . . . has been proceeding as if gender identity or transgender status is a protected class under Title VII," when this is most assuredly not the case. *E.E.O.C. v. R.G. & G.R. Funeral Homes, Inc.*, 201 F.Supp.3d 837, 860 (E.D. Mich. 2016).

[13] *Fabian v. Hospital of Central Conn.*, 172 F.Supp.3d 509, 522-23 (D.Conn. 2016)("The acknowledgement in *Price Waterhouse* that discrimination by means of gender stereotyping is discrimination 'because of sex' under Title VII eventually led to a significant shift in the direction of decisions examining alleged discrimination on the basis of transgender identity.").

[14] *Johnston v. Univ. of Pittsburgh of Com. System of Higher Educ.*, 97 F.Supp.3d 657, 674 (W.D.Penn. 2015)("nearly every federal court that has considered the question in the Title VII context has found that transgendered individuals are not a protected class under Title VII.").

[15] Former Judge Richard Posner at least had the honesty to admit that this is what judges are doing when they transform sexual orientation and gender identity into protected characteristics. *Hively v. Ivy Tech Com. Coll. of Ind.*, 853 F.3d 339, 357 (7th Cir. 2017)(Posner, J., concurring).

> (b) The majority opinion states that Congress in 1964 "may not have realized or understood the full scope of the words it chose." This could be understood to imply that the statute forbade discrimination against homosexuals but the framers and ratifiers of the statute were not smart enough to realize that. I would prefer to say that theirs was the then-current understanding of the key word—sex. "Sex" in 1964 meant gender, not sexual orientation. What the framers and ratifiers understandably didn't understand was how attitudes toward homosexuals would change in the following half century. They shouldn't be blamed for that failure of foresight. *We* understand the words of Title VII differently not because we're smarter than the statute's framers and ratifiers but because we live in a different era, a different culture. Congress in the 1960s did not foresee the sexual

If my colleagues are correct that these policies are both easy to implement and beneficial to the bottom line, most companies will adopt these policies in short order. Many have.

But they should not be compelled into doing so by judges contorting the plain text of the law to include classifications not set forth by Congress, and by federal agencies that rewrite laws through regulations and subregulatory guidance.[16]

LGBT As A Defined Class

My colleagues and the report repeatedly refer to "LGBT" as a class. In the report and often in public discourse, there is no differentiation between the four groups. Perhaps there is no rational basis for differentiation. But the report seems to make a presumption, unsupported by any empirical analysis whatsoever, that employment and workplace considerations applicable to lesbians are identical to those applicable to gays are identical to those applicable to bisexuals are identical to those applicable to transsexuals. Yet if Congress were to pass ENDA-like legislation, there is a reasonable likelihood the four different groups would not be treated as one indistinguishable mass.

Religious Liberty Concerns Regarding ENDA

There are many people who bear no ill-will toward LGBT persons as persons, but who also, for religious reasons, and in good faith, disagree with the choice to engage in a same-sex relationship or to present as a sex other than their birth sex.[17] Religious liberty will be diminished and

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revolution of the 2000s. What our court announced in *Doe v. City of Belleville*, 119 F.3d 563, 572 (7th Cir. 1997), is what Congress had declared in 1964: "the traditional notion of 'sex.' "

(c) I would prefer to see us acknowledge openly that today we, who are judges rather than members of Congress, are imposing on a half-century-old statute a meaning of "sex discrimination" that the Congress that enacted it would not have accepted. This is something courts do fairly frequently to avoid statutory obsolescence and concomitantly to avoid placing the entire burden of updating old statutes on the legislative branch. *We should not leave the impression that we are merely the obedient servants of the 88th Congress (1963–1965), carrying out their wishes. We are not.* We are taking advantage of what the last half century has taught. [emphasis added]

[16] Commissioner Heriot has written persuasively that Title IX's prohibition on sex discrimination does not encompass gender identity. It is even less likely that Title VII includes a prohibition on gender identity discrimination. The Americans with Disabilities Act explicitly excludes transgenderism from its coverage. *See Johnson v. Fresh Mark*, 337 F.Supp.2d 996, 1001 (N.D. Ohio 2003), *quoting* 42 U.S.C. § 12211(b)(1).

[17] Russell Moore, "What the Transgender Debate Means for the Church," RussellMoore.com, Feb. 23, 2017 (Dr. Moore is the President of the Southern Baptist Convention's Ethics & Religious Liberty Commission), http://www.russellmoore.com/2017/02/23/transgender-debate-means-church/; "USCCB Committee Chairmen Applaud the Repeal of 'Dear Colleague Letter on Transgender Students," U.S. Conference of Catholic Bishops, Feb. 24, 2017 ("Pope Francis has taught that 'biological sex and the socio-cultural role of sex (gender) can be distinguished but not separated' (Amoris Laetitia, no. 56)"), http://www.usccb.org/news/2017/17-045.cfm; *E.E.O.C. v. R.G. & G.R. Funeral Homes, Inc.*, 201 F.Supp.3d 837, 848 (E.D.Mich. 2016)("It is also undisputed that Rost sincerely believes that the "Bible teaches that a person's sex (whether male or female) is an immutable God-given gift and that it is wrong for a person to deny his or her God-given sex." . . . Rost believes that he "would be violating

vulnerable if Congress enacts ENDA or similar legislation. The Commission says in its recommendations:

> The Commission strongly supports religious freedom and nondiscrimination on the basis of religion. Title VII offers a workable model for protecting religious freedom in the context of federal statutory nondiscrimination protections in the workplace. In *Hosanna-Tabor Evangelical Lutheran Church and School v. Equal Employment Opportunity Commission* the Supreme Court also unanimously endorsed the common law ministerial exemption, which recognizes the right of religious groups to select their own ministers and clergy. No further expansion of exceptions to nondiscrimination protections in the workplace are necessary or warranted to balance the rights to freedom of religion and to nondiscrimination on the bases either of religion or LGBT status.

My colleagues' individual statements suggest that "strongly supports" may be overstating the matter a bit. The Chair refers to concerns over conflicts between religious liberty and nondiscrimination as "the fallacy of that putative conflict"—before stating:

> A teacher's decision to tell a devout Catholic girl she would go to hell for dating another girl lowlights the error in the assumption that LGBT persons are not simultaneously persons of faith—and underscores the distinct (and in our system of laws profoundly unconstitutional) harm that privileging one understanding of faith over another can visit on people. The teachers and administrators at that school were and are free to disapprove of same sex relationships, and even of the status of being LGBT, on religious or other bases; they were and are not, however, free to act on that disapproval in ways that harmed the students as people or as learners. Likewise in an employment context, our laws should protect LGBT employees from discrimination while also protecting all of our religious freedom.[18]

The school to which Chair Lhamon refers is a public school.[19] I see nothing in her statement, however, that suggests that she would see the matter differently if it were at a private religious school. In his statement, Commissioner Yaki attacks recent guidance from the Attorney General, describing it as "rid[ing] the Hobby Lobby toboggan as it boldly careens down a slippery slope declaring—in the apparent absence of statutory or judicial authority—'RFRA protects the exercise of religion by individuals and by corporations, companies, associations, firms, partnerships, societies, and joint stock companies.'"[20]

God's commands" if he were to permit one of the Funeral Home's male funeral directors to wear the skirt-suit uniform for female directors while at work because Rost "would be directly involved in supporting the idea that sex is a changeable social construct rather than an immutable God-given gift.").

[18] Statement of Chair Catherine Lhamon at 81.

[19] ACLU of Southern California Stands Up for Gay and Lesbian High School Students Harassed by School Officials on Basis of Sexual Orientation, ACLU of Southern California, Oct. 28, 2004, https://www.aclusocal.org/en/news/aclu-southern-california-stands-gay-and-lesbian-high-school-students-harassed-school-officials.

[20] Statement of Commissioner Yaki at 104 (quoting U.S. Department of Justice Memorandum at 4).

Commissioner Yaki contends that the Attorney General's interpretation is not based in statutory or judicial authority. Apparently it escaped Commissioner Yaki's notice that Justice Alito's analysis in *Hobby Lobby* ***begins*** with settling RFRA's definition of a "person":

> RFRA applies to "a person's" exercise of religion, 42 U.S.C. §§ 2000bb-1(a), (b), and RFRA itself does not define the term "person." We therefore look to the Dictionary Act, which we must consult "[i]n determining the meaning of any Act of Congress, unless the context indicates otherwise." 1 U.S.C. § 1.
>
> Under the Dictionary Act, "the wor[d] 'person' . . . Include[s] corporations, companies, associations, firms, partnerships, societies, and joint stock companies, as well as individuals. *Ibid; see FCC v. AT & T Inc.*, 131 S.Ct. 1177, 1182-1183(2011)('We have no doubt that 'person,' in a legal setting, often refers to artificial entities. The Dictionary Act makes that clear"). Thus, unless there is something about the RFRA context that "indicates otherwise," the Dictionary Act provides a quick, clear, and affirmative answer to the question whether the companies involved in these cases may be heard.
>
> We see nothing in RFRA that suggests a congressional intent to depart from the Dictionary Act definition, and HHS makes little effort to argue otherwise. We have entertained RFRA and free-exercise claims brought by nonprofit corporations, *see Gonzales v. O Centro Espírita Beneficente Uniao do Vegetal*, 546 U.S. 418 (2006) (RFRA); *Hosanna-Tabor Evangelical Lutheran Church and School v. EEOC*, 132 S.Ct. 694 (2012) (Free Exercise); *Church of the Lukumi Babalu Aye, Inc. v. Hialeah*, 508 U.S. 520 (1993) (Free Exercise), and HHS concedes that a nonprofit corporation can be a "person" within the meaning of RFRA. *See* Brief for HHS in No. 13–354, at 17; Reply Brief in No. 13–354, at 7–8.
>
> This concession effectively dispatches any argument that the term "person" as used in RFRA does not reach the closely held corporations involved in these cases. No known understanding of the term "person" includes *some* but not all corporations. The term "person" sometimes encompasses artificial persons (as the Dictionary Act instructs), and it sometimes is limited to natural persons. But no conceivable definition of the term includes natural persons and nonprofit corporations, but not for-profit corporations.[20] *Cf. Clark v. Martinez*, 543 U.S. 371, 378, 125 S.Ct. 716, 160 L.Ed.2d 734 (2005) ("To give th[e] same words a different meaning for each category would be to invent a statute rather than interpret one"). [citations omitted]

In other words, the Attorney General's definition of a "person" has *both* statutory and judicial support. It is taken verbatim from the Dictionary Act, which the Supreme Court stated in Hobby Lobby provided the correct definition of "person" in RFRA.

If this is what the Commission majority thinks when it is in strong support of religious freedom, I hate to think what it thinks in its less sanguine moments. Title VII provides:

> Notwithstanding any other provision of this subchapter, (1) it shall not be an unlawful employment practice for an employer to hire and employ employees, for

> an employment agency to classify, or refer for employment any individual, for a labor organization to classify its membership or to classify or refer for employment any individual, or for an employer, labor organization, or joint labor-management committee controlling apprenticeship or other training or retraining programs to admit or employ any individual in any such program, on the basis of his religion, sex, or national origin in those certain instances where religion, sex, or national origin is a *bona fide* occupational qualification reasonably necessary to the normal operation of that particular business or enterprise, and (2) it shall not be an unlawful employment practice for a school, college, university, or other educational institution or institution of learning to hire and employ employees of a particular religion if such school, college, university, or other educational institution or institution of learning is, in whole or in substantial part, owned, supported, controlled, or managed by a particular religion or by a particular religious corporation, association, or society, or if the curriculum of such school, college, university, or other educational institution or institution of learning is directed toward the propagation of a particular religion.[21]

Title VII's protections for religious liberty require a painstaking case-by-case examination of the circumstances surrounding each claim.[22] Although the exact contours of Title VII's religious employer exemption are disputed, in some circumstances it is interpreted to apply only to cases of discrimination on the basis of religion, not discrimination on the basis of another protected characteristic that is motivated by a religious belief.[23] Under this narrow construction, a Catholic school could fire a teacher who left the Catholic faith, but could not fire a teacher who entered into a civil same-sex marriage if that teacher continued to maintain that she was a member of the Catholic faith. This appears to be what is contemplated by Professor Alan Brownstein, who explained in his written statement, "[T]he Title VII amendment permitting religious discrimination in hiring cannot justify discrimination on the basis of other characteristics prohibited by Title VII, such as race or gender. . . . Pursuant to this understanding, religious organizations operated by faiths whose beliefs condemn homosexual conduct could not discriminate against gay or lesbian job applicants on the ground that the very conduct of such individuals which identified them as members of a protected class violated the dictates of the employer's faith."[24]

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[21] 42 U.S.C. § 2000e-2(e).

[22] *Spencer v. World Vision, Inc.*, 633 F.3d 723, 729 (9th Cir. 2011)("In sum, when confronted with a section 2000e-1 case, *Townley* and *Kamehameha* require us to analyze, on a case-by-case basis, whether the 'general picture' of an organization is 'primarily religious,' taking into account '[a]ll significant religious and secular characteristics.'"); *E.E.O.C. v. Kamehameha Schools/Bishop Estate*, 990 *F.2d* 458, at n. 7 (9th Cir. 1993)("In view of the narrow reach of the § 2000e-1 exemption, it is not surprising that we have found no case holding the exemption to be applicable where the institution was not wholly or partially owned by a church.").

[23] *Herx v. Diocese of Fort Wayne-South Bend, Inc.*, 772 F.3d 1085, 1087 (7th Cir. 2014).

[24] Written Statement of Alan Brownstein at 3. It should be noted that the discrimination at issue is on the basis of behavior or conduct, not identity, status, or immutable characteristics.

There are no major faiths in the United States that include racial superiority as one of their tenets. There are likely some branches of major faiths that hold views regarding gender roles that are at odds with popular opinion.[25] The vast majority of Christians have no objections to married women working outside the home. Whether or not that would have occurred without federal interference is a fair question, and whether forcing churches to change their views regarding the roles of men and women is an appropriate exercise of governmental power is another.

This is the problem with only providing Title VII's religious exemption in an ENDA-like bill, even for religious employers. If the principal of a Catholic school fired a black Catholic school teacher because of her race, the principal's actions would not be in accord with the teaching of the Catholic Church. If the principal fired a teacher who entered into a same-sex marriage, even though the teacher claimed to be Catholic and knew that the Catholic Church teaches that same-sex marriage is not marriage at all, the principal would not be defying Catholic teaching. And the ability to fire teachers and other employees in these situations is important, because actions speak louder than words.[26] A divorced woman who remarries without receiving an annulment undercuts the Church's teaching that marriage is permanent.[27] An individual who is in a civil same-sex marriage undermines the Church's teaching regarding both the indispensability of a sacramental marriage and the necessity that the spouses be male and female. For the government to come into either case and insist that the school continue to employ the teacher because the teacher identifies as Catholic is an intrusion upon church discipline and an enervation of the faith. Perhaps, to avoid this, the Church can issue a formal excommunication to the employee, although even that is arguably not a declaration that the individual is not Catholic, but rather that he is a Catholic in bad standing. But perhaps the Church hopes to bring the individual to repent of his or her sins, and thus hesitates to impose the ultimate penalty. But the Church still cannot employ this person, because to do so appears to condone his or her *behavior* and thus cause scandal.[28] These are not questions into

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[25] Popular opinion does not always proceed in the direction one would think or prefer, however. W. Bradford Wilcox and Samuel Sturgeon, "Why would millennial men prefer stay-at-home wives? Race and feminism.", Wash. Post, Apr. 5, 2017 ("the overall trend in the GSS and another survey, Monitoring the Future, is consistent with the idea that a growing minority of younger millennials hold a more traditional view on this male breadwinner-female homemaker item.").

[26] *See Herx v. Diocese of Ft.Wayne-South Bend Inc.*, 48 F.Supp.1168, 1177 (N.D. Ind. 2014).

> (d) Mrs. Herx contends that the Diocese's admission that it didn't renew her contract because she underwent in vitro fertilization treatments creates a triable fact issue as to sex discrimination because the only people who could be terminated for that reason are pregnant women and women trying to become pregnant. . . .According to Mrs. Herx, forbidding non-ministerial employees from undergoing in vitro fertilization discriminates against women because men don't (and can't) undergo the procedure.

[27] *See Little v. Wuerl*, 929 *F.2d* 944 (3rd Cir. 1991).

[28] The term "scandal" has a particular theological meaning within the Catholic Church. *See* CATECHISM OF THE CATHOLIC CHURCH, 2284, 2286, *available at* http://www.vatican.va/archive/ENG0015/_P80.HTM.

> (e) Scandal is an attitude or behavior which leads another to do evil. The person who gives scandal becomes his neighbor's tempter. He damages virtue and integrity; he may even

which the government may intrude, because the government is essentially substituting its own judgment regarding theology and morality for that of the Church. The government is arrogating to itself the authority to decide who is a Catholic in good standing, or a Southern Baptist, or a Jew.[29] This is similar to the New York legislature enacting a statute that transferred the administration of churches from the Russian Orthodox Church to an American metropolitan district.[30] The government is weighing in on an ecclesiastical dispute because it is politically aligned with one branch of the dispute.[31] That is impermissible.[32]

If the contraception mandate included in HHS's ACA-implementing regulations taught us anything, it demonstrated that efforts to make religious organizations and institutions violate their consciences quickly descend into hair-splitting examinations of exactly who is paying for what and where to draw the lines of complicity in what a religion considers sinful behavior.

We live in a time when the country is sharply divided along almost every line imaginable—politics, race, income, sex, religion, and anything that distinguishes one human being from another. It appears there may be no way to bridge many of these divides, because the differences of opinion go the heart of what one holds most dear. My colleagues' solution is for traditionalists to capitulate to secular imperatives, even giving up the modest First Amendment right to be politically incorrect or impolite by referring to someone by the pronouns associated with his birth sex rather than his preferred gender identity.[33] My solution is more modest: follow the Constitution.

> draw his brother into spiritual death. Scandal is a grave offense if by deed or omission another is deliberately led into a grave offense. . . .
>
> (f) Scandal can be provoked by laws or institutions, by fashion or opinion.

[29] *Little* at 948.

> (g) The *Maguire* case demonstrates the even graver dangers courts face when asked to rule on religious discrimination that does not follow clear denominational lines. In that sex discrimination case, a Catholic university claimed that it had refused to hire plaintiff as a theology professor because she held views on abortion that disqualified her from being a Catholic. The court properly decided that any scrutiny of that claim would violate both the free exercise and establishment clauses.

[30] *Kedroff v. St. Nicholas Cathedral of Russian Orthodox Church in North America*, 344 U.S. 94, 97-99 (1952).

[31] *Id.* at 109-110.

[32] *Id.* at 114-115 (quoting *Watson v. Jones*, 13 Wall 728-79 (1871)).

> (h) The right to organize voluntary religious associations to assist in the expression and dissemination of any religious doctrine, and to create tribunals for the decision of controverted questions of faith within the association, and for the ecclesiastical government of all the individual members, congregations, and officers within the general association, is unquestioned. All who unite themselves to such a body do so with an implied consent to this government, and are bound to submit to it. But it would be a vain consent and would lead to the total subversion of such religious bodies, if any one aggrieved by one of their decisions could appeal to the secular courts and have them reversed.

[33] *Bost v. Sam's East, Inc.*, Charge No. 430-2014-01900 (E.E.O.C. 2017), at http://transgenderlegal.org/media/uploads/doc_729.pdf.

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Surrebuttal of Commissioner David Kladney

Commissioners Kirsanow and Heriot object to the idea that LGBT people deserve federal employment protections against employers targeting them for their orientation or gender identity. They claim such protections would be too burdensome for employers and are not needed because discrimination on the basis of sexual orientation or gender identity is not a pervasive problem. Commissioner Heriot has taken my words, that "discrimination [against LGBT persons] is wrong each and every time it happens" to mean I would support laws against any employment decision which is morally wrong but, in her words "idiosyncratic." Commissioner Kirsanow has taken my praise of the business community for voluntarily adopting LGBT protections to argue that no legal protections are needed. Finally, Commissioner Heriot has taken my note that businesses derive many benefits from government (for example, through using the corporate form) and it is therefore proper to hold them to account with nondiscrimination requirements to mean I would think it proper to impose my understanding of American values on every company.

I write simply to state that these arguments are quite obviously not the case. I see discrimination against LGBT persons as a pervasive, destructive problem. I do believe it is wrong in each instance, but we are far from a day when it could be said to be idiosyncratic. I find it impossible that a fair observer of our society could come to the conclusion that LGBT persons are not systematically disadvantaged in ways heterosexual people are not. The report speaks for itself in cataloguing the existing literature on employment discrimination, but should these existing statistics not be sufficient for Commissioners Heriot and Kirsanow, I suggest they indicate their strong support for the Commission's recommendation: "Workplace discrimination data should be collected through the inclusion of sexual orientation and gender identity questions in population-based surveys of the workforce such as the Census, American Community Survey, and surveys fielded by the Bureau of Labor Statistics and other agencies."

In a thought experiment to a world where discrimination against LGBT people were vanishingly rare, Commissioner Heriot proposes that firing someone for their LGBT status would be no more offensive on a societal level than firing someone for an arbitrary reason such as the person's first name or sports team affiliation. That is not our world. In our world, LGBT people face negative employment consequences for their status, as do people of color and people of other protected statuses. In fact, employers use "idiosyncratic" reasons as pretext to hide their discrimination. Such discrimination abrogates our belief in a meritocracy. The only true open question is whether as a society we find it tolerable for LGBT people to suffer because others disapprove of them. I believe it is consistent with American values to protect people on this basis, and while I do not believe every business should be required to adopt my understanding of American values in every respect, I do believe it behooves this country to acknowledge the history of discrimination against LGBT people along with the current realities of employment discrimination and adopt employment protections. Voluntary adoption of employment protections by many companies is insufficient for

the simple reason that these policies are unenforceable, and thus offer cold comfort to those who face discrimination.

Commissioner Kirsanow uses the bulk of his rebuttal to argue for the incompatibility of LBGT employment protections with religious liberty. I disagree with Commissioner Kirsanow on this point, but write simply to say, counter to his assertions, the Commission does strongly support religious freedom and nondiscrimination on the basis of religion. Nothing in this report states otherwise, and the Commission's history demonstrates support for the tenets of religious freedom and nondiscrimination. Disagreement as to the contours of religious protections in particular instances does not indicate an abandonment of Constitutional and statutory religious protections.

TAB 181-4

RICK SCOTT
GOVERNOR

ELIZABETH DUDEK
SECRETARY

PUBERTY SUPPRESSION THERAPY
GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS (GAPMS)
DETERMINATION REPORT WITH RECOMMENDATION

Date: September 14, 2016

To: Justin Senior, Deputy Secretary for Medicaid

From: Bureau of Medicaid Policy

Subject: **Puberty Suppression Therapy**

PURPOSE

In order for the use of puberty suppression therapy to be covered under the Florida Medicaid program, it must meet medical necessity criteria as defined in Rule 59G-1.010, Florida Administrative Code (F.A.C.), and be funded through the General Appropriations Act of Chapter 216, Florida Statutes (F.S.).

Pursuant to the criteria set forth in Rule 59G-1.010, F.A.C., the use of puberty suppression therapy must be consistent with generally accepted professional medical standards (GAPMS) as determined by the Medicaid program, and not experimental or investigational.

In accordance with the determination process established in Rule 59G-1.035, F.A.C., the Deputy Secretary for Medicaid will make the final determination as to whether the use of puberty suppression therapy is consistent with generally accepted professional medical standards and not experimental or investigational.

If it is determined that puberty suppression therapy is consistent with generally accepted professional medical standards, this report will be supplemented with an addendum which analyzes additional factors to determine whether this health service should be covered under the Florida Medicaid program.

REPORT WITH RECOMMENDATION

This report with recommendation is presented as the summary assessment considering the factors identified in Rule 59G-1.035, F.A.C., based on the collection of information from credible sources of reliable evidence-based information. The intent is to provide a brief analysis with justification in support of the final recommendation.

The analysis described in this report includes:

- A high level review of relevant disease processes.
- An overview of the health service information.
- Clearance from the government regulatory body (e.g., Food and Drug Administration).

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- Evidence based clinical practice guidelines.
- A review of the literature considered by the relevant medical community or practitioner specialty associations from credible scientific evidence-based literature published in peer reviewed journals and consensus of coverage policy from commercial and other state Medicaid insurers.

HEALTH SERVICE SUMMARY

Hormones

Hormones are important chemical messengers in the body that effectively transfer signals and instructions from one set of cells to another. Hormones are secreted into the bloodstream by a collection of glands inside the body referred to as the endocrine system. A gland is a group of cells that produces and secretes chemicals into the body. The major glands that make up the endocrine system include the hypothalamus, pituitary gland, thyroid and parathyroid, adrenals, pineal body, and the ovaries and testes.

In a laboratory setting, hormones are produced synthetically and are prescribed by physicians to treat disease or hormone deficiencies. An instance where synthetic hormones may be needed is when an individual has their thyroid gland surgically removed; a practitioner may prescribe synthetic thyroid hormones to replace those that their body can no longer produce.

Over 50 different hormones have been identified in the human body, and more are still being discovered. Hormones influence and regulate practically every cell, tissue, organ, and function of the body, including growth, development, metabolism, homeostasis, and sexual and reproductive function.[20]

Reproductive Hormones

The hormones commonly considered as reproductive hormones in the body are testosterone, estrogen, and progesterone. Testosterone is often referred to as a male hormone, and estrogen and progesterone are often referred to as female hormones. However, there are no exclusively male or female hormones that have been identified. The physical manifestations of gender result from differences in the amounts of individual hormones in the body and differences in their patterns of secretion, first in utero and then again during puberty. In other words, testosterone, estrogen, and progesterone are produced by men and women, but in differing amounts and in different patterns.[20]

Reproductive Hormone Suppression Therapy

There are many disease processes in which increased levels of reproductive hormones are released. They include, but are not limited to, prostate cancer, breast cancer, severe endometriosis, and central precocious puberty. To address the over-secretion of reproductive hormones, several drugs have been developed to aid in reducing hormone levels, including those hormones released during puberty.

For the purposes of this report, an analysis is being performed on the use of hormone treatment to suppress puberty. Currently, there are a number of drugs used to suppress puberty, which all use gonadotropin-releasing hormone (GnRH) agonists. Agonists function to stop receptors from connecting with the appropriate transmitter. For a hormone to perform its primary function in the

brain and body it must find the correct receptor to transmit its response; the GnRH agonists prevent this natural cycle.[20]

Government Regulatory Body Approval

The Food and Drug Administration (FDA) has approved three drugs for the use in children for the purpose of puberty suppression therapy, as follows:

- Lupron[44]
  - Indications for use: Palliative treatment of advanced prostatic cancer and central precocious puberty in children of both sexes.
- Synarel[47]
  - Indications for use: Central precocious puberty (gonadotropin-dependent precocious puberty) in children of both sexes and endometriosis.
- Supprelin[46]
  - Indications for use: Central precocious puberty in both sexes.

Each of these drugs has specific indications for use and dosing information. Additionally, these medications have approved off-label uses. This permits usage in other than the approved FDA indications. These approved off-label uses are compiled in three compendia: American Hospital Formulary Service Drug Information (AHFS), United States Pharmacopeia-Drug Information (or its successor publications), and DRUGDEX Information System.[7] The drugs specified above are authorized in the respective compendia to treat the following conditions:

- Lupron:
  - Breast cancer
  - In vitro fertilization
  - Ovarian cancer
  - Premenstrual syndrome
  - Prostate cancer
  - Prostate cancer, Neoadjuvant treatment
  - Uterine leiomyoma
- Synarel:
  - Benign prostatic hyperplasia
  - Contraception, Female; prophylaxis
  - Contraception, Male; prophylaxis
  - Crohn's disease
  - Hirsutism
  - In vitro fertilization
  - Uterine leiomyoma
- Supprelin:
  - Acute intermittent porphyria
  - Endometriosis
  - Female infertility; Adjunct
  - Polycystic ovary syndrome
  - Uterine leiomyoma

While all of these drugs may be utilized to treat other conditions, as indicated above and specified in the compendia, none of them are authorized or specified in the compendia for use in treating individuals diagnosed with gender dysphoria.[7]

LITERATURE REVIEW

This analysis summarizes information obtained from scientific literature published in credible peer-reviewed journals related to the use of puberty suppression therapy. This section also briefly cites the positions from the relevant medical societies, and summarizes the key articles referenced in support of their positions.

Central Precocious Puberty

Central precocious puberty (CPP) develops due to premature pubertal changes and rapid bone development. CPP is associated with lower adult height and increased risk for development of psychological problems.

Reproductive hormone suppression therapy (also referred to as puberty suppression therapy in this document) has been the standard of care for CPP for the last 15-20 years. The standard treatment for CPP is GnRH analogs. Although there are many different analogs with different routes of administration, the primary agent in the United States for many years was depot intramuscular injections administered every four weeks, but in the last ten years, a subdermal or under the skin implant has been developed, which has been shown to be effective for up to two years.[17, 39, 41]

In a recent study, researchers explored the difference in cognitive function, behavior, emotional reactivity, and psychosocial problems between young females treated with GnRH and age-matched controls. They concluded that young females treated with GnRH do not differ in their cognitive functioning, behavioral, and social problems from their same age peers. However, they did find a significant difference in heart rate that increased with treatment duration and suggested a follow-up study with an emphasis on cardiac health.[05]

Gender Dysphoria

Gender dysphoria is an individual's affective or cognitive discontent with their assigned gender (gender at birth).[14] Gender dysphoria refers to the distress that may accompany the incongruence between the individual's experienced or expressed gender and their assigned gender. Evidence of this distress is the hallmark of the disorder. The diagnostic criteria are divided into a category for children and a category for adolescents and adults. The disorder is manifested differently as an individual ages or enters different developmental stages. Both categories require marked incongruence between the individual's experienced or expressed gender and their assigned gender of at least a six months' duration and clinically significant distress or impairment in social, school (occupation for adults), or other important areas of functioning.[14]

Diagnostic criteria in children include: a strong desire to be the other gender or an insistence that they are the other gender; a preference for wearing clothing associated with the other gender; preference for cross gender roles in simulated play; preference for toys games, or activities usually associated with the other gender; preference for playmates of the other gender; and the dislike of their sexual anatomy. The prevalence of this diagnosis among the general population ranges from 0.005% to 0.014% in males and 0.002% to 0.003% in females.[14]

Studies have shown that the majority of children (80%) diagnosed with gender dysphoria will not continue to be gender dysphoric after puberty.[31]

In adolescents and adults, diagnostic criteria include: a strong desire to be and to be treated as the other gender and a strong desire to have the sex characteristics of the other gender (or in the case of adolescents, the wish to prevent the development of their assigned gender's characteristics).[14]

Gender dysphoria is associated with high levels of stigmatization, discrimination, and victimization, leading to negative self-concept, increased rates of mental disorder comorbidity, school dropout, and economic marginalization.[14] Adolescents that do not receive treatment during this already vulnerable period of development might engage in risky or self-harming behaviors , such as self-harm, self-mutilation, suicidal ideation, or suicide.[22]

For the 20% of children who persist in their feelings of gender dysphoria, clinicians may begin to explore alternative treatment approaches beyond psychotherapy after the onset of puberty, including medical interventions such as the use of GnRH analogs to suppress puberty.[38] The use of puberty suppression therapy is used as a diagnostic aid in adolescents contending with gender dysphoria.[6, 10, 11, 24, 31, 50] The use of GnRH analogs is generally prescribed in adolescents ages 12-16. In addition to puberty suppression therapy, a physician may also begin to prescribe cross-sex hormones, though the latter does not generally begin until the ages of 16-18.[10, 11]

The use of GnRH analogs will delay reproductive development in this population. However, there remains a great deal of concern and lack of consensus in the medical community of the potential risks, including: misdiagnosis, sterilization, adverse medical effect on the metabolic and endocrine system, impaired bone mass and brain development, etc.[51, 6] To date, there have been no randomized controlled clinical trials on the use of GnRH analogs in the treatment of gender dysphoria (on large cohorts) that have been shown to be efficacious with tolerable side effects. This is in large part due to the small number of patients diagnosed with gender dysphoria, which makes any statement on the general efficacy of a treatment approach challenging.[31] However, there have been case-studies (qualitative) that have been conducted that review the outcomes on small cohorts. These studies have concluded that there are limited negative side effects from the use of puberty suppression drugs in adolescents contending with gender dysphoria.[54, 55]

Clinicians who support the use of puberty suppression therapy in the treatment of gender dysphoria argue that the risks of misdiagnosis are significantly reduced if the treatment is delayed until the initiation of puberty. They also contend that this treatment may relieve emotional distress in the individual (including reducing suicidal ideation in severe cases) and may "buy time" for the child to explore their feelings of gender dysphoria without contending with physical changes that cannot be undone (e.g., breast development).[22] Most treatment protocols recommend extensive psychological evaluations/assessments and psychotherapy by mental health professionals prior to the initiation of medical interventions. This is especially important given the changing thoughts and feelings of prepubescent children versus adolescents with persistent gender dysphoria and in adolescents presenting with co-morbid conditions.

It is important to note that most of the literature reviewed in development of this analysis concluded that more systematic research is required to determine the long-term efficacy of medical treatment for adolescents with gender dysphoria.[21, 24, 25, 28, 50, 51]

Evidence-Based Clinical Practice Guidelines

The American Academy of Pediatrics published a consensus statement on the use of GnRH analogs in children in March 2009. They concluded that GnRH use was undisputed in the treatment of CPP early-onset (less than six years old). However, the use of GnRH for conditions other than CPP requires additional investigation and cannot be suggested routinely.[3] The consensus statement does not specifically address the use of GnRH in the treatment of gender dysphoria.

The Endocrine Society published guidelines for the endocrine treatment of transsexual persons. The Society concluded that transsexual persons seeking to develop the physical characteristics of the desired gender require safe, effective hormone regimen that will 1) suppress endogenous hormone secretion determined by the person's genetic/biological sex and 2) maintain sex hormone levels within the normal range for the person's desired gender. They recommend that a mental health professional make the referral and participate in ongoing care and an endocrinologist must confirm the diagnostic criteria. They do not recommend endocrine treatment of prepubertal children. The recommendations are as follows:

- Treatment of transsexual adolescents (Tanner stage two, generally achieved around the age of 12 years) by suppressing puberty with GnRH analogues until the age of 16 years.
- Initiation of cross-sex hormones at the age of 16 years with continued suppression of biological sex hormones.
- Maintaining physiologic levels of gender-appropriate sex hormones and monitoring for known risks throughout adulthood.[10, 18, 32]

In making these recommendations, however, the Endocrine Society identified the strength of the evidence used to support its conclusions. For all of the recommendations listed above, the Society acknowledged the strength of the evidence as low or very low.

COVERAGE POLICY

Federal Regulations

Federal regulations for Medicaid specify that a state may limit coverage of a drug with respect to the treatment of a specific disease or condition for an identified population (if any) based on the drug's labeling, if it does not have a significant, clinically meaningful therapeutic advantage in terms of safety, effectiveness, or clinical outcome of such treatment for such population over other drugs included in the formulary. In addition, states may exclude a drug when the prescribed use of the drug is not for a medically accepted indication, either approved by the FDA or supported by information from the appropriate compendia. These guidelines apply to a state's administration of its Medicaid prescribed drug benefit in both managed care and non-managed care delivery systems.

States are also required to implement a drug use review program for covered outpatient drugs in order to assure that prescriptions are appropriate, medically necessary, and are not likely to result in adverse medical results. The program is required to assess data on drug use against predetermined standards, consistent with the following:

1. Compendia, consisting of the following:
   a. American Hospital Formulary Service Drug Information;
   b. United States Pharmacopeia-Drug Information (or its successor publications); and
   c. the DRUGDEX Information System; and
2. The peer-reviewed medical literature.

Federal law requires states to provide services to eligible recipients under the age of 21 years, if such services are medically necessary to correct or ameliorate a defect, a condition, or a physical or mental illness. This is known as the Early and Periodic Screening, Diagnostic, and Treatment (EPSDT) benefit. Included are diagnostic services, treatment, equipment, supplies, and other measures described in section 1905(a) of the Social Security Act, codified in Title 42 of the United States Code 1396d (a). As such, services for recipients under the age of 21 years exceeding any coverage limitations specified within a state's policies maybe approved, if medically necessary.

Florida Medicaid

In order to be reimbursed by Florida Medicaid, a drug must be medically necessary and either (a) prescribed for medically accepted indications and dosages found in the drug labeling or drug compendia in accordance with section 1927(k) (6) of the Social Security Act, or (b) prior authorized by a qualified clinical specialist approved by the Agency for Health Care Administration (Agency).[1]

The criteria that are utilized under the Florida Medicaid program in the authorization of drugs for off-label purposes are as follows:

1. Documentation submitted with trial and failure or intolerance to all FDA- approved medications for the indication **AND**
2. Phase III clinical studies published in peer review journals to support the non-FDA approved use **AND**
3. Usage supported by publications in peer reviewed medical literature **and** one or more citations in at least one of the following compendia:
   a. American Hospital Formulary Service Drug Information (AHFS)
   b. United States Pharmacopeia-Drug Information (or its successor publications)
   c. DRUGDEX Information System[1]

Florida Medicaid covers reproductive hormone suppression therapy (including puberty suppression therapy) for all FDA approved indications/uses or when the information in the appropriate compendium supports the use of the drug in the treatment of the specific disease state or condition. Since the use of GnRH agonists are not FDA approved or listed in the appropriate compendia for the treatment of gender dysphoria, Florida Medicaid does not authorize these drugs for such uses. However, children/adolescents diagnosed with gender dysphoria are eligible to receive an array of other medical and behavioral health interventions (e.g., individual and family therapy, psychological evaluations/assessments, other medical evaluation and management services) necessary to address their presenting signs and symptoms.

Health plans contracted to provide services under the Florida Medicaid Statewide Medicaid Managed Care program are required to cover all prescription drugs listed in the Agency's Medicaid Preferred Drug List (PDL). In addition, the health plan's prior authorization criteria and protocols may not be more restrictive than those used by the Agency as indicated in the Florida Statutes, the Florida Administrative Code, the Medicaid State Plan and those posted on the Agency website.

Florida Medicaid provides services to eligible recipients under the age of 21 years, if such services are medically necessary to correct or ameliorate a defect, a condition, or a physical or mental illness. Medical necessity in the State of Florida must meet the following conditions:

1. Be necessary to protect life, to prevent significant illness or significant disability, or to alleviate severe pain;
2. Be individualized, specific, and consistent with symptoms or confirmed diagnosis of the illness or injury under treatment, and not in excess of the patient's needs;
3. Be consistent with generally accepted professional medical standards as determined by the Medicaid program, and not experimental or investigational;
4. Be reflective of the level of service that can be safely furnished, and for which no equally effective and more conservative or less costly treatment is available statewide; and
5. Be furnished in a manner not primarily intended for the convenience of the recipient, the recipient's caretaker, or the provider.

If a service exceeds the coverage described within a Florida Medicaid policy or the associated fee schedule, a request (along with all supporting documentation) may be submitted to the Agency or its designee for review.

Medicare

Medicare covers reproductive hormone suppression for all FDA approved use. The *Medicare Benefit Policy Manual*, Chapter 15, page 15, subsection 50.4.2, discusses the unlabeled use of a drug. The policy states that "FDA approved drugs used for indications other than what is indicated on the official label may be covered under Medicare if the carrier determines the use to be medically accepted, taking into consideration the major drug compendia, authoritative medical literature and/or accepted standards of medical practice."[5] However, because Medicare covers primarily elderly adults and disabled adults, its coverage policies have little or no application in this analysis.

State Medicaid Programs

All state Medicaid programs cover reproductive hormone suppression therapy for the approved FDA indications and when the criteria for off-label use are met. Some state Medicaid programs are also adopting coverage policies that allow for reimbursements of puberty suppression therapy in adolescents diagnosed with gender dysphoria. It appears at this time as though most states do not cover this service although that may change over time. This report highlights the coverage policies for four Medicaid programs that do cover the service, as follows:

1. Colorado Medicaid covers behavioral health services, GnRH analogs/agonists, cross-sex hormone therapy, gender confirmation surgery, and pre and post-operative care.
2. Maryland Medicaid covers GnRH treatment if the recipient has a diagnosis of gender dysphoria.
3. Rhode Island Medicaid covers behavioral health services, pharmacological and hormonal therapy to delay physical changes of puberty, and pharmacological and hormonal therapy that is non-reversible and produces masculinization or feminization. Some services require prior authorization.
4. Washington State Medicaid covers behavioral health services, puberty suppression therapy, hormonal therapy, and gender reassignment surgery.

GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS RECOMMENDATION

Puberty suppression therapy is considered a health service that is consistent with generally accepted professional medical standards for the approved FDA indications (i.e., central precocious puberty) and for off-label use when supported by citations in at least one of the compendia. Since Florida Medicaid already provides coverage of puberty suppression therapy in the treatment of central precious puberty and for use in treating the conditions cited in the compendia, no further policy coverage analyses are needed to supplement this report on this point.

Based upon the available published literature, it is inconclusive whether puberty suppression therapy is considered a health service that is consistent with generally accepted professional medical standards in the treatment of gender dysphoria. Most of the studies published thus far on the use of puberty suppression in gender dysphoric children/adolescents have concluded that further systematic research is required to determine the long-term safety and efficacy of this approach and there remains a lack of consensus within the medical community on its appropriateness (both from an ethical and safety perspective). As the research on this topic continues to evolve, more conclusive evidence may emerge that supports the long-term efficacy and effectiveness of this treatment approach. At any time, a follow-up analysis can be performed that could change this recommendation.

EPSDT Considerations:

While the Agency cannot make a blanket determination on puberty suppression therapy for gender dysphoria, we also cannot categorically exclude this treatment for children. Clinical guidelines from the Endocrine Society do recommend this therapy for certain adolescents, albeit based upon a combination of weak and very weak evidence. In certain circumstances, the risks of not treating an adolescent may be worse than the potential long-term consequences of treatment. Moreover, it is noted extensively in the literature that adolescents contending with gender dysphoria often experience a myriad of emotional, physical, and societal challenges. Unresolved, the distress can manifest into a host of behavioral health problems including depression, anxiety, and suicidal ideation and self-mutilation. Florida pays for services for children when they protect life and /or prevent significant disability or harm, in accordance with the state's medical necessity definition.

Given these concerns, while it is not recommended that any further analyses be conducted to expand Florida Medicaid's coverage of puberty suppression therapy beyond those indications/uses approved by the FDA or authorized in the appropriate compendium, it is recommended that any individualized request for such therapy be reviewed as a part of the Agency's special services process. Consistent with EPSDT requirements, the request can be evaluated on an individualized basis to determine if the service is medically necessary (e.g. it is administered to protect life and/or prevent significant disability, such as to prevent suicide or self-mutilation) to ensure that all less invasive interventions have been exhausted, and to ensure that this treatment approach presents as the best alternative given the adolescent's psychological state and presenting signs and symptoms.

✓ **Concur** ____**Do not Concur**

Comments:

____

____

[signature] for Justin Senior — 9/15/16

Deputy Secretary for Medicaid (or designee) — Date

TAB 181-24

Division: Pharmacy Policy	Subject: Prior Authorization Criteria
Original Development Date: Original Effective Date: Revision Date:	September 20, 2016 September 18, 2017 November 17, 2017

SPECIAL SERVICES CRITERIA
PUBERTAL SUPPRESSION WITH GONADOTROPIN-RELEASING HORMONE ANALOG AGENT FOR GENDER DYSPHORIA

LENGTH OF AUTHORIZATION: THREE MONTHS

CLINICAL CRITERIA:
Gender dysphoria is defined as distress or discomfort caused by a discrepancy between a person's assigned sex at birth and a person's gender identity. Unresolved, the distress or discomfort can manifest into a host of behavioral health problems including depression, anxiety, suicidal ideation and self-mutilation. The purpose of pubertal suppression is to alleviate suffering caused by the development of secondary sex characteristics, in order to provide time to make a balanced decision regarding the actual gender reassignment.[1]

REVIEW CRITERIA:
- A comprehensive mental health evaluation is required and must include the diagnosis of gender dysphoria, using the current Diagnostic and Statistical Manual of Mental Disorders-5 by a mental health professional (MHP) licensed in accordance with s. 490 or s. 491, Florida Statutes (supporting documentation required).[2]
- The diagnosis must be confirmed by an endocrinologist.[2]
- The MHP clinical notes must reflect the MHP's professional judgment that not treating the patient is likely to be worse than the potential long-term consequences of the treatment. The treatment must be medically necessary (e.g. it is administered to protect life and/or prevent significant disability, such as to prevent suicide or self-mutilation), and must ensure that the pubertal suppression treatment approach presents as the best alternative given the patient's psychological state and presenting signs and symptoms (supporting documentation required).
- The patient must have been in psychotherapy for a minimum of six months since diagnosed with gender dysphoria prior to consideration for pubertal suppression therapy.
- Females and males must have reached a Tanner stage 2 or Tanner stage 3 prior to consideration of pubertal suppression therapy and have confirmed pubertal levels of estradiol and testosterone.
- If treatment is being prescribed for adolescents under the age of 12, additional documentation is required to support the request.
- The MHP clinical notes must address the patient's readiness for pubertal suppression treatment and ensure psychotherapy will continue to be offered while on pubertal suppression therapy.[3]
- Parental consent is required during treatment for patients under the age of 18.[4] The patient and the legal guardian/parents must demonstrate knowledge and understanding of the expected

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Division: Pharmacy Policy	Subject: Prior Authorization Criteria
Original Development Date: Original Effective Date: Revision Date:	September 20, 2016 September 18, 2017 November 17, 2017

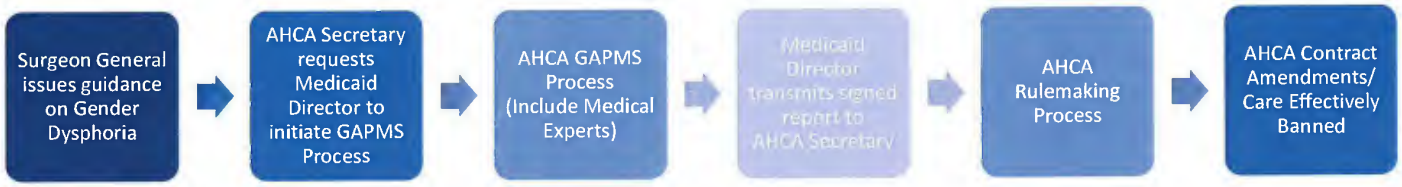
outcomes of suppression of pubertal hormones including the reversible and irreversible effects of pubertal suppression therapy (supporting documentation required).[2]

- Documentation must include evidence that other psychiatric or medical comorbidities that may interfere with the diagnostic work-up or treatment have been ruled out.[3]
- Documentation of treatment adherence is required.

[1]The Standards of Care for Gender Identity Disorders (5th Ed) Harry Benjamin International Gender Dysphoria Association, Inc. Available at: http://www.tc.umn.edu/~colem001/hbigda/hstndrd.htm Accessed September 9, 2016
[2]Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2009; 94:3132-3154
[3] Vance SR, Ehrensaft D, Rosenthal SM, et al. Psychological and Medical Care of Gender Nonconforming Youth Pediatrics 2014; 134:1184-1192
[4] Cavanaugh T Cross-Sex Hormone Therapy. Available at: http://www.lgbthealtheducation.org/wp-content/uploads/Cross-Sex-Hormone-Therapy1.pdf Accessed September 9, 2016

TAB 182-35

Gender Dysphoria/Transgender Health Care Non-Legislative Pathway



EOG_008240

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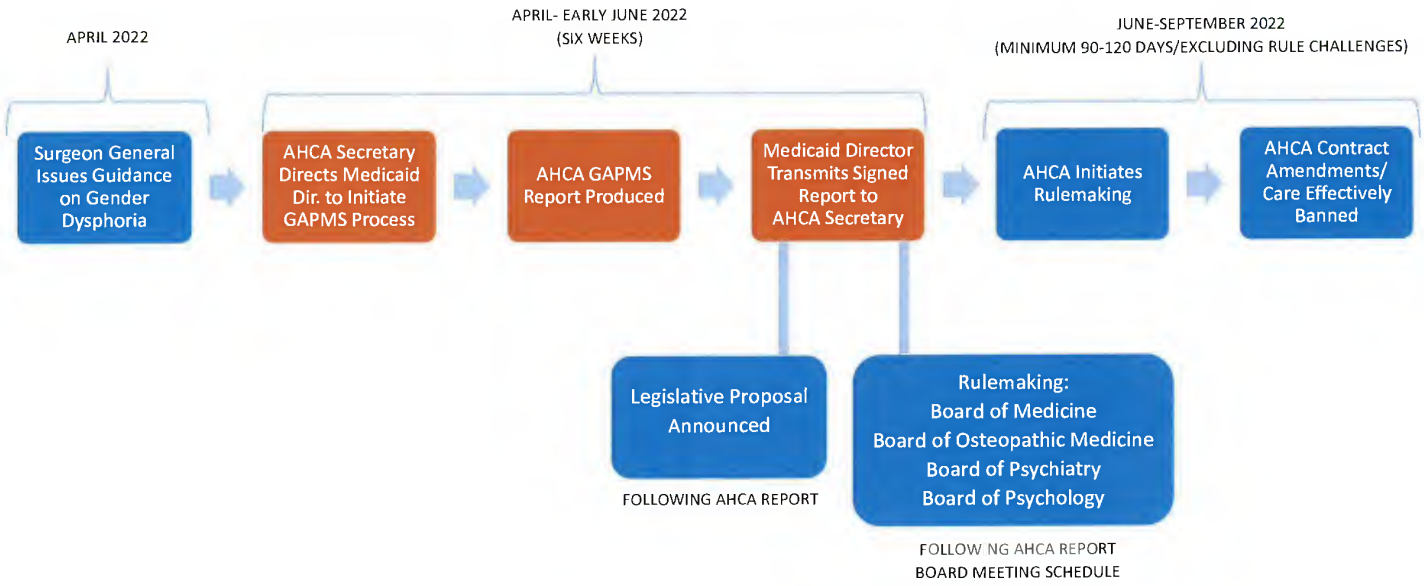
TAB 182-36

Gender Dysphoria/Transgender Health Care Policy Pathway



^ GAPMS: Determining Generally Accepted Professional Medical Standards

EOG_008241

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TAB 182-38

Medicaid Policy Routing and Tracking Form

Date:	6/1/2022
Assignment Title:	GAPMS Report
Assignment Type:	GAPMS
Final Due Date:	6/2/2022
Extensions:	No
Reassigned:	No
Reassigned to:	
Reassigned from:	
Date of Completion:	
Assignment Summary (brief):	GAPMS review for services
Attachment(s):	Attachment Document.docx Please upload your draft documents/responses
Section:	Canadian Prescription Drug Importation Program
Prepared By:	Brackett, Matt
Position:	Other
Preparer Phone:	850-412-4151
Preparer Room Number:	2249

Reviewed by and Routing Timeline(s):

MB for DVP

Name	Title	Start Date	End Date	Date Received	Todays Date and Initial		Approval
Devona (D.D.) Pickle	AHC Administrator	6/1/2022	6/1/2022	6/1/22	6/1/22		☑
Ann Dalton	Bureau Chief	6/1/2022	6/1/2022	6/1/22	6/1/22	AD	☑
Jason Weida	ADS Policy/Quality	6/1/2022	6/1/2022	6/1/22	6/1/22	JW	☑
Tom Wallace	Deputy Secretary for Medica	6/2/2022	6/2/2022	6/1/22	6/2/22	TW	☑
							☐
							☐
							☐

Notes:

Edits	Edits
Edit 1	Edit 2
Edit 3	Edit 4

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Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

June 2022

Ron DeSantis, Governor
Simone Marstiller, Secretary

Contents

Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term "gender" in reference to the construct of male and female identities and the term "sex" when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).[1]

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one's gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender." As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having "a strong desire to be of the other gender or an insistence that one is the other gender" or "a strong preference for cross-gender roles in make-believe or fantasy play." The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include "a strong desire to be the other gender" or "a strong desire to be rid of one's primary and/or secondary sexual characteristics." The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition "is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

[1] The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money's theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money's ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth." Additionally, the Merck Manual further states that "gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold" (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.[2]

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman's study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V's criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA's definition. They further asserted that the APA intended to "reduce pathologization" by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA's definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V's criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one's gender as a disorder. In addition, the APA considers gender as part of one's identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

[2] Following the release of the Florida Department of Health's guidelines for treating gender dysphoria, Merck removed its definition for "gender dysphoria" from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the "effort to reduce stigma" (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one's gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies "a marked incongruence between one's experienced/expressed gender and natal sex, of at least 6 months' duration" as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for "marked." This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)[3], behavioral health professionals are supposed to "find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment." WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

[3] The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as "gender affirming" surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a "standard of care" and that its grades for available services are low or very low (Endocrine Society, 2017).[4]

[4] Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient's overall behavioral health and that providing a "surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it" (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.[5]
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

[5] Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozlowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozlowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozlowska et al also cite other studies that indicate a high correlation between gender dysphoria and "adverse childhood events" and further assert that the condition "needs to be conceptualized in the context of the child's lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway" (Kozlowska et al, 2021).

For their study, Kozlowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child's developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozlowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of "adverse childhood events" such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported "instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures." These results led Kozlowska et al to conclude that gender dysphoria can be "associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion." The study also cites that treatment requires "a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child's presentation" (Kozlowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual's gravitation to the opposite sex documented over multiple years) but rather exposure to "social and peer contagion." Littman uses this term in the context of definitions cited in academic literature, stating that "social contagion is the spread of affect or behaviors through a population" and that "peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others." Examples of the latter's negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that "online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria." The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozlowska et al's study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman's research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a "maladaptive coping mechanism" for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman's study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential "gateway drug" for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who "wished they were the other sex" were more likely to become desisters and that those who "believed that they were the other sex" persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrect Gender Dysphoria Scale and Children's Global Assessment Scale)[6] to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

[6] Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is "variable." The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	**Reversible or Irreversible**
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017[7]

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

[7] This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as "irreversible" in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are "gender affirming." This decision mirrors the DSM-V's interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an "affirmation and acceptance of who they (i.e., patient) have always been" (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP's endorsement of "gender affirming" treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP's position is based on research that does not support intervention but rather supports "watchful waiting" because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites "gender affirming" interventions as the only effective method. To conclude, he states the organization is "advocating for something far in excess of mainstream practice and medical consensus" (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP's endorsement as a basis for "gender affirming" treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.[8] WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

[8] Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a "cure" to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al's study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).[9] Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden's overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al's conclusions were "too strong" and that further analysis by the authors revealed that the new "results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

[9] Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison" (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al's findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al's research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient's perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the "lifesaving" potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline "Almost half of LGBTQ youths 'seriously considered suicide in the past year'" (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that "there is great uncertainty about the effects" of sex reassignment treatments and that the "evidence alone is not sufficient to support" using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on "gender affirming" treatments. The authors noted this research had a "critical risk of bias" and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that "transgender youth who socially transitioned at early ages" will continue "to identify that way." While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their "assigned gender at birth," the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V's diagnostic criteria for gender dysphoria and that the children's families supported the decisions to transition. Instead, the authors relied on a child's chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study's publication under the headline "Few Transgender Children Change Their Minds After 5 Years" (New York Times, 2022). Such a title can add to the public's perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments "constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety." The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that "children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function" (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a "case-by-case" basis.[10] CMS specifically noted that the decision memo is not a National Coverage Determination and that "no national policy will be put in place for the Medicare program" (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that "the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up." In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo's criteria (CMS, 2017).

The basis for Medicare's decision is that the "clinical evidence is inconclusive" and that "robust" studies are "needed to ensure that patients achieve improved health outcomes." In its review of available literature, CMS sought to answer whether there is "sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria." After evaluating 33 studies that met inclusion criteria, CMS's review concludes that "not enough high-quality evidence" is available "to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively." Additionally, out of the 33 studies, just 6 provided "useful information" on the procedures' effectiveness, revealing that their authors "assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies" that "did not demonstrate clinically significant changes or differences in psychometric test results" following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).[11]

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).[12]

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[10] The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.
[11] Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.
[12] The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery.[13] The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

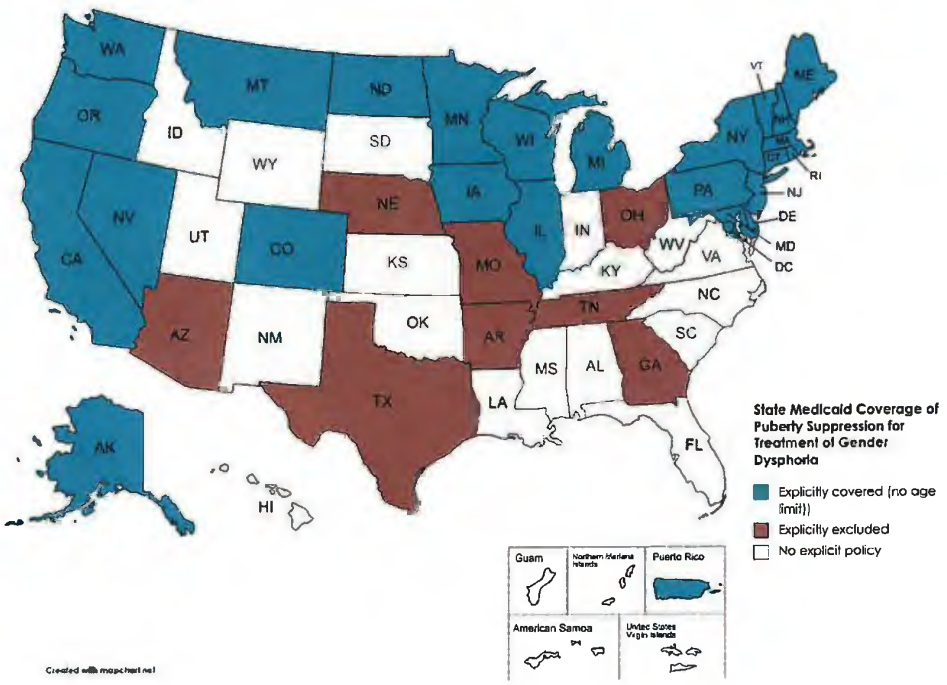
- "Social gender transition should not be a treatment option for children or adolescents."
- "Anyone under 18 should not be prescribed puberty blockers or hormone therapy."
- "Gender reassignment surgery should not be a treatment option for children or adolescents."
- "Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider."

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment's ability to improve mental health (DOH, 2022).

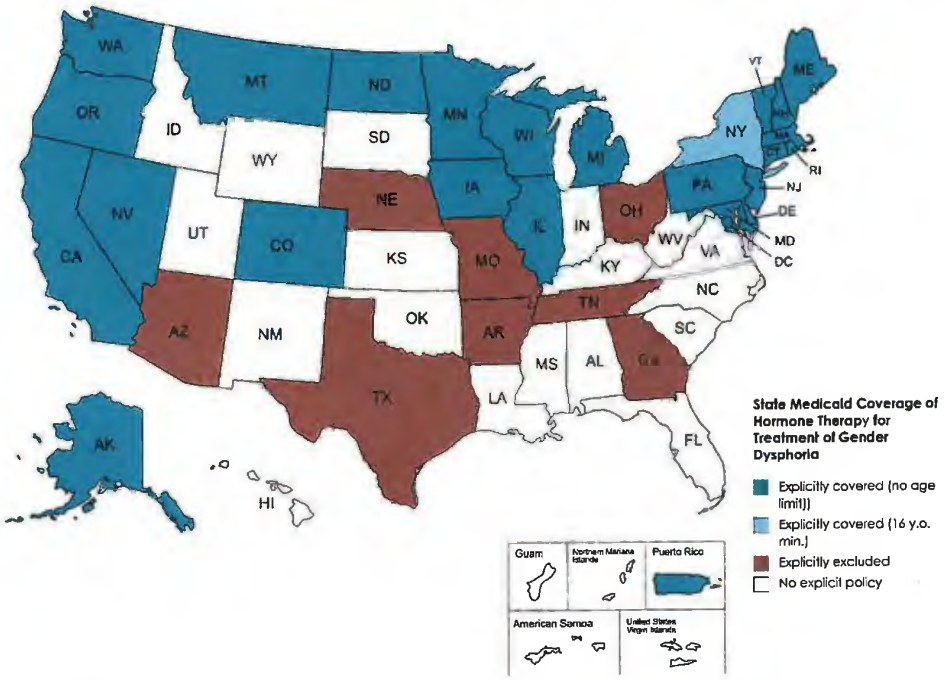
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

[13] Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida's public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

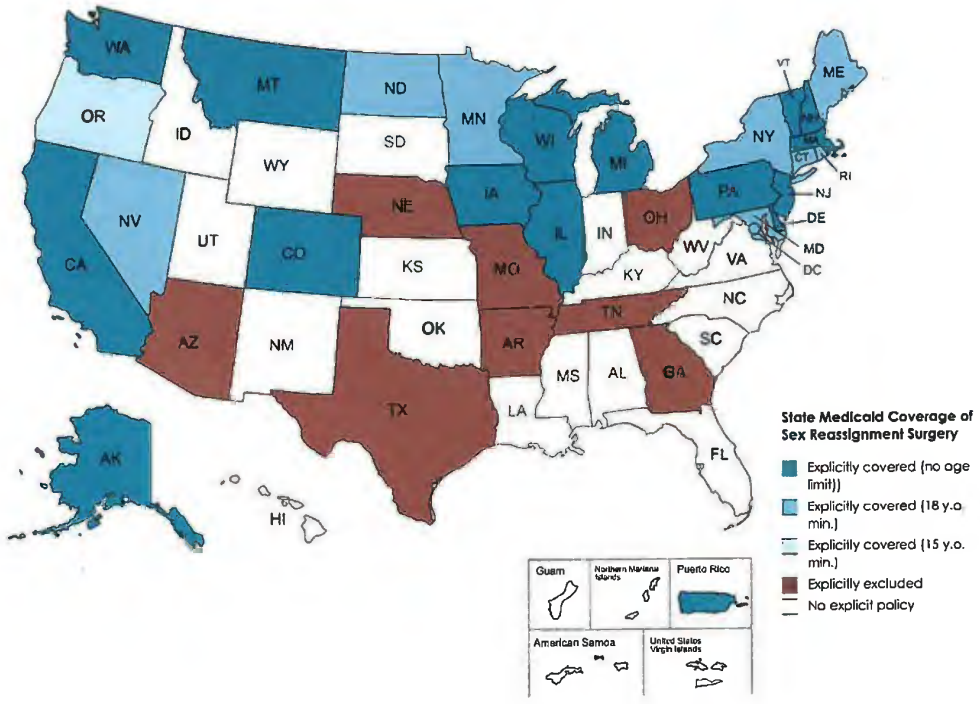
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

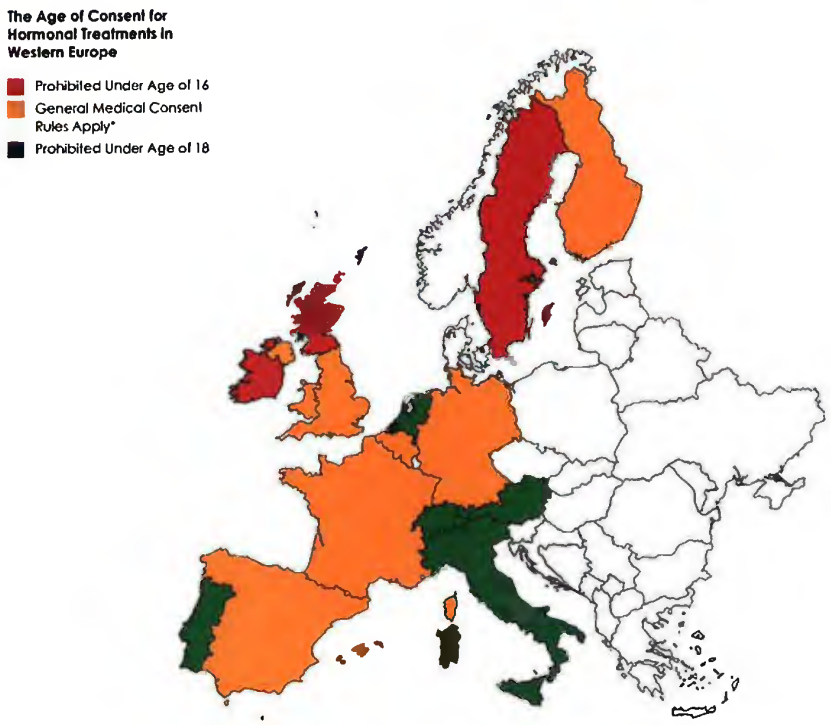
Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that "the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits." With the exception of youths who exhibited "classic" signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors "is an experimental practice" and that "no irreversible treatment should be initiated." The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.'s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

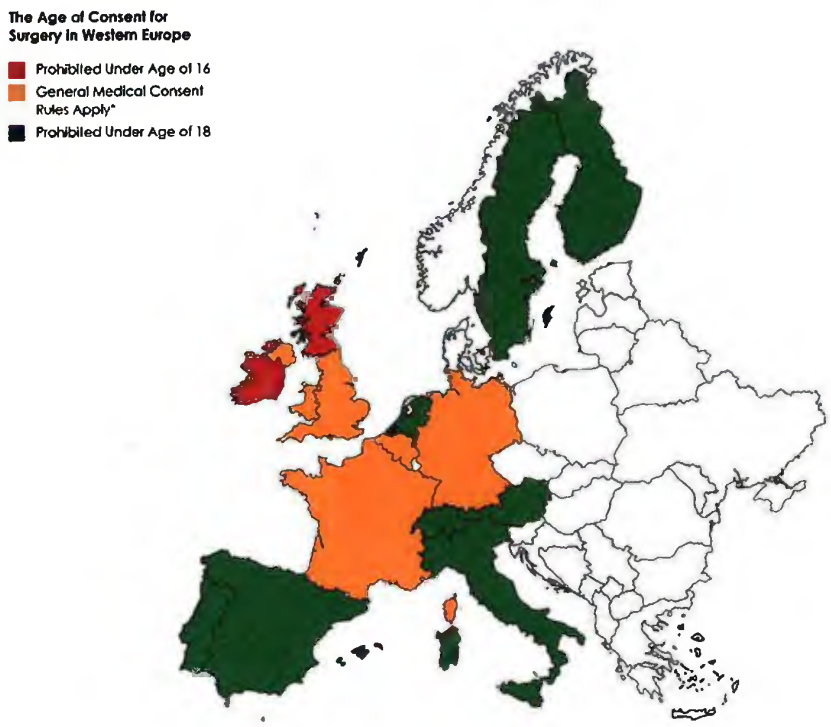
Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

✓ **Concur** ____ **Do not Concur**

Comments:

_____

_____

_____

_____ 6/2/22
Deputy Secretary for Medicaid (or designee) *Date*

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

TAB 183-4

From: Cogle, Christopher
Subject: Re: GAPMS process
To: ""English"","" Jeffrey; Jeffrey.English@ahca.myflorida.com
Sent: June 27, 2022 2:52 PM (UTC-04:00)

Thank you.

And thank you for standing up for the true credibility of the GAPMS process.

I will read the SOP attachment you sent and think about it more.

Your dedication and work are appreciated.

Chris

Christopher R. Cogle, M.D.
Chief Medical Officer for Florida Medicaid

2727 Mahan Drive
Bldg 3 Room 2421-A MS8
Tallahassee, FL 32308
Mobile: (850) 228-2868

From: English, Jeffrey <Jeffrey.English@ahca.myflorida.com>
Sent: Monday, June 27, 2022 2:30:05 PM
To: Cogle, Christopher <Christopher.Cogle@ahca.myflorida.com>
Subject: RE: GAPMS process

Good afternoon, Dr. Cogle,

There is a SOP for GAPMS.

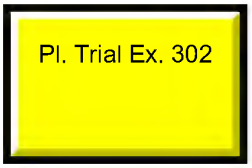
Typically, the requests for consideration of coverage come in either through a health service research email address or from leadership (less often).

The GAPMS process exists to determine whether the service/device requested for coverage is "experimental/investigational" or "medically necessary".

The request gets run through the attached checklist, and once it is determined to be an actual GAPMS (rather than a decision point or "simple" coverage determination) I reach out to the requestor and schedule a time to gently walk them thru the process.

We ask that the requestor(s) send us a host of information, much of which is included on the checklist. They often send us published research about the service/device under consideration, relevant national or local coverage determination information, and as many examples as they have of coverage by other states or major insurers. The amount of information provided by the requestors can vary quite a bit in quality and completeness.

Their request is added to our GAPMS queue to be worked on, typically in the order in which they have been received. We do tend to reward requestors who maintain contact, provide updates, and respond in a timely manner to any inquiries we might have.



Assuming they check off all the boxes on the checklist, so to speak, we begin the process.

- I determine what similar services or alternative treatments we already cover. I verify that the service/device requested has FDA approval and a dedicated billing code.
- I utilize Policy Reporter to determine which states currently include the service/device on their respective fee schedules. I also research and verify any existing coverage among the major insurance companies. I look for any existing national or local coverage determinations.
- The greatest amount of time is spent researching the existing professional literature on the subject, ideally well designed, non-industry sponsored studies, in peer-reviewed journals. Systematic reviews and meta-analyses, when existing, play a big role and can often provide a heads up regarding the quality of the literature as well as any gaps that may exist. The quality can of course vary considerably depending on the item in question and how long it has existed as a treatment option. I also look for any existing clinical guidelines that might exist related to the request, as well as consulting various sites like AHRQ, Cochrane, NICE, etc. What do they have to say about it? Also, are their any ongoing trials identifiable through clinicatrials.gov that might shed more substantial light on the matter at a future date?
- I also pull any relevant articles pertaining to cost analyses that might indicate potential for cost saving for Florida Medicaid.
- Assuming (and for some of these that is a big "If") they check all the right boxes on all of the above, I will submit a request to MPF, along with a minimum of three price examples from other states that currently provide coverage, for a cost analysis. Anything added (with some exceptions) to the fee schedule must be budget neutral. So, we ask, what do we already pay for, can this new service/device offset any existing coverage, and does it lead to healthier outcomes at similar or less cost?

Once everything has been received, researched, and reviewed, I prepare a report that is roughly a template insofar as it is divided into sections ranging from "literature" to "existing coverage among other states" etc. Once the report has been completed, it goes to my immediate supervisor who reviews it for content and then forwards it to the Bureau Chief. Usually there would be a meeting with her, questions asked and answered, and then the report moves on to Tom for his signature, yay or nay, as final approval. Then the requestor is contacted and given a final copy of the report. If it is determined medically necessary and budget neutral, the code is then added to the fee schedule based on the normal fee schedule update timeline.

All of that is the ideal. The reality is that the reviews get done, the reports get written, and then they all bottleneck with leadership because GAPMS are fairly low on the totem pole of priorities, particularly since the pandemic began. It is also extremely common for a request to come in (most of them, really) that are asking for coverage long before the necessary information exists to justify coverage. Manufacturers will have a newfangled device with a tiny evidence base or will make the request before their most significant and enlightening trials/studies have even been completed. I have often said that a lot of what I am asked to look at will likely eventually gain coverage. But it is common for the request to outpace the evidence, and they are often several years away from finalizing their best case.

I believe there are currently about seven completed that are still awaiting review and approval from leadership. Some of them have been written for over two years. I have re-reviewed them and made any necessary updates concerning coverage, research, etc. I typically do that twice a year.

Of course, the requestors are always free to resubmit after a denial, so some of these never really die. But the resubmissions go to the back of the queue and are taken in the order they arrive.

If you will excuse me, I feel obligated to include this information: I was not informed or consulted, did not in any way participate, and did not write the GAPMS concerning gender dysphoria treatment. That particular GAPMS did not come through the traditional channels and was not handled through the traditional GAPMS process. Every report I have written represents my best effort at determining the most timely and accurate information available on the subject under consideration. I do not cherry pick data or studies and would never agree to if I were so asked. All I can say about that report, as I have read it, is that it does not present an honest and accurate assessment of the status of the current evidence and practice guidelines as I understand them to be in the existing literature. I sincerely apologize if I come across as a bit agitated about it, but as the "GAPMS guy" around here, lots of assumptions have been made by those

who do not know me well. I'm a different sort of person than the author of that report. I can't speak for them. I conduct myself and my work with integrity and I do not play favorites, yay or nay. Full stop, period.

Thanks so much for your help Friday. That shaved a few minutes off a tight deadline for me. Please let me know if you have any additional or questions or would like any additional information or clarification.

Take care.

Jeff

From: Cogle, Christopher <Christopher.Cogle@ahca.myflorida.com>
Sent: Saturday, June 25, 2022 9:13 PM
To: English, Jeffrey <Jeffrey.English@ahca.myflorida.com>
Subject: GAPMS process

Hello, Jeff. Good talking with you this past Friday.

Are there standard operating procedures for GAPMS?

If so, can I review them?

If no SOPs, then can I help you develop a SOP for GAPMS?

Thank you,

Chris

Christopher R. Cogle, M.D.
Chief Medical Officer for Florida Medicaid

2727 Mahan Drive
Bldg 3 Room 2421-A MS8
Tallahassee, FL 32308
Mobile: (850) 228-2868

TAB 183-7

HCA Hearing on General Medicaid Policy Rule

July 2022

The purpose of the amendment to Rule 59G-1.050 – General Medicaid Policy – is to update covered Medicaid services for gender dysphoria. The rule specifies covered services and clarifies definitions.

Cabinet

- Cole Gearing – Program Administrator in AHCA Medicaid Policy Bureau
- Jason Weida – Asst. Deputy Secretary for Medicaid Policy Bureau
- Matt Brackett – Program Consultant in AHCA Medicaid Policy Bureau
- Sheena Grant – Chief Counsel and Rules Coordinator in AHCA General Counsel Office
- Mohammad Jazil and Gary Perko of Holtzman and Vogel Law Firm – AHCA Outside Counsel
- Dr. Andre Van Mol – Board-certified family physician
- Dr. Quentin Van Meter – Board-certified pediatric endocrinologist
- Dr. Miriam Grossman – Board-certified child, adolescent, and adult psychiatrist

Key Points:

- April 20, 2022 – FDOH issued guidance on the treatment of gender dysphoria in children and adolescents
- Secretary Simone Marstiller requested the division of Medicaid to determine what treatments are consistent with the process described in Florida Administrative Code 59G-1.035 with generally accepted professional medical standards
- As a result, Subsection 7 would be added to Rule 59G-1.050 to AHCA's general Medicaid policy
    - Subsection 7a provides that the Florida Medicaid program does not cover, and therefore, will not reimburse for the following services for the treatment of gender dysphoria:
        1. Puberty Blockers
        2. Hormones and Hormone Antagonists
        3. Sex Assignment Surgeries
        4. Any other procedures that alter primary or secondary sexual characteristics
    - Subsection 7b provides that for the purposes of determining medical necessity, including the early public screening of diagnosis of treatment, the services listed in Subsection 7a do not meet the definition of medical necessity I accordance with Rule 59G-1.104 Florida Administrative Code
- Rule 59G-1.035 identifies specific factors for determining guidelines that are covered by the Florida Medicaid program including:
    - Evidence-based clinical practice guidelines
    - Published reports and articles in the authoritative medical and scientific literature related to health services

Pl. Trial Ex. 305

Updated July 26, 2022

- Effectiveness of the health service in improving the individual's prognosis or health outcomes
- Utilization trends
- Coverage policies by other credible insurance payor services
- Recommendations or assessments by clinical or technical experts on the subject or field

- Cabinet's determination in the case and its report were published on AHCA's website on June 2, 2022
  - Document explains that the Florida Medicaid program determines that the effectiveness of the services listed above are "low to very low quality" and insufficient to demonstrate that such treatments conform with the guidelines set forth with Rule 59G-1.035
  - Florida Medicaid program determined that the specific services will not be covered

Comments:

Each speaker was allotted two minutes of speaking time. The speakers are listed below in the order in which they spoke. Those individuals whose names were inaudible are represented by "NAME." Those in favor of Rule 59G-1.050 are highlighted in blue while those opposed are highlighted in violet.

- Chloe Cole
  - 17-year-old detransitioner from California
  - Medically transitioned from ages 13-16
  - Was taken to therapist to affirm "male identity"
  - Took puberty blockers and injections
  - Had a double mastectomy at age 14
  - Experiencing many health complications

- Sophia Galvin
  - 22-year-old detransitioner
  - Began transitioning at 18
  - History of mental health
  - Had a double mastectomy at age 19

- NAME
  - Without her consent:
    - 16-year-old daughter was injected with hormones
    - At 17, Medicaid paid surgeons to perform double mastectomy and hysterectomy as an outpatient
    - At 19, Medicaid paid for her to undergo a vaginoplasty
  - Private insurance was bypassed

- Janette Cooper – Partners of Ethical Care
- Hannah Lambert
- Gerald Hustin – Christian Pastor
- Brady Hendricks
- Sabrina Clarksville
- Simone Christ – Director of the Transgender Rights Initiative at Southern Legal Counsel
- Dr. Matthew Benson – Board-certified pediatric endocrinologist
- Karen Schoen – Florida Citizens Alliance
- Bill Snyder
- NAME – Christian Family Coalition
- Richard Carlins
- Amber Hand
- Joan Hazen
- Leonard Lavon

- Pam Olsen
- John Harrison – Public Policy Director for Equality Florida
- Anthony Verdugo – Founder and Executive Director of the Christian Family CoalitioN
- NAME
- Michael Howeler – Professor and Chief of the Pediatric Neurology Division at University of Florida
- Robert Youells
- Keith Law – Florida SIDS Alliance
- Robert Roper
- Karl Charles – Senior Attorney with Atlanta, GA Office of Lambda Legal
- Ed Wilson
- Suzanne Zimmerman
- Judy Hollen
- Ezra Stone – Licensed Clinical Social Worker
- Peggy Joseph

- Jack Walton – Christian Family Coalition and Pastor
- Jose Button – Christian Family Coalition
- Bob Johnson
- Sandy West – Christian Family Coalition
- Gayle Carlin – Christian Family Coalition
- Dorothy Barron – Christian Family Coalition
- Troy Peterson – Christian Family Coalition and President of Warriors of Faith in Florida
- Janet Rath
- Harold Lower
- NAME – Pastor and Director of Protect Our Children Project
- Paul Aarons – Physician
- January Littlejohn – Licensed Mental Health Counselor
- Kendra Parris – Mental Health Attorney
- Nathan Bruemmer – Florida's LGTBQ Consumer Advocate (Appointed by Commissioner of Agriculture Nikki Fried)

- NAME

- Dottie McPherson – Florida Federation of Republican Women

- Maria Calkins

- James Calkins

- NAME

TAB 183-20

Florida Medicaid

Estrogen

Children

FY	Recipient Count	No.of prescriptions
FY2017-18	72	185
FY2018-19	87	212
FY2019-20	89	224
FY2020-21	151	391
Total	399	1,012

Adults

FY	Recipient Count	No.of prescriptions
FY2017-18	148	392
FY2018-19	168	486
FY2019-20	174	484
FY2020-21	223	688
Total	713	2,050

Puberty Blockers

Children

FY	Recipient Count	No.of prescriptions
FY2017-18	15	59
FY2018-19	23	58
FY2019-20	37	108
FY2020-21	55	180
Total	130	405

Testosterone

Children

FY	Recipient Count	No.of prescriptions
FY2017-18	130	330
FY2018-19	191	434
FY2019-20	248	615
FY2020-21	346	925
Total	915	2,304

Adults

FY	Recipient Count	No.of prescriptions
FY2017-18	63	174
FY2018-19	84	190
FY2019-20	87	210
FY2020-21	143	373
Total	377	947

Pl. Trial Ex. 317

Florida Medicaid

Children

Procedure Code	FY1718		FY1819		FY1920		FY2021	
	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count
19303-Mastectomy Simple Complete					2	4	3	6
19325-Breast Augmentation W/IMPLT								
53430-Reconstruction Of Urethra							1	1
54125-Amputation of penis; complete.							1	1
54520-Removal Of Testis	1	2					2	2
55180-Scrotoplasty; complicated.							1	1
55980-Sex Transformation F To M								
56805-Clitoroplasty							1	1
57110-Remove Vagina Wall Complete							1	1
57292-Construction of artificial vagina; with graft.							1	1
57335-Vaginoplasty							1	1
58571-Tlh W/T/O 250 G Or Less								
Total	**1**	**2**			**2**	**4**	**12**	**15**

Adults

Procedure Code	FY1718		FY1819		FY1920		FY2021	
	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count	Recipient Count	Procedure Code count
19303-Mastectomy Simple Complete	1	1	1	1	1	3	6	10
19325-Breast Augmentation W/IMPLT	1	1	1	2				
53430-Reconstruction Of Urethra							1	1
54125-Amputation of penis; complete.	1	1			1	1	1	1
54520-Removal Of Testis	1	1	1	1	5	7	2	3
55180-Scrotoplasty; complicated.								
55980-Sex Transformation F To M					1	1		
56805-Clitoroplasty	1	1					1	1
57110-Remove Vagina Wall Complete			1	1				
57292-Construction of artificial vagina; with graft.			1	1	2	2	1	1
57335-Vaginoplasty	1	1						
58571-Tlh W/T/O 250 G Or Less					1	1	1	2
Total	**6**	**6**	**5**	**6**	**11**	**15**	**13**	**19**

Florida Medicaid

H2019-Ther Behav Svc		
Children		
FY	Recipient Count	No.of prescriptions
FY2017-18	143	1,024
FY2018-19	192	1,467
FY2019-20	183	1,440
FY2020-21	233	1,775
Total	751	5,706

Adults		
FY	Recipient Count	No.of prescriptions
FY2017-18	15	69
FY2018-19	20	128
FY2019-20	19	140
FY2020-21	33	320
Total	87	657

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
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TAB 183-26

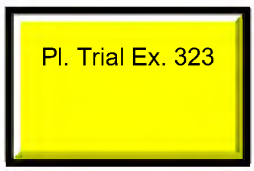
From: FL-Rules@dos.state.fl.us
Sent: Thursday, July 7, 2022 6:05 PM EDT
To: Cole.Giering@ahca.myflorida.com
Subject: One-time User Comment From FLRules.com

FLRules.com one-time comment:

Name: Ms.Mila Becker
Email: mbecker@endocrine.org
Title: 59G-1.050 General Medicaid
Comment: To Whom It May Concern:
The Endocrine Society strongly opposes the proposed rule, which would deny access to gender affirming care to the Florida Medicaid population. The Endocrine Society is the world's oldest and largest organization of scientists devoted to hormone research and physicians who care for people with hormone-related conditions. Many of our 18,000 members are recognized for their expertise in transgender medicine and research.

Our comments below are focused on responding to inaccurate and misleading statements about the Endocrine Society's clinical practice guidelines made in the report Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria (GAPMS) developed by Florida Medicaid in June 2022, which is used to justify the proposed rule.

Quality of Endocrine Society Clinical Practice Guidelines on Endocrine Treatment of Gender Dysphoric/Gender Incongruent Persons and the GRADE System
The Institute of Medicine (IOM) (now known as the National Academy of Medicine) defined clinical practice guidelines as "recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options." While guidelines are not standards of care that clinicians are legally bound to follow, they provide a framework for best practices, and deviations must be justified.
Endocrine Society guidelines are developed using a robust and rigorous process that adheres to the highest standards of trustworthiness and transparency as defined by the IOM. The Endocrine Society follows the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology to develop its recommendations. GRADE is the most accepted and internationally recognized standard for guideline development. Of the over 100 international groups that endorse GRADE, other prominent organizations using this methodology include the U.S. Agency for Healthcare Research and Quality, the U.S. Centers for Disease Control and Prevention, England's National Institute for Health and Care Excellence, and the World Health Organization. GRADE is a transparent framework for summarizing evidence and provides a systematic approach for making clinical practice recommendations.
GRADE begins with the formulation of clinical questions followed by a systematic review of the evidence that supports those questions. This evidence is used to develop and support the clinical recommendations that form the basis of the guideline. A certainty of evidence assessment is made for the overall body of evidence for a particular question on a scale from very low, low, moderate, to high. While some of the recommendations in the Endocrine Society's guideline are based on low or very low certainty evidence, strong recommendations can be made for low and very low certainty evidence in the GRADE system in some circumstances (Life threatening situation; uncertain benefit, certain harm; potential equivalence, one option clearly less risky or less costly, high certainty in similar benefits, one option potentially more risky or costly; potential catastrophic harm.) Additionally, the GRADE methodology does not account only for the certainty of the evidence when developing recommendations.
Systematic reviews of the effects of an intervention provide essential, but not sufficient information for making informed decisions. There are other factors that GRADE methodology requires guideline authors to account for including, most importantly, patient values and preferences, in making trade-offs between alternative courses of action.
Additionally, Endocrine Society guidelines are not developed in a vacuum. Guidelines take an average of 2-3 years to be developed through a multi-step drafting, comment, review, and approval process. This includes a public comment period and expert review period, and all comments are addressed by the guideline development panel prior to publication. Expert reviewers are subject to the same conflict of interest rules as panel members. There is ample opportunity for feedback and debate through this years-long development process.



Consequently, the Endocrine Society's guidelines represent a high-quality resource to be used for patient care based on medical evidence, author expertise, rigorous scientific review, and a transparent process. In contrast, GAPMS did not include endocrinologists with expertise in transgender medicine, misunderstands the use of the GRADE methodology and the notion of standard of care, and makes sweeping statements against gender affirming medical care that are not supported by evidence or references provided. Most disturbing, GAPMS does not acknowledge the data showing harm reduction and improvements in behavioral health issues, such as depression and anxiety, with gender affirming care.

Sufficiency of Evidence and Bar for Gender Affirming Care

The Endocrine Society and other medical and mental health organizations representing professionals who treat gender dysphoria/gender incongruence firmly believe there is sufficient evidence to support gender affirming care and to support that harm can occur if these people are not treated. The statement in GAPMS that "low quality" studies provide insufficient evidence for gender affirming care demonstrates a failure to understand medical literature. The medical literature terminology is appropriately conservative. But "low-quality" studies are typical for much of medical care and much better than "expert opinion," also common for medical care.

The Endocrine Society believes Florida is imposing a bar for care that is too high, will result in harm to people with gender dysphoria/incongruence, and is not used for other patients. GAPMS suggests that because puberty blockers are used off-label they are experimental and not safe. The fact is many treatments used in medicine are used off-label. That just means that medication is used for a purpose other than that for which the pharmaceutical company did the paperwork. Such prescribing is common. That is part of the reason states license physicians, to make those prescribing decisions. FDA approval and randomized controlled trials are simply too stringent. Most medical care occurs appropriately without those in place.

Scientific Evidence Indicates the Effectiveness of Treating Gender Dysphoria According to the Guidelines

The results of multiple studies indicate that adolescents suffering from gender dysphoria who receive medical interventions as part of their gender-affirming care experience improvements in their overall well-being. Eight studies have been published that investigated the use of puberty blockers in the care of adolescents suffering from gender dysphoria and six studies have been published that investigated the use of hormone therapy to treat adolescents suffering from gender dysphoria. These studies find positive mental health outcomes for those adolescents who received puberty blockers or hormone therapy, including statistically significant reductions in anxiety, depression, and suicidal ideation.

For example, a 2020 study analyzed survey data from 89 transgender adults who had access to puberty blockers while adolescents and from more than 3,400 transgender adults who did not. The study found that those who received puberty blocking hormone treatment had lower likelihood of lifetime suicidal ideation than those who wanted puberty blocking treatment but did not receive it, even after adjusting for demographic variables and level of family support. Approximately nine in ten transgender adults who wanted puberty blocking treatment but did not receive it reported lifetime suicidal ideation. Additionally, a longitudinal study of nearly 50 transgender adolescents found that suicidality was decreased by a statistically significant degree after receiving gender-affirming hormone treatment. As another example, a prospective two-year follow-up study of adolescents with gender dysphoria published in 2011 found that treatment with puberty blockers was associated with decreased depression and improved overall functioning. A six-year follow-up study of 55 individuals from the 2011 study found that subsequent treatment with hormone therapy followed by surgery in adulthood was associated with a statistically significant decrease in depression and anxiety. "Remarkably, this study demonstrated that these transgender adolescents and young adults had a sense of well-being that was equivalent or superior to that seen in age matched controls from the general population." As scientists and researchers, the Endocrine Society always welcomes more research, including on this crucial topic. However, the available data indicate that the gender-affirming treatments that would be denied by the proposed rule are effective for the treatment of gender dysphoria. For these reasons, the use of the gender-affirming medical interventions specified in the Endocrine Society's guidelines is supported by all mainstream pediatric organizations, representing thousands of physicians across multiple disciplines.

Statements in GAPMS are Factually Inaccurate and Ignore the Recommendations of the Medical Community

GAPMS asserts that most adolescents who experience gender dysphoria will later overcome it by confirming to their natal sex. This assertion lacks scientific support. While some prepubertal children who experience gender dysphoria may go on to identify with their sex assigned at birth by the time they reach puberty, there are no studies to support the proposition that adolescents with gender dysphoria will come to identify with their sex assigned at birth, whether they receive treatment or not. On the contrary, "[l]ongitudinal studies have indicated that the emergence or

worsening of gender dysphoria with pubertal onset is associated with a very high likelihood of being a transgender adult."
Further, GAPMS relies upon controversial research not recognized in the mainstream transgender medicine community. For example, it refers to a paper by Lisa Littman on Rapid Onset Gender Dysphoria (ROGD) – a condition that does not exist -- to justify not supporting gender affirming medical care for adolescents with gender dysphoria without noting the methodological concerns that have been raised regarding this paper, including the fact that only parents (recruited from anti-transgender websites) and none of the youth with gender dysphoria participated in the study, and that parents were not recruited from websites supportive of transgender youth. These methodological concerns prompted publication of a correction by the original author.

The Proposed Rule Would Irreparably Harm Many Adolescents with Gender Dysphoria by Denying Access to the Treatment They Need
The proposed rule would deny Medicaid beneficiaries with gender dysphoria access to medical interventions that alleviate suffering, are grounded in science, and are endorsed by the medical community. The medical treatments prohibited by the proposed rule can be a crucial part of treatment for people with gender dysphoria and necessary to preserve their health. As discussed above, research shows that people with gender dysphoria who receive puberty blockers and/or hormone therapy experience less depression, anxiety, and suicidal ideation. Several studies have found that hormone therapy is associated with reductions in the rate of suicide attempts and significant improvement in quality of life. In light of this evidence supporting the connection between lack of access to gender-affirming care and lifetime suicide risk, banning such care can put patients' lives at risk.
The Endocrine Society is eager to work with Florida to address these concerns and would be happy to connect Florida Medicaid with our transgender medicine experts. If we can be of assistance or provide any additional information, please contact our Chief Policy Officer at mbecker@endocrine.org.

Sincerely,

Ursula Kaiser, MD
President, Endocrine Society

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TAB 183-27

July 8, 2022

VIA E-MAIL AND WEBSITE

Simone Marstiller, Secretary
Tom Wallace, Deputy Secretary for Medicaid
Florida Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308
MedicaidRuleComments@ahca.myflorida.com

Re: Rule No. 59G-1.050: General Medicaid Policy

Dear Secretary Marstiller and Deputy Secretary Wallace:

We are writing to submit a public comment on a proposed amendment to Section 59G-1.050 of the Florida Administrative Code (the "Proposed Rule"), which, if adopted, would deny medical treatment to transgender individuals.[1] The Proposed Rule would apply to Medicaid members of any age and would deny coverage for puberty blockers, hormones, "sex reassignment surgeries," and "any other procedures that alter primary or secondary sexual characteristics."[2]

We are a group of seven scientists and a law professor, and we are deeply dismayed by the content of the Proposed Rule, which will deny long-established, effective, and evidence-based medical care to thousands of Florida Medicaid patients.[3] We are also distressed as scientists and stewards of public health by the shoddy quality of the purported scientific report offered to justify the Proposed Rule. The report, issued by the Florida Agency for Health Care Administration ("AHCA") on June 2, 2022 (hereinafter, "June 2 Report"), disregards well-established clinical practice guidelines and scientific research showing that standard medical treatments for gender dysphoria are "consistent with generally accepted professional medical standards" and are not "experimental or investigational."[4]

As discussed in depth below, we strongly oppose the adoption of the Proposed Rule. The Proposed Rule would violate the sex discrimination protections provided by the U.S. and Florida Constitutions and the federal statute that governs Medicaid by discriminating against transgender people on the basis of their sex, transgender status, and gender identity.[5] We are confident that other comments will focus in depth on the legal authorities that pre-empt the Proposed Rule.

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[1] 48 Fl. Admin. Reg. 2461 (June 17, 2022). The Notice of Development of Rulemaking was published in 48 Fl. Admin. Reg. 2270 (June 3, 2022) without any specification of the subject of the rulemaking.
[2] The Proposed Rule would add new subsection (7) to Fl. A dmin. Code Section 59G-1.050. See 48 Fl. Admin. Reg. 2461 (June 17, 2022).
[3] Our comments reflect our views and not those of the University of Alabama, the University of Texas, or Yale University.
[4] Division of Florida Medicaid, Agency for Health Care Adm inistration, Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria, June 2022, at https://www.ahca.myflorida.com/letkidsbekids/docs/AHCA_GAPMS_June_2022_Report.pdf ("June 2 Report").
[5] See Bostock v. Clayton County, 590 U.S. __ (2020); Kadel v. Folwell, M.D. N.C., Mem. Op. 6-10-22 (applying Bostock to public health plan coverage); 42 U.S.C. 18116 (requiring nondiscrimination in Medicaid plans).

Pl. Trial Ex. 324

Our comments focus instead on the absence of any persuasive scientific or medical justification for the Proposed Rule. The June 2 Report purports to be a review of the scientific and medical evidence but is, in fact, fundamentally unsound from a scientific perspective. The June 2 Report disregards established scientific knowledge, ignores longstanding clinical practice recommendations developed by authoritative bodies of medical experts, and unaccountably dismisses the medical recommendations of more than 20 medical societies.

As scientists, we are alarmed that Florida's health care agency has adopted a purportedly scientific report that so blatantly violates the basic tenets of scientific inquiry. The report contains glaring errors regarding science, statistical methods, and medicine. Ignoring established science, the report instead relies on biased and discredited sources, stereotyping, and purported "expert" reports that carry no scientific weight.

These fundamental flaws thoroughly discredit the conclusions of the June 2 Report, with two legal consequences. First, the complete absence of scientific foundation for the Proposed Rule renders it an arbitrary and capricious use of rulemaking power. Second, the Florida AHCA cannot characterize the Proposed Rule as a valid interpretation of the existing Florida regulations on generally accepted professional medical standards, because the June 2 Report fails to satisfy Florida's own regulatory requirements for scientific review.[6]

The seven scientists in our group hold academic appointments at the University of Alabama, the University of Texas Southwestern, and Yale University. (The law professor is a tenured professor at the Yale Law School.) We include three Ph.D child and adolescent psychologists and four M.D. physicians with specialties in pediatric endocrinology, child and adolescent psychiatry, and adolescent medicine. All seven are also clinicians who treat transgender youth on a daily basis. Among us, we have accumulated more than 57 years of clinical practice and have treated more than 2,100 transgender youth. We received no funding for our work and have no conflicts of interest to declare.

We are writing to comment on the Proposed Rule because we are concerned that it will harm transgender people in Florida and set a misleading and dangerous national precedent. We are committed to the integrity of science and law, and we strongly oppose legal actions that, like the Proposed Rule and the June 2 Report, claim the authority of science but provide only biased and misleading information. Youth, families, and medical providers in Florida deserve a higher standard of protection and service from their government.

In this comment letter, we focus on the science governing the treatment of gender dysphoria. Our observations are relevant to the treatment of both youth and adults. For example, we show that the June 2 Report falsely claims that the evidence for medical treatment for gender dysphoria does not meet generally accepted professional medical standards and is experimental. We also show that the June 2 report relies on purported "expert" reports that appear to be highly biased and with undisclosed conflicts of interest. To keep our comments focused and manageable in length, the one issue that we do not address is the science of genital surgery used to treat gender dysphoria, which is typically not performed before the age of majority. We are confident that the

[6] See Fl. Admin. Code Section 59G-1.035(1) and (4).

evidence base for surgical procedures is sound, and we are confident that others will address the June 2 Report's erroneous claims regarding surgery.

Throughout our comments, we refer to our companion report, *A Critical Review of the June 2022 Florida Medicaid Report on the Medical Treatment of Gender Dysphoria*, which is attached as Appendix A. The report goes into greater detail on many of the points we raise here.

Background

The AHCA appears to have taken a belt-and-suspenders approach to denying Medicaid coverage for standard medical treatment for gender dysphoria: the agency appears to be pursuing two legal strategies simultaneously. The June 2 Report reflects the first strategy, which frames the denial of care as an interpretation of the existing Florida Medicaid coverage regulations.[7] The Florida Medicaid program covers only health services that are "medically necessary" and excludes services that do not meet "generally accepted professional medical standards or are "experimental or investigational." The existing regulations permit the AHCA to determine when health services are consistent with generally accepted professional medical standards (GAPMS).

Specifically, the existing regulations authorize the Florida Deputy Secretary for Medicaid to make a final coverage determination; however, the Deputy Secretary does not have unfettered interpretive authority. The Florida Administrative Code sets out a detailed process, which requires the AHCA to prepare a report that considers scientific evidence including "evidence-based clinical practice guidelines" and "published reports and articles in the authoritative medical and scientific literature related to the health service (published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations)."[8] The June 2 Report purports to be such a report. It is titled a "Generally Accepted Professional Medical Standards Determination" and concludes that standard medical treatments for gender dysphoria "do not conform to GAPMS and are experimental and investigational."[9]

The AHCA has also pursued, simultaneously, a second legal strategy by publishing the Proposed Rule on June 17. The Proposed Rule makes no reference to the June 2 Report and contains no independent justification for the rule. The Proposed Rule would add a new subsection to Section 59G-1.050 of the Florida Administrative Code, Section (7), which would deny Medicaid coverage in Florida for medical care for gender dysphoria. The Proposed Rule would apply to Medicaid members of any age and would deny coverage for puberty blockers, hormones, "sex reassignment surgeries," and "any other procedures that alter primary or secondary sexual characteristics.[10] According to the Notice of Proposed Rule published in the Florida Administrative Register, a public hearing will be held on July 8, 2022, and public comments on the Proposed Rule may be submitted through that date.[11]

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[7] See June 2 Report, p. 2 (noting that the Secretary of the Florida Agency for Health Care Administration requested the report from the Florida Division of Medicaid pursuant to Section 59G1.035 of the Florida Administrative Code,
[8] Fl. Admin. Code Section 59G-1.035(4).
[9] The report makes specific reference to these rules.June 2 Report, p. 2.
[10] 48 Fl. Admin. Reg. 2461 (June 17, 2022).
[11] See id. and the instructions at https://www.flrules.org/Gateway/View_notice.asp?id=25979915

Analysis

In our comments below, we show that there is no scientific justification for the Proposed Rule and no scientific justification for the conclusions drawn in the June 2 Report.

1. The Proposed Rule would deny Florida Medicaid coverage for standard medical care for gender dysphoria, which is supported by a robust scientific consensus, meets generally accepted professional medical standards, and is neither experimental nor investigational.

The conclusion of the June 2 report – that medical treatments for gender dysphoria "do not conform to [generally accepted professional medical standards] and are experimental and investigational" -- is demonstrably false.

Medical care for the treatment of gender dysphoria, which for youth under the age of majority can include gonadotropin releasing hormone agonists ("GnRHa" or puberty blockers) and hormone therapy, has been vetted and approved by international bodies of experts based on the scientific evidence. Two authoritative bodies of scientists, the World Professional Association for Transgender Health (WPATH) and The Endocrine Society, have published extensive clinical practice guidelines for treating gender dysphoria.[13] These clinical guidelines are based on rigorous, structured processes. Each involves the work of a committee of scientific experts and peer review by additional experts. The guidelines are based on careful reviews of the scientific literature and are revised periodically to reflect scientific developments.

These longstanding clinical practice guidelines have been used by clinicians for decades. WPATH issued its initial guidelines in 1979 and updated them in 1980, 1981, 1990, 1998, 2001, and 2012. The eighth version remains in process, and it incorporates systematic literature reviews and ample opportunities for peer review and revision.[14] The original Endocrine Society guidelines were published in 2009 and updated in 2017.[15]

Reflecting this scientific and medical consensus, medical care for gender dysphoria has been confirmed as standard care by every relevant medical organization in the United States, including the American Academy of Pediatrics, the American Psychological Association, and the American Academy of Child and Adolescent Psychiatry.[16] In 2022, these organizations united

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June 2 Report, p. 2.

[13] See Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming Peopd, World Professional Association for Transgender Health (7th version, 2012), at https://www.wpath.org/publications/soc ("WPATH (2012)"); Wylie C. Hembree, et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, 102(11) J. Clin. Endocrinol. Metab. 38693903 (2017) ("Endocrine Society (2017)").

[14] See World Professional Association for Transgender Health (WPATH), Methodology for the Development of Standards of Care 8 (Soc 8), at https://www.wpath.org/soc8/Methodology

[15] Endocrine Society (2017), supra note 13.

[16] Jason Rafferty, Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents, 142(4) Pediatrics E20182162 (2018); American Psychological Association, Guidelines for Psychological Practice with Transgender and Gender Nonconforming People, 70(9) American Psychologist 832-64 (2015); Stewart L. Adelson, Practice Parameter on

with the American Medical Association, the American Academy of Family Physicians, the American College of Obstetricians and Gynecologists, and other groups to file an amicus brief representing a total of 20 major medical societies. The brief reaffirms that puberty blockers and hormone treatments for gender dysphoria are standard medical care and opposes legal measures that would limit patient access to this standard care.[17]

The weight and volume of these endorsements, across diverse medical specialties, sharply contradicts the June 2 Report's conclusion and undermines any purported scientific justification for the Proposed Regulation.

As further evidence, it is critical to note that the medications used to treat gender dysphoria are used commonly and safely in cisgender patients. Puberty blockers are the main treatment for central precocious puberty. Estrogen is prescribed for patients of all ages to manage fertility and reduce heavy menstrual bleeding (to give just two examples of its many uses). Testosterone is prescribed to address hypogonadism, and spironolactone (androgen blockade) is used to treat hirsutism and acne.

The Florida Medicaid program covers all these uses without question. The program authorizes physicians to tailor treatments to cisgender patients' needs and trusts patients (and, in the case of children, their parents) to make informed decisions. The Proposed Rule would deny coverage only for gender dysphoria, discriminating against transgender patients.

2. The June 2 Report appears to be a scientific report, but its veneer hides a flawed analysis that ignores the scientific evidence and relies on pseudo-science that does not meet Florida's own standards for review. The June 2 Report provides no scientific foundation for the Proposed Rule and fails to meet Florida's own regulatory requirements for Medicaid coverage determinations.

The Florida report dismisses or ignores the WPATH and Endocrine Society clinical practice guidelines and the science that underlies them and instead relies on five attached documents that, the report claims, constitute "clinical and technical expert assessments."[18]

Despite their billing as "expert" reports, the attachments to the June 2 report are unpublished, non-peer-reviewed documents written by authors with questionable claims to expertise and with red flags for undisclosed author bias. These documents should be given no weight in a serious scientific process.

The June 2 Report purports to be a coverage determination pursuant to Fl. Admin. Code Section 59G-1.035, but its reliance on these five documents constitutes a gross violation of the process set out in that regulation. The regulation requires that the AHCA consult actual scientific evidence, including "evidence-based clinical practice guidelines" and "*published* reports and

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Gay, Lesbian, or Bisexual Sexual Orientation, Gender Nonconformity, and Gender Discordance in Children and Adolescents, 51(9) J. Am. Acad. Child & Adolescent Psychiatry, 957 -974 (2012).

[17] Brief of Amicus Curiae American Academy of Pediatrics and Additi onal National and State Medical and Mental Health Organizations in Support of Plaintiffs' Motion for Temporary Restraining Order and Preliminary Injunction, Eknes-Tucker v. Ivey (later redesignated Eknes-Tucker v. Abbott), May 5, 2022, at https://www.aamc.org/media/60556/download

[18] June 2 Report, p. 2.

articles in the authoritative medical and scientific literature related to the health service (published in *peer-reviewed* scientific literature generally recognized by the relevant medical community or practitioner specialty associations)."[19]

The June 2 Report reads like a roadmap for how to violate these rules. The report disregards the evidence-based clinical practice guidelines published by WPATH and The Endocrine Society and relies entirely on the five attachments, which are not published, are not peer-reviewed, and are written by inexpert and biased authors.

A. The purported "expert" documents attached to the June 2 Report are unpublished and not peer-reviewed, and they are written by authors whose expertise has been successfully challenged in legal proceedings and whose professional histories raise red flags for bias.

None of the documents attached to the June 2 Report meet standard criteria for expert scientific investigations, because none is published or peer reviewed. Publication and peer review are fundamental to science, as they ensure that a scientist's data and conclusions are open to scrutiny from scientific experts.

Florida's own standards for the determination of medical necessity recognize this point when they state that determinations of Medicaid coverage must consult "*published* reports and articles in the authoritative medical and scientific literature related to the health service (*published in peer-reviewed scientific literature* generally recognized by the relevant medical community or practitioner specialty associations)."[20] It is thus both unscientific and a violation of the regulations for the June 2 Report to rely on unpublished documents as its principal evidence base.

Further, the attachments raise red flags for author bias. The June 2 Report does not disclose how these "experts" were identified or by what criteria their expertise was assessed. The opacity of the Florida AHCA process for identifying experts is particularly troubling because at least four of the five experts have strong indications of bias. Further, the qualifications and credibility of two of the experts have been successfully challenged in litigation.[21] The endorsement of these individuals as Florida's banner "experts" raises the appearance of bias – that the AHCA sought a pre-ordained outcome, not a true scientific perspective.

Adding to these red flags for bias, none of the authors of the attachments provide a statement of funding and conflicts of interest. This omission violates a strong norm in scientific writing, which requires authors to declare any professional or financial arrangements that could call into question their independence of judgment.[22] That strong norm also requires authors to disclose

[19] Fl. Admin. Code Section 59G-1.035(4).
[20] Fl. Admin. Code Section 59G-1.035(4).
[21] See Stephen Caruso, A Texas Judge Ruled That This Doctor Was Not an Expert, Pennsylvania Capital-Star, Sept. 15, 2020 (reporting that van Meter was disqualified as an expert in a Texas divorce case, now sealed).
[22] For example, the conflict of interest rules for JAMA, one of the premier medical journals in the United States and the world state that "[a]uthors are expected to provide detailed information about all relevant financial interests, activities, relationships, and affiliations (other than those affiliations listed in the title page of the manuscript) including, but not limited to, employment, affiliation, funding and grants received or pending, consultancies, honoraria or payment, speakers' bureaus, stock ownership or options, expert testimony, royalties, donation of

whether projects have been funded and if so, by whom and whether the authors have engaged in expert testimony. Without these statements, the Florida AHCA and the public cannot detect biases that could affect the integrity of these written products.

These are more than theoretical concerns: *four of the attachments have notable indicators of conflicts of interest and bias*. (Note that these are the only four we examined in detail, and so we do not imply that the other one is free from such bias.)

The author of the document provided as Attachment E is Quentin van Meter, whose history indicates bias and lack of expertise. Although the AHCA presents van Meter as an expert in medical treatment for gender dysphoria, at least one court barred him from providing expert testimony on the issue.[23] Van Meter is the president of the American College of Pediatricians (the "ACP"), which presents itself as a scientific group (and might be confused, by a non-expert, with the authoritative American Academy of Pediatrics). The ACP is, in fact, a political group that opposes same-sex marriage,[24] supports mental health providers practicing conversion therapy,[25] and describes gender dysphoria as "confusion."[26] Troublingly, the van Meter attachment, proffered by the AHCA as a scientific report, contains several passages of uncredited, verbatim language that appears in a "position statement" published by the ACP.[27] The van Meter attachment appears to be a re-use of paid testimony rather than an original product.[28]

James Cantor's document, presented as Attachment D to the June 2 Report, also faces serious questions about bias and lack of expertise. In a 2022 case, a federal court took a skeptical view of Cantor's purported expertise, giving his testimony little weight because Cantor has "no clinical experience in treating gender dysphoria in minors and no experience monitoring patients receiving drug treatments for gender dysphoria.[29] Cantor's document is nearly identical to what

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medical equipment, or patents planned, pending, or issued." JAMA Network, Instructions for Authors, visited June 22, 2022, at https://jamanetwork.com/journals/jama/pages/instructionsfor-authors#SecConflictsofInterestandFinancialDisclosures

[23] Caruso, supra note 21.

[24] Den Trumbull, Defending Traditional Marriage, American College of Pediatricians (2013), https://acpeds.org/position-statements/defending-traditional-marriage. See Jack Turban, The American College of Pediatricians is an Anti-LGBTQ Group, Psychology Today, May 8, 2017.

[25] Christopher Rosik and Michelle Cretella, Psychotherapy for Unwanted Homosexual Attraction Among Youth, American College of Pediatricians (2 016), https://acpeds.org/position-statements/psychotherapy-for-unwanted-homosexual-attraction-among-youth.

[26] Michelle Cretella, Gender Dysphoria in Children, American College of Pediatricians (2018), https://acpeds.org/position-statements/gender-dysphoria-in-children (site visited June 22, 2022). The author of the ACP position paper is Michelle Cretella, who was publicly rebuked by the Society for Adolescent Health and Medicine, the leading society for adolescent medicine in the United States, for "pushing political and ideological agendas not based on science and facts." https://www.adolescenthealth.org/Advocacy/Advocacy-Activities/2017-Activity/Senate-Bill-439-(2).aspx

[27] The similarity was shown by a Word comparison of the van Meter report provided as Attachment E to the June 2 Report with a "position statement" published on the ACP website, with authorship credit given on the website to Michelle Cretella. See Michell e Cretella, Gender Dysphoria in Children, supra note 26.

[28] The van Meter document attached to the June 2 Report is substantially identical to his expert declaration in Adams v. School Board of St. Johns County, Florida. https://files.eqcf.org/wp-content/uploads/2017/12/41-D-AMENDED-Notice-Documents-iso-Response-to-PI.pdf.

[29] Opinion and Order, Eknes-Tucker v. Marshall, 2:22-CV-184-LCB, M.D. Alabama, May 13, 2022.

appears to be paid testimony in another case, where Cantor's declaration was used to support legislation barring transgender athletes from sports teams,[30] Troublingly, Cantor's appearance in that case seems to have been funded by the Alliance Defending Freedom ("ADF"), [31] a religious and political organization that opposes legal protections for transgender people and same-sex marriage[32] and defends the criminalization of gay sex.[33]

Romina Brignardello-Petersen is one of two authors of the document provided as Attachment C to the June 2 Report. Although Brignardello-Petersen claims to have no research interests in medical care for transgender youth,[34] she has conducted research for the Society for Evidence-Based Gender Medicine ("SEGM").[35] Although SEGM claims to be an international medical society, it is, in fact, an advocacy group that opposes standard medical care for gender dysphoria. The SEGM has no publications or conferences and seems to consist solely of a website. The group appears to be run by a small group of people with limited or no scientific credentials and the website presents a cherry-picked collection of studies and narrative content that is full of scientific errors.[36]

Patrick Lappert, whose document is attached to the June 2 Report as Attachment F, has been disqualified as an expert in a recent federal court decision in North Carolina. [37] The judge found that the evidence "calls Lappert's bias and reliability into serious question" and noted that Lappert has worked closely with ADF and has actively lobbied for legal bans on medical care for

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[30] The case is BPJ v. West Virginia State Board of Education, and the Alliance Defending Freedom takes credit for it here: https://adfmedia.org/case/bpj-v-west-virginia-state-board-education. Cantor's declaration appears here: https://adfmedialegalfiles.blob.core.windows.net/files/BPJCantorDeclaration.pdf

[31] The ADF seems to take credit for the case in this press conference notice: https://adfmedia.org/case/bpj-v-west-virginia-state-board-education

[32] Marriage is the Future, American College of Pediatricians, https://adflegal.org/issues/marriage/overview (site visited July 2, 2022. Content on the page includes this statement: "Marriage is about equality and diversity. It's about joining the two equally important and diverse halves of humanity represented in men and women."

[33] Southern Poverty Law Center, Dangerous Liaisons, July 10, 2013, https://www.splcenter.org/20130709/dangerous liaisons [visited July 2, 2022].

[34] Like the van Meter and Cantor attachments, the BPW document provides no express statement of conflicts of interest. The BPW document does offer a statement of "credentials and expertise," in which she declares that "her research interests are not in this area," meaning apparently research on medical care for gender dysphoria. BPW Document, p. 1.

[35] BPW document, p. 1. For one example of the purported research that Brignardello-Petersen apparently assisted in, see Alison Clayton et al., Commentary: the Signal and the Noise– Questioning the Benefits of Puberty Blockers for Youth with Gender Dysphoria – A Commentary on Rew et al. (2021), Child and Adolescent Mental Health, Dec. 22, 2021, at https://acamh.onlinelibrary.wiley.com/doi/10.1111/camh.12533 In the "Acknowledgements" section, the authors state, "We would also like to thank the Society for Evidence-based Gender Medicine (SEGM) for providing access to several experts who helped shape this commentary and ensure its accuracy. Specifically, we would like to thank Dr. Romina Brignardello Petersen [sic] for contributing her methodological expertise."

[36] Susan Boulware et al., Biased Science: The Texas and Alabama Measures Criminalizing Medical Treatment for Transgender Children and Adolescents Rely on Inaccurate and Misleading Scientific Claims (April 28, 2022), at 28-29 (Appendix A) available at https://medicine.yale.edu/childstudy/policy-and-social-innovation/lgbtq-youth/.

[37] Kadel v. Folwell, 1:19CV272, M.D. N.C. June 10, 2022. The judge ruled that Lappert was not qualified to "render opinions about the diagnosis of gender dysphoria, its possible causes, the efficacy of the DSM, the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for mental health professionals or endocrinologists, or any opinion on the non-surgical treatments." Lappert was also disqualified from opining on "the efficacy of randomized clinical trials, cohort studies, or other longitudinal, epidemiological, or statistical studies of gender dysphoria." Id.

transgender youth.[38] The judge gave no weight to Lappert's testimony about informed consent, finding that it was unsupported by scientific evidence.[39] The judge also found that "Lappert has provided the Court with no data or methodology used to draw his conclusion that surgical treatment for gender dysphoria has "never been generally accepted by the relevant scientific community."[40]

B. The linchpin of the June 2 Report is the analysis by Brignardello-Petersen and Wiercioch (the "BPW document"), provided as Attachment C, which purports to be a comprehensive review of the scientific literature but, in fact, is extremely narrow in scope and so flawed in its analysis that it merits no scientific weight at all.

The BPW document, like the other attachments to the June 2 Report, is an unpublished, non-peer-reviewed document. It is written by inexpert authors who construct an arbitrarily truncated sample and adopt a method that violates scientific guidelines and produces a biased result. The authors describe their findings in deceptive language and jargon predictably mislead the reader. Our review shows that *nothing in the BPW document calls into question the scientific foundations of the WPATH and the Endocrine Society clinical practice guidelines.*

The BPW document seems scientific on its face, because it uses technical jargon and includes numerous tables and charts. But a closer examination shows that it violates established standards for medical research and shows signs of being engineered to produce a pre-ordained and inaccurate result.

The bottom line is that, contrary to the BPW document's claims, there is a large body of reliable scientific literature that supports standard medical treatment for gender dysphoria.

(1) The BPW document lacks scientific credibility due to the authors' lack of relevant qualifications and their ties to an activist group.

The BPW document purports to be a systematic review of the scientific literature on medical treatment for gender dysphoria, but it is full of errors and omissions, resulting in a biased and misleading result. Here, we describe just three of the notable defects that undercut entirely the document's claim to objectivity and sound method. We provide additional detail on these errors in the Appendix to these comments.

First, *neither of the BPW authors are experts* in medical care for gender dysphoria, either as researchers or clinicians. One author (Brignardello-Petersen) has not previously studied the subject, except in her work for the ideological organization SEGM.org, noted just above. Her only clinical experience appears to be in dentistry.[41] The other author (Wiercioch) is a junior researcher (a postdoctoral fellow) with no prior research or clinical experience in this field.[42]

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[38] Id.
[39] Id., pp. 29-30.
[40] Id., p. 31.
[41] Romina Brignardello bio, at https://experts.mcmaster.ca/display/brignarr[visited July 2, 2022]
[42] Google Scholar, Wojtek Wiercioch, visited June 22, 2022, https://scholar.google.com/citations?user=vdi3r_AAAAAJ&hl=en

The authors' lack of interest and experience renders the BPW work inexpert rather than objective, and it violates the National Academy of Medicine standards for systematic reviews.[43] By analogy, one would not rely on, say, two dermatologists to conduct a review of the scientific literature on neurosurgery and to make recommendations for clinical practice.

Second, not only is the study not formally peer-reviewed, the BPW authors violate scientific norms and standards by *failing to engage at all with their peers or with actual experts* in the subject matter.[44] The BPW authors appear not to have published their protocol in advance or otherwise to have submitted their protocol for peer review.

Third, the BPW document raises red flags for opinion bias. Buried in the methodology pages of the BPW document is the fact that the authors include the fringe website SEGM.org.[45] As noted above, the group's website posts are not peer-reviewed or published, and its cherry-picked content is assembled by activists and is often full of errors.[46] Troublingly, this is the group to which one of the authors, Brignardello-Petersen, has ties, as noted above.

(2) The BPW document violates scientific standards for evaluating medical evidence. The picture that emerges is of a rushed and inexpert report with indications of bias.

The BPW document has a patina of scientific expertise. It invokes the respected GRADE standards for rating the quality of studies, and it occupies many pages with tables and technical specifications. When a reader looks past the jargon, however, the BPW authors adopt a method that violates scientific standards and appears to be jury-rigged to reach a foregone conclusion. The authors convey their conclusions in misleading language. *Contrary to the BPW authors' claims, their study does not call into question the scientific and clinical importance of the established science that supports medical care for gender dysphoria.*

The BPW analysis incorporates numerous decisions that bias the results, and the authors describe their findings in grossly misleading terms. To begin, the BPW document reviewed only a small sample of the relevant scientific literature. In the introduction, the BPW authors initially claim to have reviewed 61 systematic reviews of medical treatment for gender dysphoria.[47] But buried in

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[43] Committee on Standards for Systematic Reviews of Comparati ve Effectiveness Research, Institute of Medicine, Finding What Works in Health Care: Standards for Systematic Reviews, National Academies (Jill Eden et al., eds 2011), p. 48 (Standard 2.1.1 states that teams for systematic reviews should include expertise in pertinent clinical content areas). Background: The Institute of Medicine, now called the National Academy of Medicine, is one of three branches of the National Academies of Science, Engineering, and Medicine. The National Academy of Science dates to 1963 and was established by Congress; the Institute of Medicine was established as a separate entity in 1970 and serves as the nation's leading authority on scientific research and knowledge. National Academy of Medicine, About the National Academy of Medicine, website visited June 22, 2022, https://nam.edu/about-the-nam/ The standards for systematic reviews were published in 2011, responding to a Congressional request to set benchmarks for high-quality systematic reviews that could reliably guide physicians and healthcare providers in making informed, scientific judgments about health care.

[44] For additional detail, see the Appendix.

[45] BPW document, Methods section, p. 2.

[46] See Boulware et al., supra note 36, pp. 28-29 (Appendix A).

[47] BPW document, Introduction Section, p. 2.

the middle of the document is the admission that the analysis is based on a sample of 27 systematic reviews, not 61 as claimed.[48]

Troublingly, the authors also embed in the middle of their technical document an unjustified decision to limit their analysis to studies published from 2020 to the present. The authors disclose that they "prioritized" studies from the last 30 months (two full years plus four months in 2022), but they do not defend that priority. The reader is left to wonder whether this truncation served only to help the authors produce their analysis in a very short time frame.

Further, the BPW authors mechanically apply a series of rating systems (AMSTAR and GRADE) for assessing the quality of scientific evidence, but their use violates key principles for using these systems. Based on this mechanical review of truncated sources, the BPW analysis reaches the conclusion that there is little or no evidence for the benefits of medical care for gender dysphoria.[49]

But the BPW analysis is deceptive, because it dismisses nearly all existing studies of medical treatment for gender dysphoria as "low quality," without explaining that this is a highly technical term and not a natural-language condemnation of the studies. By contrast, the GRADE system, which the authors purport to use, is quite clear about its quality rating systems and its limitations.[50] We provide additional detail on the authors' misuse and deceptive statements in the Appendix.

The key point is that "low quality" in this context is a technical term and not a condemnation of the evidence, because "low quality" studies regularly guide important aspects of clinical practice. Indeed, the GRADE system, which the BPW document claims to use, specifically notes that GRADE should *not* be used to dismiss observational studies or to give absolute priority to RCTs:

> Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not imply a particular strength of recommendation. *Sometimes, low or very low quality evidence can lead to a strong recommendation*.[51]

The methodology adopted by the BPW document will thus, predictably, conclude that any body of scientific literature that does not contain RCTs is "low" in quality. The 30 pages that it takes the authors to lay out their methodology is thus extremely misleading: a knowledgeable reader

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[48] BPW document, Results Section, p. 1.

[49] For example, the BPW document states that there is *evidence* about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. BPW document, Results section, p. 4.

[50] See Howard Balshem et al., GRADE Guideline: 3. Rating the Quality, 64 J. Clinical Epidemiology P401-406 (2011), Table 3, p. 404

[51] Balshem et al., supra note 50, at 402 (emphasis added).

would know that if there are few or no RCTs in the literature, then the BPW technical conclusion is foregone, and, as importantly, is not a sound guide for clinical recommendations.

Put in simpler terms, if we coded apples as "high quality fruit" and bananas as "low quality fruit," then any fruit bowl that has only bananas would predictably be technically coded as "low quality." But that technical conclusion conveys very little information without context. For example, if no apples exist, then bananas may be a nutritious choice.

The drafters of the GRADE system emphasize that technically "low quality" evidence can support a strong clinical treatment recommendation. For example, pediatricians now agree – and every parent has been told -- that children should not be given aspirin for fevers. This recommendation is based on observational studies that showed an association between aspirin treatment during viral illnesses and the development of Reyes syndrome (a rapid and progressive disease of neurological dysfunction that can be fatal). Based on those studies, it would be unethical to conduct an RCT giving some children aspirin, and so the strong, consensus treatment recommendation is based entirely on "low quality" studies.[52]

The critical fact is that RCTs are not, and cannot be, the gold standard for medical research on gender dysphoria, due to strong ethical constraints. Medical care has long been shown, by reliable scientific methods, to address gender dysphoria and improve mental health: as we have repeatedly noted, these treatments have been recommended by rigorous clinical practice guidelines issued by WPATH and the Endocrine Society and endorsed by every major medical organization. Given this medical consensus, which is based on solid scientific evidence, it would be unethical to conduct an RCT that involved denying standard medical care to a control group of individuals.

It is thus simply a mistake – and a mischaracterization of medical research – to conclude that the absence of RCTs means that there is "no evidence" for the efficacy of medical treatment for gender dysphoria.

3. The June 2 Report reflects a faulty understanding of statistics, medical regulation, and scientific research, and it repeats discredited claims and engages in speculation and stereotyping without scientific evidence. The report therefore provides no scientific support for the Proposed Rule or for an interpretation of existing Florida Medicaid standards.

The June 2 Report provides no credible scientific support for the Proposed Rule, because its analysis is full of errors and misstatements. In this section, we offer seven examples, all of which are documented in more detail in the Appendix to these comments.

> A. The June 2 Report repeatedly and erroneously dismisses solid studies as "low quality." If Florida's Medicaid program applied the June 2 Report's approach to all medical procedures equally, it would have to deny coverage for widely-used medications like statins (cholesterol-lowering drugs taken by millions of older Americans) and common medical procedures like mammograms and routine surgeries.

[52] Balshem et al., supra note 50, at 402.

In its opening words, the June 2 Report makes an error that is repeated throughout the document: "Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased."

As we document in Section 2.B., above, it is an outright mistake to conclude that a study in the technical category of "low quality" is unreliable or poor evidence for clinical practice.[53] We provide additional analysis of the misuse of this language in the June 2 Report in the Appendix.

It is quite common for consensus medical practices to be supported only by technically "low quality" but respected observational studies – without RCTs. For example, the famous Framingham Heart Study provided the framework for clinical practice guidelines that support the use of statins, a cholesterol-lowering drug that is effective in preventing cardiovascular death.[54]

The statins example shows that the June 2 Report rests on a fundamental misunderstanding of medical research and clinical practice. If the Florida Medicaid program actually adopted the standard of evidence urged by the June 2 report, the program would not cover statins, which are prescribed to 28% of adults over the age of 40.[55] Other common practices that would have to be reconsidered under this logic include post-menopausal hormone replacement therapy (which reduces lifetime risk of heart attacks and stroke) and mammography screening for breast cancer.

The same point is true of the technically "low quality" evidence base for many surgical procedures, including minimally invasive gall bladder surgery, which has a solid evidence base in observational studies. We think it unlikely that Florida's Medicaid program will begin to refuse to pay for statins, mammograms, and routine surgeries. If not, then the June 2 Report and the Proposed Rule reflect an untenable and discriminatory double standard.

> B. The June 2 Report disregards robust clinical research studies and instead relies on sources with no scientific credibility. The report's analysis fails to satisfy Florida's own regulatory standards for Medicaid coverage decisions and provides no scientific foundation for the Proposed Rule.

The June 2 Report repeatedly cites sources with little or no scientific credibility – including journalism, a student blog, a website, and letters to the editor – rather than peer-reviewed empirical research, in violation of Florida's own regulatory standards.[56] At the same time, the

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[53] Balshem et al., supra note 50, at 404 ("Well-conducted studies may be part of a body of evidence rated low quality because they only provide indirect or imprecise evidence for the question of interest.")

[54] Neil J. Stone, et al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Red uce Atherosclerotic Cardiovascular Risk in Adults, 129(25) Circulation S1 -S45 (2014).

[55] Joseph A. Salami et al., National Trends in Statin Use and Expenditures in the U.S. Adult Population From 2002 to 2013, 2(1) JAMA Cardiology 56-65 (2017).

[56] Sources from journalism include Jon Brown, Medical Textbook Strips Gender Dysphoria Definition after Being Cited by Florida, Fox News, May 8, 2022, at 8 https://www.foxnews.com/politics/textbook-strips-gender-dysphoria-definition-cited-florida [visited July 3, 2022; Lawrence S. Mayer and Paul McHugh, Sexuality and Gender: Finding from the Biological,Psychological, and Social Science, The New Atlantis (Fall 2016), https://www.thenewatlantis.com/wp-content/uploads/legacy-pdfs/20160819_TNA50SexualityandGender.pdf [visited July 3, 2022]. The citation to the student blog is Hong Phuong Nhi Le, Eminence-Based Medicine vs. Evidence-Based Medicine, Students 4 Best Evidence

report makes baseless or exaggerated criticisms of solid studies. Here, we offer only brief examples, with additional illustrations in the Appendix showing how selective and ungrounded criticism permeates the June 2 Report and further undermines its scientific credibility.

For example, the June 2 report attacks a 2015 study by Costa et al., claiming that the study design is flawed because it did not include a control group of adolescents without gender dysphoria.[57] This point is incorrect: as the Appendix to this report explains, the Costa et al. study did include an appropriate control group.

In addition to glaring technical errors, the June 2 Report's criticism of Costa makes an even more fundamental error: the June 2 report levels baseless criticisms at a single study *and fails to acknowledge that the weight of the literature as a whole strongly supports the same results Costa et al. report*. Scientific knowledge is, importantly, cumulative. It is thus entirely misleading – and unscientific – to dismiss the effectiveness of puberty blockers by criticizing studies in isolation. Put simply, the June 2 Report fails to acknowledge the number of solid studies that all find that puberty blockers are effective.[58] Indeed, at least 16 studies show that puberty blockers and hormones benefit patients with gender dysphoria, and the benefits have been documented across study designs, including retrospective report, cross sectional, longitudinal, and qualitative.[59]

The June 2 Report also grossly misleads the reader in its discussion of a study by Chen et al. in 2020[60] and a study by DeSanctis et al. in 2019.[61] The Appendix discusses these examples at

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[blog], https://s4be.cochrane.org/blog/2016/01/12/eminence-based-medicine-vs-evidence-based-medicine/#:~:text=What%20is%20eminence-based%20medicine [visited July 3, 2022]. The website is SEGM.org, which we discuss in the text in Section 2. Citations to letters and opinion pieces include, inter alia, Andre van Mol, et al., Gender-Affirmation Surgery Conclusion Lacks Evidence, 177(8) Am. J. Psychiatry 765-766 (2020); Michael Laidlaw, et al., The Right to Best Care for Children Does Not Include the Right to Medical Transition, 19(2) Am. J. Bioethics 75-77 (2019); Michael Laidlaw, et al., Letter to the Editor: "Endocrine Treatment of Dysphoric/Gender Incongruent Persons: An Endocrine Society Clinical Prace Guideline," 104(3) J. Clinical Endocrinology and Metabolism 686687 (2018); Andre van Mol, et al., Gender-Affirmation Surgery Conclusion Lacks Evidence, 177(8) Am. J. Psychiatry 765 -766 (2020).

[57] June 2 Report, p. 15 ("Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control"). The Costa study is Rosalia Costa et al., Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria, 12 (11) J. Sexual Medicine P2206-2214 (2015) (hereinafter, "Costa et al. (2015)."

[58] See Luke R. Allen, et al., Well-Being and Suicidality Among Transgender Youth after Gender -Affirming Hormones, 7(3) Clinical Practice in Pediatric Psychology 302 -11 (2019); Amy E. Green, et al., Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth, 70(4) J. Adolescent Health 643-649 (2022); Jack L. Turban, et al., Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145(2) Pediatrics e20191725 (2020); Maureen D. Connolly, et al., The Mental Health of Transgender Youth: Advances in Understanding59(5) J. Adolescent Health 489-95 (2016); Gemma L. Witcomb et al., Levels of Depression in Transgender People and its Predictors: Results of a Large Matched Control Study with Transgender People Accessing Clinical Services, J. Affective Disorders (2018)..

[59] For citations, see Boulware et al., supra note 36, at n. 43.

[60] Diane Chen, et al., Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Pubertal Suppression in Transgender Youth, Transgender Health 246257 (2020).

[61] Vincenzo De Sanctis, et al., Long-Term Effects and Significant Adverse Drug Reactions (ADRs)Associated with the Use of Gonadotropin-Releasing Hormone Analogs (GnRHa) for Central Precocious Puberty: a Brief Review of Literature, 90(3) Acta Biomed. 345-359 (2019).

length. As a final example, the June 2 Report criticizes a 2019 preliminary study by Kuper et al. without acknowledging the existence of a more extensive 2020 study by Kuper et al.[62] The earlier study presented data on the mental health of adolescents when initially presenting for care; only the later study presented full data that demonstrated the benefit of treatment.

> C. The June 2 Report mistakenly claims that puberty blockers and hormones are experimental because they are used "off-label" and not approved by the FDA. In fact, off-label use, when supported by scientific evidence, as here, is extremely common in medical practice and especially in pediatrics.

The June 2 Report repeatedly notes that the FDA has not approved the use of puberty blockers and hormones for the treatment of gender dysphoria in minors.[63] The report infers that lack of FDA approval renders a treatment unauthorized and experimental, but this is false. Once again, the June 2 Report (mis)uses technical language to confuse readers.

The term "off-label" has a very specific meaning: a drug is off-label if the FDA has not approved a particular medication for a particular use in a specific population. The off-label use of medications for children is common and often necessary, because an "overwhelming number of drugs" have no FDA-approved instructions for use in pediatric patients.[64]

The lack of FDA approval does not imply that the use of medications should be restricted. There is a consensus in the medical community that off-label use is necessary because of limits imposed by burdensome and expensive regulatory processes. Pharmaceutical companies often lack financial incentives to support research required for FDA approval for specific use in children.[65]

The American Academy of Pediatrics, recognizing these facts, specifically authorizes the off-label use of drugs:

> The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, *the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use.* Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient.[66]

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[62] June 2 Report, p. 16. The earlier Kuper et al. study is Laura E. Kuper et al., Baseline Mental Health and Psychosocial Functioning of Transgender Adolescents Seeking Gender-Affirming Hormone Therapy, 40(8) J. Dev. Behav. Pediatr. 589-596 (2019). The later study is Laura E. Kuper et al., Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy, 145(4) Pediatrics e20193006 (2020).

[63] June 2 Report, pp. 8, 14, 15, 19.

[64] Boulware et al, supra note 36, quoting Kathleen A. Neville, et al., American Academy of Pediatrics Committee on Drugs, Off-label use of drugs in children, 133(3) Pediatrics 563-7 (2014) ("AAP Committee on Drugs")

[65] AAP Committee on Drugs (2014), supra note 64.

[66] AAP Committee on Drugs (2014), supra note 64 (emphasis added). See also Lenneke Schrier, et al., Off-label Use of Medicines in Neonates, Infants, Children, and Adolescents: a Joint Policy Statement by the European Academy of Paediatrics and the European Society for Developmental Perinatal and Pediatric Pharmacology, 179(5) Eur. J. Pediatr 839-845 (2020).

Off-label use is so common in pediatrics that off-label drugs are prescribed in 20% of patient visits.[67] We discuss numerous examples in the Appendix, but a few familiar examples provide illustrations of day-to-day, off-label use in pediatrics.[68]

As many parents know, the use of steroids for croup is a life-saving treatment that is off-label. The medication helps toddlers get through severe, potentially airway-obstructing illnesses safely. Ondansetron (Zofran) is used off-label for nausea and vomiting to prevent dehydration.

In psychiatry, some of the most commonly-prescribed medications for youth are off label. For example, selective serotonin reuptake inhibitors (SSRIs) are used to treat major depressive disorder in adolescents and have been shown to be effective, even though several are off-label.[69] Another common example is clonidine, which is FDA-approved for attention deficit hyperactivity disorder (ADHD) but is used off-label for anxiety, insomnia, and post-traumatic stress disorder (PTSD).[70]

Finally, the June 2 Report notes that testosterone is a controlled substance and is subject to risk of abuse, but, once again, this is misleading. The inclusion of testosterone on the schedule of controlled substances reflects the misuse of the drug by some individuals and communities (e.g., weightlifters and athletes who may use the drug to build muscle). The classification does not in any way imply that physicians should not dispense the drug if medically necessary. No special license is necessary for prescribing the medication, which is routinely prescribed to cisgender men with testosterone deficiency.

> D. The June 2 Report falsely claims that medical care for gender dysphoria is provided to a large percentage of children who will come to regret their treatment. In fact, patients with gender dysphoria have vanishingly low rates of regret regarding their medical treatment.

The June 2 Report attempts to cast doubt on medical treatment for gender dysphoria by repeating the debunked claim that most transgender teens ultimately reject their transgender identity. Below, we analyze two related claims made in the report and show why both are refuted by sound evidence. We provide additional detail in the Appendix.

First, the report claims that "the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex."[71] This is false. We have refuted this claim in detail in prior work. The key point is that *adolescents with gender dysphoria rarely find*

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[67] Diya Hoon, et al., Trends in Off-Label Drug Use in Ambulatory Settings: 2006-2015, 144(4) Pediatrics 1-10 (2019) (emphasis added).
[68] These examples are drawn from the list of off-label uses in AAP Committee on Drugs (2014) and reflect our clinical experience in major hospitals and clinics.
[69] For AACAP guidelines, see Boris Birmaher and David Brent, Practice Parameter for the Assessment and treatment of Children and Adolescents with Depressive Disorders, 46(11) J. Am. Acad. Child and Adolescent Psychiatry P1503-1526 (2007).
[70] Rama Yasaei and abdolreza Saadabadi, Clonidine, National Library of Medicine (2022), at https://www.ncbi.nlm.nih.gov/books/NBK459124/[visited July 4, 2022].
[71] June 2 Report, p. 14.

that their dysphoria resolves without treatment.[72] Because medical treatment for gender dysphoria begins only in adolescence, and only if medically necessary, medical treatment is thus provided only to a group known to be quite stable in their gender identity.

Second, the June 2 report claims that many transgender people regret their medical treatment. This is false. We provide a detailed discussion in the Appendix, but the scientific evidence is clear: solid studies show very low percentages of regret (typically under 1%) among transgender people who receive medical treatment for gender dysphoria. For example, Bustos et al. (2021) found regret expressed by one percent or fewer of transgender patients who underwent gender-affirming surgery, and Danker et al. (2018) report a rate of far less than 1%, as do Wiepjes et al. (2015).[73]

> E. The June 2 Report repeats discredited claims that "social contagion" is leading teens to become transgender. Scientific evidence refutes this claim, which is based on a single, discredited study whose results have not been replicated by more rigorous studies.

The June 2 Report claims that "social factors (e.g., peer influences and media) may be contributing factors to gender dysphoria,"[74] citing as evidence a single, discredited study by Littman. We have addressed this claim at length in other work and note that the study incorporated such serious methodological errors that the journal of publication required an extensive correction because of the article's misstatements. [75]

Littman's sensationalist hypothesis has been widely covered in the press, but no clinical studies have found that rapid-onset gender dysphoria exists. Further, no professional organization has recognized "rapid-onset gender dysphoria" as a distinct clinical condition or diagnosis.

Most recently, an April 2022 study of 173 youth presenting at Canadian gender clinics *found no evidence of rapid-onset dysphoria or social contagion.* The researchers posited that if "rapid onset" gender dysphoria were a real phenomenon, then teens who had more recently begun identifying as transgender would (per the Littman hypothesis) also be more likely to report online support and engagement in their gender identity. They might also (per Littman's hypothesis) be more likely to struggle with mental health concerns.

An April 2022 study of 173 youth found no such correlations, strongly undercutting the "rapid-onset" hypothesis endorsed by the June 2 report. The researchers controlled for age and sex assigned at birth and looked for correlations with recent gender knowledge (defined as less than one to two years having passed since "you realized your gender was different from what other people called you"). Recent gender knowledge was *not* significantly associated with depressive symptoms, psychological distress, past diagnoses with comorbid mental health issues or neurodevelopmental disorders, or self-harm. Nor was it associated with having gender-

[72] Boulware et al., supra note 36, at 17-19.
[73] Id.
[74] June 2 Report, p. 12.
[75] Boulware et al., supra note 36, at 20-21 (internal citations omitted).

supportive online friends, general support from online friends or transgender friends, or gender support from parents.[76]

Data do substantiate that younger people today are more likely to identify as transgender than are older people, but this does not substantiate the idea of social contagion. The increase may be due to a cohort effect associated with the increasing social acceptance of gender diversity (i.e., older people grew up in a much more restrictive and transphobic social environment). In fact, adolescent presentation of transgender identity is often observed and should not be pathologized.[77]

Further, the data do not show a massive wave of transgender identity even among teens. A 2022 study by the Williams Institute found that, using an expansive definition of "transgender," about 0.5% of adults now identify as transgender, while 1.4% of youth aged 13-17 do, or about 300,000 young people.[78] This is not a large percentage or a large absolute number.

The June 2 Report's social contagion claim also disregards the enormous social pressure on teenagers to adopt a cisgender identity; transgender teens face significant discrimination and violence by asserting their gender identity and report very high rates of bullying at school.[79] Further, the evidence shows that teens (like adults) tend to use social media for emotional support and to access a helpful peer group that may not be available in person.[80]

Ultimately, however, the social contagion hypothesis is irrelevant to the question whether medical care for gender dysphoria is effective. As we have noted, medical treatments are not offered to all gender-questioning youth. Instead, the WPATH and Endocrine Society standards recommend drug therapies for transgender adolescents whose interdisciplinary medical team has determined that they have lasting and intense gender dysphoria and that treatment is medically necessary.

> F. The June 2 Report claims that inappropriate medical care is provided to adolescents with gender dysphoria who also have anxiety, depression, and other mental health conditions. These assertions are unsupported by evidence and disregard evidence-based clinical practice guidelines that provide sound guidance for treating complex cases.

The June 2 Report speculates that because "a high proportion" of youth receiving medical care for gender dysphoria also have a behavioral health disorder, "available research raises

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[76] Greta R. Bauer, et al., 243 J. Ped iatrics 224-227 (2022).

[77] In the largest U.S. sample of transgender adults, over half reported first starting to realize that they were transgender in adolescence (57% ages 11-20) and roughly half (47%) started to disclose their identity during this time frame. Sandy E. James, et al., The Report of the 2015 U.S. Transgender Survey, National Center for Transgender Equality (2015).

[78] Jody L. Herman, et al., How Many Adults and Youth Identify as Transgender in the United States?, U.C.L.A. School of Law, Williams Institute (2022).

[79] See, Joseph G. Kosciw, et al., The 2019 National School Climate Survey, GLSEN (2019), https://www.glsen.org/sites/default/files/2021-04/NSCS19-FullReport-032421-Web_0.pdf [visited July 3, 2020].

[80] Ashley Austin, et al., It's My Safe Space: The Life -Saving Role of the Internet in the Lives of Transgender and Gender Diverse Youth 21(1) Int'l J. Transgender Health 33-44 (2020); Ellen Selkie, et al., Transgender Adolescents' Uses of Social Media for Social Support, 66(3) J. Adolescent Health 275280 (2020).

questions as to whether the [individuals'] distress is secondary to pre-existing behavioral health disorders and not gender dysphoria."[81] In simpler terms, the June 2 Report speculates that perhaps gender dysphoria is not real but is, rather, an imagined by-product of underlying mental illness.

A close examination shows that this claim has no foundation in science; it rests on unexamined and harmful stereotypes and unaccountably dismisses the scientific knowledge and clinical skill of child and adolescent psychologists and psychiatrists. Here, we briefly explain why the June 2 Report's speculations are scientifically unfounded. We provide further detail on these points in the Appendix.

The June 2 Report implicitly posits that behavioral health disorders cause gender dysphoria, but this hypothesis is completely unsupported by scientific evidence, which strongly suggests that the direction of causation runs the other way. It is well-established that being transgender leads to mental health concerns because of the social stress and discrimination of being transgender in our society.[82] Although the effects of gender minority stress are well-known, the June 2 Report makes no mention of the literature.

Further, the co-occurrence of psychological distress among individuals with gender dysphoria provides no reason for denying care. Any population of individuals – cisgender or transgender -- will include some with mental health concerns. In response, the WPATH and Endocrine Society guidelines include a careful psychological assessment of each adolescent as part of the process for determining whether medical treatment for gender dysphoria is appropriate.

Importantly, experts in child and adolescent psychiatry, child psychology, and adolescent medicine have established that youth – including youth with mental health conditions -- can make complex medical decisions. The scientific literature specifically demonstrates that transgender youth with co-occurring mental health conditions can competently participate in medical decision-making.[83]

> G. The June 2 Report speculates, without evidence, that psychotherapy alone is as effective as medical treatment for gender dysphoria. This claim contradicts the findings of solid scientific studies.

The June 2 Report argues, without scientific evidence, that youth with gender dysphoria should not be offered medical treatment but instead should only receive psychotherapy, an approach that

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[81] June 2 Report, p. 6.
[82] Rylan J. Testa, et al., Development of the Gender Minority Stress and Resilience Measure, 2(1) Psychology of Sexual Orientation and Gender Diversity 65-77 (2015); Rylan J. Testa, et al., Suicidal Ideation in Transgender People: Gender Minority Stress and Interpersonal Theory Factors, 126(1) J. Abnormal Psychology 125-36 (2017); Alexandrai M. Delozier, et al., Health Disparities in Transgender and Gender Expansive Adolescents: A Topical Review from a Minority Stress Framework, 45(8) J. Pediatric Psychology 842-847 (2020); Jessica Hunter, et al., Gender Minority Stress in Trans and Gender Diverse Adolescents and Young People, 26(4) Clinical Child Psychology and Psychiatry 1182-1195 (2021).
[83] Lieke J. Vrouenraets, et al., Assessing Medical Decision-Making Competence in Transgender Youth, 148(6) Pediatrics e2020049643 (2021).

it mistakenly terms "watchful waiting."[84] This statement is false. Here we provide an overview of the actual science, with more detail in the Appendix.

Several solid, recent studies have demonstrated that medical care for gender dysphoria has positive effects on mental health that are not associated with psychotherapy alone. Costa et al. in 2015 found that puberty blockers improve psychosocial functioning in teens with gender dysphoria, compared to teens who receive psychotherapy but not blockers.[85] In a 2022 study, Tordoff et al. clearly found that youth with gender dysphoria reported better outcomes if they received puberty blockers, even after controlling for the effects of psychotherapy.[86] A 2020 study by Laura Kuper et al. also shows that hormone treatment for gender dysphoria is effective above and beyond the benefits of psychotherapy and psychiatric medications. [87]

Conclusion

Our analysis demonstrates that the June 2 Report carries no scientific weight. The report disregards established clinical guidelines and peer-reviewed studies and instead relies on purported "expert" reports that raise major red flags for lack of expertise, close ties to advocacy groups, and financial conflicts of interest. The report makes repeated errors about scientific research and medical regulation, and it engages in ungrounded speculation and stereotyping.

Accordingly, the Proposed Rule is ungrounded in scientific research and is arbitrary and capricious. Further, because the June 2 report violates Florida's own standards for scientific review, it cannot support the Proposed Rule as an interpretation of the existing Florida regulatory scheme.

We respectfully submit this letter of comment for your consideration.

Very truly yours,

Anne L. Alstott

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[84] For example, at p. 12, the June 2 Report asks, "[S] hould conventional behavioral health services be utilized without proposing treatments that pose irreversible effects [i.e., drug therapies]? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects {i.e., the watchful waiting approach)?" At p. 20, t he June 2 Report misuses the term "watchful waiting" to describe the denial of medical care to adolescents with gender dysphoria, and the report miscites its own purported expert report. The Cantor document discusses "watchful waiting" meaning the denial of social transition to prepubertal children, not the denial of medical treatment to adolescents. Cantor document, p. 10-11.

[85] Costa et al., supra note 57.

[86] Diana M. Tordoff et al., Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care, 5(2) JAMA Network Open e220978 (2022).

[87] Laura E. Kuper, et al., Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy, 145(4) Pediatrics e20193006 (2020).

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Appendix

July 8, 2022

A Critical Review of the June 2022 Florida Medicaid Report on the Medical Treatment of Gender Dysphoria

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Introduction

On June 2, 2022, the Florida Agency for Health Care Administration ("AHCA") issued a purported scientific report (hereinafter, "June 2 Report") concluding that standard medical care

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for gender dysphoria does not meet generally accepted medical standards and is experimental and investigational.[88]

We are a group of seven scientists and a law professor, and we have concluded, after a careful examination of the June 2 Report, that its conclusions are incorrect and scientifically unfounded. The June 2 Report purports to be a review of the scientific and medical evidence but is, in fact, fundamentally unscientific.

We are alarmed that Florida's health care agency has adopted a purportedly scientific report that so blatantly violates the basic tenets of scientific inquiry. The report makes false statements and contains glaring errors regarding science, statistical methods, and medicine. Ignoring established science and longstanding, authoritative clinical guidance, the report instead relies on biased and discredited sources, including purported "expert" reports that carry no scientific weight due to lack of expertise and bias.

So repeated and fundamental are the errors in the June 2 Report that it seems clear that the report is not a serious scientific analysis but, rather, a document crafted to serve a political agenda.

The AHCA has offered the June 2 Report as justification for a proposed rule that would deny Florida Medicaid coverage for gender dysphoria to people of all ages (the "Proposed Rule").[89] We strongly oppose the Proposed Rule and have documented our reasons in public comments submitted to the AHCA on July 8, 2022. This report provides our detailed reasons for concluding that the June 2 Report provides no scientific support for Florida's proposed action.

Executive Summary

As we note in our comments on the Proposed Rule, we strongly oppose Florida's proposal to deny Medicaid coverage to standard medical care for gender dysphoria. In this report, we show that the June 2 Report is so thoroughly flawed and biased that it deserves no scientific weight. Although our focus is on the science, we also note that the Proposed Rule would violate the sex discrimination protections provided by the U.S. and Florida Constitutions and the federal statute that governs Medicaid by discriminating against transgender people on the basis of their sex, transgender status, and gender identity.[90]

In this report, we examine closely the "scientific" claims made in the June 2 Report, and we show that its basic conclusion is incorrect. Medical treatment for gender dysphoria does meet generally accepted professional medical standards and is not experimental or investigational. We also show that the June 2 report reflects a faulty understanding of statistics, medical regulation, and scientific research. The report ignores solid scientific evidence and instead

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[88] Division of Florida Medicaid, Agency for Health Care Administration, Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria, June 2022, at https://www.ahca.myflorida.com/letkidsbekids/docs/AHCA_GAPMS_June_2022_Report.pdf("June 2 Report").
[89] 48 Fl. Admin. Reg. 2461 (June 17, 2022).
[90] See Bostock v. Clayton County, 590 U.S. __ (2020); Kadel v. Folwell, M.D. N.C., Mem. Op. 6-10-22 (applying Bostock to public health plan coverage); 42 U.S.C. 18116 (requiring nondiscrimination in Medicaid plans).

repeats discredited claims, cites to sources with no scientific merit, and engages in unfounded speculation based on stereotypes rather than science.

Specifically, we show that:

- Contrary to the June 2 Report's repeated claims, medical care for gender dysphoria is supported by a robust scientific consensus, meets generally accepted professional medical standards, and is neither experimental nor investigational.
- The June 2 Report appears to be a scientific report, but its veneer hides a flawed analysis that ignores the scientific evidence and relies instead on pseudo-science, particularly purported "expert" reports that are biased, inexpert, and full of errors. The claimed "expert" reports are written by authors whose testimony has been disqualified in court and who have known ties to anti-LGBTQ advocacy groups.
- Nothing in the June 2 Report calls into question the scientific foundations of standard medical care for gender dysphoria. The June 2 Report makes unfounded criticisms of robust and well-regarded clinical research and instead cites sources with little or no scientific merit, including journalism, a blog entry, letters to the editor, and opinion pieces.
- The linchpin of the June 2 Report is an analysis by two epidemiologists that claims to undermine the scientific evidence supporting medical care for gender dysphoria. Their analysis is extremely narrow in scope, inexpert, and so flawed that it merits no scientific weight at all.
- The June 2 Report repeatedly and erroneously dismisses solid studies as "low quality." If Florida's Medicaid program applied the June 2 Report's approach to all medical procedures equally, it would have to deny coverage for widely-used medications like statins (cardioprotective cholesterol-lowering drugs taken by millions of older Americans) and common medical procedures like mammograms and routine surgeries.

I. Contrary to the June 2 Report's repeated claims, medical care for gender dysphoria is supported by a robust scientific consensus, meets generally accepted professional medical standards, and is neither experimental nor investigational.

The conclusion of the June 2 report – that medical treatments for gender dysphoria "do not conform to [generally accepted professional medical standards] and are experimental and investigational"[91] – is demonstrably false.

Medical care for the treatment of gender dysphoria, which for youth under the age of majority can include gonadotropin releasing hormone agonists ("GnRHa" or puberty blockers) and hormone therapy, has been vetted and approved by international bodies of experts based on the scientific evidence. Two authoritative bodies of scientists, the World Professional Association for Transgender Health (WPATH) and The Endocrine Society, have published extensive clinical practice guidelines for treating gender dysphoria.[92] These clinical guidelines are based on

[91] June 2 Report, p. 2.

[92] See Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, World Professional Association for Transgender Health (7th version, 2012), at https://www.wpath.org/publications/soc ("WPATH (2012)"); Wylie C. Hembree, et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent

rigorous, structured processes that include a committee of scientific experts and peer review by additional experts. The guidelines are based on careful reviews of the scientific literature and are revised periodically to reflect scientific developments.

These longstanding clinical practice guidelines have been used by clinicians for decades. WPATH issued its initial guidelines in 1979 and updated them in 1980, 1981, 1990, 1998, 2001, and 2012. The eighth version remains in process, and it incorporates systematic literature reviews and ample opportunities for peer review and revision.[93] The original Endocrine Society guidelines were published in 2009 and updated in 2017.[94]

Reflecting this scientific and medical consensus, medical care for gender dysphoria has been confirmed as standard care by every relevant medical organization in the United States, including the American Academy of Pediatrics, the American Psychological Association, and the American Academy of Child and Adolescent Psychiatry.[95] In 2022, these organizations united with the American Medical Association, the American College of Obstetricians and Gynecologists, and other groups to file an amicus brief representing a total of 20 major medical societies. The brief reaffirms that puberty blockers and hormone treatments for gender dysphoria are standard medical care and opposes legal measures that would limit patient access to this standard care.[96]

The weight and volume of these endorsements, across diverse medical specialties, sharply contradicts the June 2 Report's conclusions.

II. The June 2 Report appears to be a scientific report, but its veneer hides a flawed analysis that ignores the scientific evidence and relies instead on pseudo-science. The report heavily relies on five purported "expert" documents that are biased, inexpert, and full of errors.

The Florida report dismisses or ignores the WPATH and Endocrine Society clinical practice guidelines and the science that underlies them and instead relies on five attached documents that, the report claims, constitute "clinical and technical expert assessments."[97]

Persons: An Endocrine Society Clinical Practice Guideline, 102(11) J. Clin. Endocrinol. Metab. 3869-3903 (2017) ("Endocrine Society (2017)").

[93] See World Professional Association for Transgender Health (WPATH), Methodology for the Development of Standards of Care 8 (Soc 8), at https://www.wpath.org/soc8/Methodology

[94] Endocrine Society (2017), supra note 5.

[95] Jason Rafferty, Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents, 142(4) Pediatrics E20182162 (2018); American Psychological Association, Guidelines for Psychological Practice with Transgender and Gender Nonconforming People, 70(9) American Psychologist 832-64 (2015); Stewart L. Adelson, Practice Parameter on Gay, Lesbian, or Bisexual Sexual Orientation, Gender Nonconformity, and Gender Discordance in Children and Adolescents, 51(9) J. Am. Acad. Child & Adolescent Psychiatry, 957 -974 (2012).

[96] Brief of Amicus Curiae American Academy of Pediatrics and Additi onal National and State Medical and Mental Health Organizations in Support of Plaintiffs' Motion for Temporary Restraining Order and Preliminary Injunction, Eknes-Tucker v. Ivey (later redesignated Eknes-Tucker v. Abbott), May 5, 2022, at https://www.aamc.org/media/60556/download

[97] June 2 Report, p. 2.

Despite their billing as "expert" reports, the attachments to the June 2 report are unpublished, non-peer-reviewed documents written by authors with questionable claims to expertise and with red flags for undisclosed author bias. These documents should be given no weight in a serious scientific process.

> A. The purported "expert" documents attached to the June 2 Report carry no scientific weight. They are unpublished and not peer-reviewed, and they are written by authors whose expertise has been successfully challenged in legal proceedings and whose backgrounds raise red flags for bias.

None of the documents attached to the June 2 Report meet standard criteria for expert scientific investigations, because none is published or peer reviewed. Publication and peer review are fundamental to science, as they ensure that a scientist's data and conclusions are open to scrutiny from scientific experts.

Florida's own standards for the determination of medical necessity recognize this point when they state that determinations of Medicaid coverage must consult "*published* reports and articles in the authoritative medical and scientific literature related to the health service (*published in peer-reviewed scientific literature* generally recognized by the relevant medical community or practitioner specialty associations)."[98] It is thus both unscientific and a violation of the regulations for the June 2 Report to rely on the unpublished documents as its principal evidence base.

Further, the attachments all raise red flags for author bias. The June 2 Report does not disclose how these "experts" were identified or by what criteria their expertise was assessed. The opacity of the Florida AHCA process for identifying experts is particularly troubling because at least four of the experts have strong indications of bias. Further, the qualifications and credibility of two of the experts have been successfully challenged in litigation.[99] Two of the expert reports duplicate, word-for-word (or with very slight edits) testimony that was offered, apparently for pay, in litigation. Both have connections to advocacy organizations that oppose LGBTQ rights across the board. The endorsement of these individuals as Florida's banner "experts" raises the appearance of bias – that the AHCA sought a pre-ordained outcome, not a true scientific perspective.

Adding to these red flags for bias, none of the authors of the attachments provide a statement of funding and conflicts of interest. This omission violates a strong norm in scientific writing, which requires authors to declare any conflicts of interest; these include any professional or financial arrangements that could call into question their independence of judgment.[100] That

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[98] Fl. Admin. Code Section 59G-1.035(4).

[99] See Stephen Caruso, A Texas Judge Ruled That This Doctor Was Not an Expert, Pennsylvania Capital-Star, Sept. 15, 2020 (reporting that van Meter was disqualified as an expert in a Texas divorce case, now sealed).

[100] For example, the conflict of interest rules for JAMA, one of the premier medical journals in the United States and the world state that "[a]uthors are expected to provide detailed information about all relevant financial interests, activities, relationships, and affiliations (other than those affiliations listed in the title page of the manuscript) including, but not limited to, employment, affiliation, funding and grants received or pending, consultancies, honoraria or payment, speakers' bureaus, stock ownership or options, expert testimony, royalties, donation of medical equipment, or patents planned, pending, or issued." JAMA Network, Instructions for Authors, visited June

strong norm also requires authors to disclose whether projects have been funded and if so, by whom and whether the authors have engaged in expert testimony. Without these statements, the Florida AHCA and the public cannot detect biases that could affect the integrity of these written products.

These are more than theoretical concerns: at least four of the attachments have notable indicators of conflicts of interest and bias. (Note that these are the only four we examined in detail, and so we do not imply that the other one is free from such bias.)

The author of the document provided as Attachment E is Quentin van Meter, whose history indicates bias and lack of expertise. Although the AHCA presents van Meter as an expert in medical treatment for gender dysphoria, at least one court barred him from providing expert testimony on the issue.[101] Van Meter is the president of the American College of Pediatricians (the "ACP"), which presents itself as a scientific group (and might be confused, by a non-expert, with the authoritative American Academy of Pediatrics). The ACP is, in fact, a political group that opposes same-sex marriage,[102] supports mental health providers practicing conversion therapy,[103] and describes childhood gender dysphoria as "confusion."[104] Troublingly, the van Meter attachment, proffered by the AHCA as a scientific report, contains several passages of uncredited, verbatim language that appears in a "position statement" published by the ACP.[105] The van Meter attachment appears to be a re-use of paid testimony rather than an original product.[106]

James Cantor's document, presented as Attachment D to the June 2 Report, also faces serious questions about bias and lack of expertise. In a 2022 case, a federal court took a skeptical view of Cantor's purported expertise, noting that "the Court gave [Cantor's] testimony little weight because he admitted, inter alia, to having no clinical experience in treating gender dysphoria in minors and no experience monitoring patients receiving drug treatments for gender dysphoria.[107]

22, 2022, at https://jamanetwork.com/journals/jama/pages/instructions-for-authors#SecConflictsofInterestandFinancialDisclosures

[101] Caruso, supra note 12.

[102] Den Trumbull, Defending Traditional Marriage, American College of Pediatricians (2013), https://acpeds.org/position-statements/defending-traditional-marriage. See Jack Turban, The American College of Pediatricians is an Anti-LGBTQ Group, Psychology Today, May 8, 2017.

[103] Christopher Rosik and Michelle Cretella, Psychotherapy for Unwanted Homosexual Attraction Among Youth, American College of Pediatricians (2016), https://acpeds.org/position -statements/psychotherapy-for-unwanted-homosexual-attraction-among-youth.

[104] Michelle Cretella, Gender Dysphoria in Children, American College of Pediatricians (2018), https://acpeds.org/position-statements/gender-dysphoria-in-children (site visited June 22, 2022). The author of the ACP position paper is Michelle Cretella, who was publicly rebuked by the Society for Adolescent Health and Medicine, the leading society for adolescent medicine in the United States, for "pushing political and ideological agendas not based on science and facts." https://www.adolescenthealth.org/Advocacy/Advocacy-Activities/2017-Activity/Senate-Bill-439-(2).aspx

[105] The similarity was shown by a Word comparison of the van Meter report provided as Attachment E to the June 2 Report with a "position statement" published on the ACP website, with authorship credit given on the website to Michelle Cretella. See Michelle Cretella, Gender Dysphoria in Children, supra note 17.

[106] The van Meter document attached to the June 2 Report is substantially identical to his expert declaration in Adams v. School Board of St. Johns County, Florida. https://files.eqcf.org/wp-content/uploads/2017/12/41-D-AMENDED-Notice-Documents-iso-Response-to-PI.pdf.

[107] Opinion and Order, Eknes-Tucker v. Marshall, 2:22-CV-184-LCB, M.D. Alabama, May 13, 2022.

Cantor's document is nearly identical to what appears to be paid testimony in another case, where Cantor's declaration was used to support legislation barring transgender athletes from sports teams,[108] Troublingly, Cantor's appearance in that case seems to have been funded by the Alliance Defending Freedom ("ADF"), [109] a religious and political organization that opposes legal protections for transgender people and same-sex marriage[110] and defends the criminalization of sexual activity between partners of the same sex.[111] Because Cantor provides no conflicts of interest disclosure, readers cannot ascertain whether Florida AHCA also paid for Cantor's report and whether Florida officials were aware that the Cantor report reused his work for (apparently) the ADF.

Romina Brignardello-Petersen is one of two authors of the document provided as Attachment C to the June 2 Report. Although Brignardello-Petersen claims to have no research interests in medical care for transgender youth,[112] she has conducted research for the Society for Evidence-Based Gender Medicine ("SEGM").[113] Although SEGM claims to be an international medical society, it is actually an activist group that opposes standard medical care for gender dysphoria. The SEGM has no publications or conferences and seems to consist solely of a website created by a small group of people with limited or no scientific credentials or clinical experience. The site presents a cherry-picked collection of studies and narrative content that is full of scientific errors.[114]

Patrick Lappert, whose document is attached to the June 2 Report as Attachment F, has been disqualified as an expert in a recent federal court decision in North Carolina. [115] The judge found

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[108] The case is BPJ v. West Virginia State Board of Education, and the Alliance Defending Freedom takes credit for it here: https://adfmedia.org/case/bpj-v-west-virginia-state-board-education. Cantor's declaration appears here: https://adfmedialegalfiles.blob.core.windows.net/files/BPJCantorDeclaration.pdf

[109] The ADF seems to take credit for the case in this press conference notice: https://adfmedia.org/case/bpj-v-west-virginia-state-board-education

[110] Marriage is the Future, American College of Pediatricians, https://adflegal.org/issues/marriage/overview(site visited July 2, 2022. Content on the page includes this statement:"Marriage is about equality and diversity. It's about joining the two equally important and diverse halves of humanity represented in men and women."

[111] Southern Poverty Law Center, Dangerous Liaisons, July 10, 2013, https://www.splcenter.org/20130709/dangerousliaisons [visited July 2, 2022].

[112] Like the van Meter and Cantor attachments, the BPW document provides no express statement of conflicts of interest. The BPW document does offer a statement of "credentials and expertise," in which she declares that "her research interests are not in this area," meaning apparently research on medical care for gender dysphoria. BPW Document, p. 1.

[113] BPW document, p. 1. For one example of the purported research that Brignardello -Petersen apparently assisted in, see Alison Clayton et al., Commentary: the Signal and the Noise– Questioning the Benefits of Puberty Blockers for Youth with Gender Dysphoria– A Commentary on Rew et al. (2021), Child and Adolescent Mental Health, Dec. 22, 2021, at https://acamh.onlinelibrary.wiley.com/doi/10.1111/camh.12533 In the "Acknowledgements" section, the authors state, "We would also like to thank the Society for Evidence -based Gender Medicine (SEGM) for providing access to several experts who helped shape this commentary and ensure its accuracy. Specifically, we would like to thank Dr. Romina Brignardello Petersen [sic] for contributing her methodological expertise."

[114] Susan Boulware et al., Biased Science: The Texas and Alabama Measures Criminalizing Medical Treatment for Transgender Children and Adolescents Rely on Inaccurate and Misleading Scientific Claims (April 28, 2022), at 28-29 (Appendix A) available at https://medicine.yale.edu/childstudy/policy-and-social-innovation/lgbtq-youth/.

[115] Kadel v. Folwell, 1:19CV272, M.D. N.C. June 10, 2022. The judge ruled that Lappert was not qualified to "render opinions about the diagnosis of gender dysphoria, its possible causes, the efficacy of the DSM, the efficacy of puberty blocking medication or hormone treatments, the appropriate standard of informed consent for mental health professionals or endocrinologists, or any opinion on the non-surgical treatments." Lappert was also

that evidence "calls Lappert's bias and reliability into serious question" and noted that Lappert has worked closely with ADF and has actively lobbied for legal bans on medical care for transgender youth.[116] The judge gave no weight to Lappert's testimony about informed consent in that case, finding that it was unsupported by scientific evidence.[117] The judge also found that "Lappert has provided the Court with no data or methodology used to draw his conclusion that surgical treatment for gender dysphoria has "never been generally accepted by the relevant scientific community."[118]

B. The linchpin of the June 2 Report is the analysis by Brignardello-Petersen and Wiercioch (the "BPW document"), provided as Attachment C, which purports to be a comprehensive review of the scientific literature on medical treatment for gender dysphoria but, in fact, is extremely narrow in scope and so flawed in its analysis that it merits no scientific weight.

The BPW document, like the other attachments to the June 2 Report, is an unpublished, non-peer-reviewed document. It claims to conduct a systematic review of the relevant scientific literature, but in fact, it is written by inexpert authors who construct an arbitrarily truncated sample and adopt a method that violates scientific guidelines and produces a biased result. The authors describe their findings in deceptive language and jargon predictably mislead the reader. Our review shows that *nothing in the BPW document calls into question the scientific foundations of the WPATH and the Endocrine Society clinical practice guidelines.*

The BPW document seems scientific on its face, and it may be impressive to non-experts, because it uses technical jargon and includes numerous tables and charts. But a closer examination shows that it violates established standards for medical research and shows signs of being engineered to produce a pre-ordained and inaccurate result: the false claim that there is no scientific evidence base for medical treatment for gender dysphoria. Contrary to the authors' claims, there is a large body of reliable scientific literature that supports standard medical treatment for gender dysphoria and spans decades.

The bottom line is that, contrary to the BPW document's claims, there is a large body of reliable scientific literature that supports standard medical treatment for gender dysphoria.

(1) The BPW document lacks scientific credibility due to the authors' lack of relevant qualifications and their ties to an activist group.

The BPW document purports to be a systematic review of the scientific literature on medical treatment for gender dysphoria. But the document, like the other attachments to the June 2 Report, is not published or peer-reviewed, and its design and execution raise numerous red flags for bias. Here, we describe just four of the notable defects that undercut entirely the document's claim to objectivity and sound method.

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disqualified from opining on "the efficacy of randomized clinical trials, cohort studies, or other longitudinal, epidemiological, or statistical studies of gender dysphoria." Id.

[116] Id.

[117] Id., pp. 29-30.

[118] Id., p. 31.

First, neither of the BPW authors are experts in medical care for gender dysphoria, either as researchers or clinicians. One author (Brignardello-Petersen) has not previously studied the subject, except in her work for the ideological organization SEGM.org, noted just above. Her only clinical experience appears to be in dentistry.[119] The other author (Wiercioch) is a junior researcher (a postdoctoral fellow) with no prior research or clinical experience in this field.

The authors' lack of interest and experience renders the BPW work inexpert rather than objective, and it violates the National Academy of Medicine (formerly, Institute of Medicine) standards for systematic reviews. By analogy, one would not rely on, say, two dermatologists to conduct a review of the scientific literature on neurosurgery and to make recommendations for clinical practice.

Second, not only is the study not formally peer-reviewed, the BPW authors violate scientific norms and standards by *failing to engage at all with their peers or with actual experts in the subject matter*. As experts in research methodology should know, any sound systematic review should propose explicit and reproducible methods to methodically summarize the existing literature; the protocol (i.e., the research design) is then published to solicit input and criticisms from potential users of the review and experts in the field. Peer review of the literature review and publication of the protocol are not optional or merely window-dressing; they reflect bedrock commitments of the scientific method. These processes help ensure that the authors of any review understand the existing research and craft a research design that will usefully build on and add to prior work.

The BPW document violates these standards, raising questions about whether this was a rushed study designed to serve a political agenda – rather than a considered, comprehensive, scientific enterprise. The BPW document does not contain a review of the existing literature, and it does not acknowledge the WPATH and Endocrine clinical practice guidelines, which are themselves based on careful systematic reviews. The BPW authors appear not to have published their protocol in advance or otherwise to have submitted their protocol for peer review. That is, there is no indication that they vetted their research design in consultation with subject-matter experts.

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[119] Romina Brignardello bio, at https://experts.mcmaster.ca/display/brignarr [visited July 2, 2022]
Google Scholar, Wojtek Wiercioch, visited June 22, 2022, https://scholar.google.com/citations?user=vdi3r_AAAAAJ&hl=en
Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine, Finding What Works in Health Care: Standards for Systematic Reviews, National Academies (Jill Eden et al., eds 2011), p. 48 (Standard 2.1.1 states that teams for systematic reviews should include expertise in pertinent clinical content areas). Background: The Institute of Medicine, now called the National Academy of Medicine, is one of three branches of the National Academies of Science, Engineering, and Medicine. The National Academy of Science dates to 1963 and was established by Congress; the Institute of Medicine was established as a separate entity in 1970 and serves as the nation's leading authority on scientific research and knowledge. National Academy of Medicine, About the National Academy of Medicine, website visited June 22, 2022 https://nam.edu/about-the-nam/ The standards for systematic reviews were published in 2011, responding to a Congressional request to set benchmarks for high-quality systematic reviews that could reliably guide physicians and healthcare providers in making informed, scientific judgments about health care.
Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, Institute of Medicine, supra note 34, at pp. 72-75.

Third, the BPW document raises red flags for opinion bias. Buried in the methodology pages of the BPW document is the fact that the authors uncritically include politically biased "grey literature" sources, giving them equal weight to peer-reviewed, published literature. Specifically, the authors include in their search the fringe website SEGM.org. As noted above, the group's website posts are not peer-reviewed or published, and its content is assembled by a small group of activists with few or no expert credentials and is often full of errors. Troublingly, this is the group to which one of the authors, Brignardello-Petersen, has ties, as noted above.

> *(2) The BPW document examines a truncated sample of the literature and adopts a methodology that violates scientific standards for evaluating medical evidence. The authors compound this bias by describing their results using overstated and deceptive language. The picture that emerges is of a rushed and inexpert report with indications of bias.*

The BPW document has a patina of scientific expertise. It invokes the respected GRADE standards for rating the quality of studies, and it occupies many pages with tables and technical specifications. When a reader looks past the jargon, however, the BPW authors adopt a method that actually violates GRADE standards and appears to be jury-rigged to reach a foregone conclusion. The authors then convey their conclusions in misleading language. *Contrary to the BPW authors' claims, their study does not call into question the scientific and clinical importance of the established science that supports medical care for gender dysphoria.*

The BPW analysis incorporates numerous decisions that bias their results, and they make numerous misleading statements. First, the BPW document reviewed only a small sample of the relevant scientific literature. In the introduction, the BPW authors initially claim to have reviewed 61 systematic reviews of medical treatment for gender dysphoria. But buried in the middle of the document is the admission that the analysis is based on a sample of 27 systematic reviews, not 61 as claimed. The result is that the BPW analysis excludes a great deal of relevant evidence, and the authors provide no rationale for this "prioritization," as they call it. Troublingly, although the BPW document claims to be conducting a review of the literature that analyzes existing systematic reviews, the 27 studies they analyze are not all systematic reviews. Three of the 27 are mislabeled as systematic reviews but are actually practice bulletins, unpublished protocols or unlocatable.

Troublingly, the authors also embed in the middle of their document a*n unjustified decision to limit their analysis to studies published from 2020 to the present, and their project has strong indications that it was rushed work.* The authors disclose that they "prioritized" studies from the last 30 months (two full years plus four months in 2022), but they do not defend that priority.

BPW document, Methods section, p. 2.
See Boulware et al., supra note 27 pp. 28-29 (Appendix A).
BPW document, Introduction Section, p. 2.
BPW document, Results Section, p. 1.

The reader is left to wonder whether this truncation served only to help the authors produce their analysis in what was apparently a very short time frame.

The truncation of the literature sample to the period from 2020 to early 2022 is worrisome because that period coincides with the worst global public health emergency in generations. The pandemic disrupted many institutions, straining the health care system and putting immense pressure on clinicians. It is likely that the pandemic stalled the production and publication of non-COVID research during this period, calling into sharp question the BPW authors' sampling strategy.

The BPW sample is also questionable because the authors choose, without justification, a small subsection of databases to search and have likely missed important literature as a result. Specifically, they chose not to source from other important databases such as Embase, PsycInfo, Web of Science, Scopus, or Cochrane. They also limited their scope to works published in English only, an exclusion that can introduce bias.

Second, the BPW authors misused and mechanically applied a well-regarded rating system known as AMSTAR, which is intended to evaluate the methodological strength of systematic reviews. They misused this rating system because their so-called group of systematic reviews included documents that cannot correctly be included (practice bulletins, unpublished protocols, and unlocatable documents) and thus led to a negative bias. The BPW error is further amplified because the authors used the flawed results of the AMSTAR phase to inform their next level of analysis, the GRADE system (which assesses the quality of medical evidence of pooled systematic reviews). Based on this flawed and purely mechanical review of truncated sources, the BPW analysis reaches the conclusion that there is little or no evidence for the benefits of medical care for gender dysphoria.

The BPW analysis is highly deceptive, because it dismisses nearly all existing studies of medical treatment for gender dysphoria as "low quality," without explaining that this is a highly technical term and not a natural-language condemnation of the studies. By contrast, the GRADE system, which the authors purport to use, is quite clear about its quality rating systems and its limitations. In general, only randomized controlled trials (RCTs) are coded as "high" quality evidence in the GRADE system. A randomized controlled trial is a study that divides patients randomly into a control group (no treatment) and a treatment group. In contrast, an observational study records information about patients in a real-world setting that is more reliably generalizable, e.g., a cohort of patients seen at a clinic. Under the GRADE guidelines, observational studies are coded as "low" in quality.

The authors disclose that they conducted their initial literature searches– the first step in the review process – at the end of April 2022. BPW document, Methods section, p. 2.

For example, the BPW document states that there is *evidence* about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. BPW document, Results section, p. 4.

See Howard Balshem et al., GRADE Guideline: 3. Rating the Quality, 64 J. Clinical Epidemiology P401 -406 (2011), Table 3, p. 404

The key point is that "low quality" in this context is a technical term and not a condemnation of the evidence, because "low quality" studies regularly guide important aspects of clinical practice. Indeed, the GRADE system, which the BPW document claims to use, specifically notes that GRADE should *not* be used to dismiss observational studies or to give absolute priority to RCTs:

> Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not imply a particular strength of recommendation. *Sometimes, low or very low quality evidence can lead to a strong recommendation.*[130]

The methodology adopted by the BPW document will thus, predictably, conclude that any body of scientific literature that does not contain RCTs is "low" in quality. Had BPW begun, as they should have, with a literature review of the evidence on puberty blockers and hormones, they would have seen that the evidence consists primarily of observational studies (for the good reasons discussed below). Thus, the 30 pages that it takes the authors to lay out their methodology is misleading: a knowledgeable reader would know that if there are few or no RCTs in the literature, then the BPW technical conclusion is foregone and, as importantly, is not a sound guide for clinical recommendations.

Put in simpler terms, if we coded apples as "high quality fruit" and bananas as "low quality fruit," then any fruit bowl that has only bananas would predictably be technically coded as "low quality." But that technical conclusion conveys very little information without context. For example, if no apples exist, then bananas may be a nutritious choice.

The drafters of the GRADE system emphasize that technically "low quality" evidence can support a strong clinical treatment recommendation. For example, pediatricians now agree that children should not be given aspirin for fevers. This recommendation is based on observational studies that showed an association between aspirin treatment during viral illnesses and the development of Reyes syndrome (a rapid and progressive disease of neurological dysfunction that can be fatal). Based on those studies, it would be unethical to conduct an RCT giving some children aspirin, and so the strong, consensus treatment recommendation is based entirely on "low quality" studies.[131]

The critical fact is that RCTs are not, and cannot be, the gold standard for medical research on gender dysphoria. In the context of treatments for gender dysphoria, randomized controlled trials would often be inappropriate for ethical reasons. Medical care has long been shown, by reliable scientific methods, to address gender dysphoria and improve mental health: as we have repeatedly noted, these treatments have been recommended by rigorous clinical practice guidelines issued by WPATH and the Endocrine Society and endorsed by every major medical organization. Given this medical consensus, which is based on solid scientific evidence, it would be unethical to conduct an RCT that involved denying standard medical care to a control group of individuals.

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[130] Balshem et al., supra note 42, at 402 (emphasis added).
[131] Id.

Similar ethical issues, along with practical barriers, leave many areas of consensus medicine supported by observational studies and not RCTs. Many surgical procedures, for example, are not supported by RCTs.[132] Nor are standard protocols for lowering cholesterol using statins, one of the most widely-prescribed drugs in the United States. (See Section III.A of this report.)

It is thus simply a mistake – and a mischaracterization of medical research across fields of medicine – to conclude that the absence of RCTs means that there is "no evidence" for the efficacy of medical treatment for gender dysphoria. Medical research requires, instead, that researchers evaluate the design and conduct of specific observational studies and do so with an awareness of clinical context.[133]

In sharp contrast to BPW, this is precisely what the authors of the Endocrine Society did in their 2017 clinical guidelines, which use the GRADE system but, in addition, carefully discuss the characteristics of the studies supporting each treatment guideline.[134] The Endocrine Society discloses the GRADE rankings for each treatment recommendation in order to be transparent about the evidence base for each of its recommendations. Then, following National Academy of Medicine (formerly, Institute of Medicine) standards for clinical practice guidelines, they proceed to a qualitative review of the evidence, place the evidence in clinical context, and discuss openly the values at stake in making a clinical practice recommendation.[135]

III. The June 2 Report reflects a faulty understanding of statistics, medical regulation, and scientific research, and it repeats discredited claims and engages in speculation and stereotyping without scientific evidence.

The June 2 Report is full of errors and misstatements. Disregarding solid scientific evidence, the report relies on debunked studies and sheer speculation, and it levels criticisms at solid evidence that betray a poor understanding of medical research and statistics.

A. The June 2 Report repeatedly and erroneously dismisses solid studies as "low quality." If Florida's Medicaid program applied the June 2 Report's approach to all medical procedures equally, it would have to deny coverage for widely-used medications like statins (cholesterol-lowering drugs taken by millions of older Americans) and common medical procedures like mammograms and routine surgeries.

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[132] See, e.g., Peter McCulloch, et al., Randomised Trials in Surgery: Problems and Possible Solutions, 324 (7351) BMJ 1448-1451 (2002).

[133] See Balshem et al., supra note 42 at 405 ("[W] e caution against a mechanistic approach toward the application of the criteria for rating the quality of the evidence up or down…. Fundamentally, the assessment of evidence quality is a subjective process, and GRADE should not be seen as obviating the need for or minimizing the importance of judgment or as suggesting that quality can be objectively determined"). See also the National Institute of Medicine (Institute of Medicine) Standards, supra note 34, at 176: ("We are disappointed when a systematic review simply lists the characteristics and findings of a series of singlestudies without attempting, in a sophisticated and clinically meaningful manner, to discover the pattern in a body of evidence. Although we greatly value meta -analyses, we look askance if they seem to be mechanistically produced without careful consideration of the appropriateness of pooling results or little attempt to integrate the finds into the contextual background.")

[134] Endocrine Society (2017), supra note 5.

[135] Id.

In its opening words, the June 2 Report makes an error that is repeated throughout the document: "Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased."

As we document in Section II.B., above, it is an outright mistake to conclude that a study in the technical category of "low quality" is unreliable or poor evidence for clinical practice.[136] Thus, it is frank error for the June 2 Report to dismiss well-done, scientifically important studies because they rank as "low quality" using specialized, technical terms.

Like the BPW document, the June 2 Report thus relies on a deceptive use of technical terminology that is at odds with the standards used in medical research. It simply is not – and cannot be – the case that all clinical recommendations must be based on RCTs. Many areas of medicine do not lend themselves to ethical and practical RCTs. It is unethical to conduct an RCT when randomizing a patient to a control group would cause harm by denying treatments of known efficacy. For example, it would be unethical to conduct an RCT on the treatment of juvenile diabetes by randomizing some participants to receive insulin and others to receive no treatment.[137]

It is quite common for the medical community to adopt important, consensus clinical practices supported by observational studies alone. For example, observational studies, notably the famous Framingham Heart Study, provided the framework for clinical practice guidelines in prevention and treatment of cardiovascular disease. In 2013, the American College of Cardiology and the American Heart Association issued updated clinical practice guidelines on the treatment of cholesterol to reduce heart disease risk in adults (the "Cholesterol Guidelines").[138] These authoritative guidelines have been widely used in clinical practice but are based not only on RCTs but on a great deal of observational evidence, including studies technically ranked as "low quality."[139] Concretely, many of the original treatment recommendations regarding statins are based on observational studies, not RCTs.[140] The authors of the Cholesterol Guidelines, very much like the Endocrine Society authors, are quite careful to grade their evidence. But they do not rest their treatment guidelines on a mechanical assessment of technical quality. Instead, they (like the Endocrine Society) carefully explain why particular bodies of evidence should be given weight in clinical decisionmaking.

The cholesterol example shows that the June 2 Report rests on a fundamental misunderstanding of medical research and clinical practice. If the Florida Medicaid program actually adopted the standard of evidence urged by the June 2 report, the program would not cover statins (drugs to

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[136] Balshem et al., supra note 42, at 404 ("Well-conducted studies may be part of a body of evidence rated low quality because they only provide indirect or imprecise evidence for the question of interest.")
[137] RCTs have other limitations as well. For example, RCTs often have strict exclusionary criteria that recruit healthier and more homogenous study populations than observational studies. Thus, this can lead to results that are not easily generalizable in real-world settings.
[138] Neil J. Stone, et al., 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults, 129(25) Circulation S1 -S45 (2014).
[139] Id., Tables 3 and 4.
[140] Syed S. Mahmood, et al., The Framingham Heart Study and the Epidemiology of Cardiovascular Disease: a Historical Perspective, 383 Lancet 999-1008 (2014).

lower cholesterol) for many patients, which are prescribed to 28% of adults over the age of 40 and are one of the most effective ways to prevent cardiovascular death.[141] Other common practices that would have to be reconsidered under this logic include: post-menopausal hormone replacement therapy (which reduces lifetime risk of heart attacks and stroke) and mammography screening for breast cancer.

The same point is true of the technically "low quality" evidence base for many surgical procedures, including minimally invasive gall bladder surgery, which have long since had a foundational grounding in observational studies. We think it unlikely that Florida's Medicaid program will begin to refuse to pay for statins, mammograms, and routine surgeries. If not, then the June 2 Report reflects an untenable and discriminatory double standard.

Thus, the June 2 Report not only relies on the biased and methodologically flawed evidence in the BPW document, as documented in Section II above; it also misuses scientific terminology in an effort to mislead readers and to support the unwarranted conclusion that medical treatment for gender dysphoria is "experimental."

> B. The June 2 Report disregards robust clinical research studies and instead relies on letters to the editor and opinion pieces. The report's analysis fails to satisfy Florida's own regulatory standards for Medicaid coverage decisions and does not undermine the scientific research that supports medical treatment for gender dysphoria.

The June 2 Report repeatedly cites sources with little or no scientific credibility – including journalism, a student blog, a website, and letters to the editor – rather than peer-reviewed empirical research.[142] At the same time, the report makes baseless or exaggerated criticisms of solid studies. The report's objections to these studies incorporate mistakes about basic statistics and often misrepresent the aims and findings of studies. Here, we offer several examples, but the problem of selective and ungrounded criticism permeates the June 2 Report and further undermines its scientific credibility.

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[141] Joseph A. Salami et al., National Trends in Statin Use and Expenditures in the U.S. Adult Population From 2002 to 2013, 2(1) JAMA Cardiology 56-65 (2017).

[142] Sources from journalism include Jon Brown, Medical Textbook Strips Gender Dysphoria Definition after Being Cited by Florida, Fox News, May 8, 2022, at 8 https://www.foxnews.com/politics/textbook-strips-gender-dysphoria-definition-cited-florida [visited July 3, 2022; Lawrence S. Mayer and Paul McHugh, Sexuality and Gender: Finding from the Biological, Psychological, and Social Science, The New Atlantis (Fall 2016), https://www.thenewatlantis.com/wp-content/uploads/legacy-pdfs/20160819_TNA50SexualityandGender.pdf[visited July 3, 2022]. The citation to the student blog is Hong Phuong Nhi Le, Eminence-Based Medicine vs. Evidence-Based Medicine, Students 4 Best Evidence [blog], https://s4be.cochrane.org/blog/2016/01/12/eminence-based-medicine-vs-evidence-based-medicine/#:~:text=What%20is%20eminence-based%20medicine [visited July 3, 2022]. The website is SEGM.org, which we discuss in the text in SectionII.B and Section III.A. Citations to letters and opinion pieces include, inter alia, Andre van Mol, et al.,Gender-Affirmation Surgery Conclusion Lacks Evidence, 177(8) Am. J. Psychiatry 765-766 (2020); Michael Laidlaw, et al., The Right to Best Care for ChildrenDoes Not Include the Right to Medical Transition, 19(2) Am. J. Bioethics 75 -77 (2019); Michael Laidlaw, et al., Letter to the Editor: "Endocrine Treatment of Dysphoric/Gender Incongruent Persons: An Endocrine Society Clinical Prace Guideline," 104(3) J. C linical Endocrinology and Metabolism 686-687 (2018); Andre van Mol, et al., Gender-Affirmation Surgery Conclusion Lacks Evidence, 177(8) Am. J. Psychiatry 765 -766 (2020).

For example, the June 2 report attacks a 2015 study by Costa et al., claiming that the study design is flawed because it did not include a control group of adolescents without gender dysphoria.[143] This point is simply incorrect. The Costa study was designed to measure the impact of puberty blockers on gender dysphoria. To do so, the authors validly compared outcomes in teens with dysphoria who received treatment with blockers and those who did not. They were able to do this ethically because the control group of teens (who received psychotherapy but not puberty blockers) were not yet eligible for blockers or were eligible but chose to delay or forgo blockers. The study found that puberty suppression was associated with improvements in psychosocial functioning.

The Costa study is, despite the June 2 Report's claims, a solid methodology. In the context of this study, adding a third "control group" of teens without gender dysphoria would serve no scientific purpose. Further, the June 2 Report also criticizes Costa for "rel[ying] heavily on self-assessments."[144] But this is a wildly off-base criticism. Costa et al. measure psychosocial functioning using a widely-used and accepted instrument, the Children's Global Assessment Scale. Psychological research typically relies on such assessments, which are carefully constructed and psychometrically validated. This is one example of the June 2 Report's poor understanding of research in psychology and medicine.

In addition to these glaring errors, the June 2 Report's criticism of Costa makes an even more fundamental error: the June 2 report levels baseless criticisms at a single study *and fails to acknowledge that the weight of the literature as a whole strongly supports the same results that Costa et al. report*. Scientific knowledge is, importantly, cumulative. It is thus entirely misleading – and unscientific – to dismiss the effectiveness of puberty blockers by criticizing studies in isolation. Put simply, the June 2 Report fails to acknowledge the number of solid studies that all find that puberty blockers are effective.[145] Indeed, at least 16 studies show that puberty blockers and hormones benefit patients with gender dysphoria, and the benefits have been documented across study designs, including retrospective report, cross sectional, longitudinal, and qualitative studies.[146]

To take another example, the June 2 Report grossly misleads the reader in its discussion of a study by Chen et al. in 2020.[147] The report cherry-picks quotes from Chen et al. to the effect

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[143] June 2 Report, p. 15 ("Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control"). The Costa study is Rosalia Costa et al., Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria, 12 (11) J. Sexual Medicine P2206-2214 (2015) (hereinafter, "Costa et al. (2015)").
[144] Id.
[145] See Luke R. Allen, et al., Well-Being and Suicidality Among Transgender Youth after Gender -Affirming Hormones, 7(3) Clinical Practice in Pediatric Psychology 302 -11 (2019); Amy E. Green, et al., Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth, 70(4) J. Adolescent Health 643-649 (2022); Jack L. Turban, et al., Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation, 145(2) Pediatrics e20191725 (2020); Maureen D. Connolly, et al., The Mental Health of Transgender Youth: Advances in Understanding, 59(5) J. Adolescent Health 489-95 (2016); Gemma L. Witcomb et al., Levels of Depression in Transgender People and its Predictors: Results of a Large Matched Control Study with Transgender People Accessing Clinical Services, J. Affective Disorders (2018).
[146] For citations, see Boulware et al., supra note 27, at n. 43.
[147] Diane Chen, et al., Consensus Parameter: Research Methodologies to Evaluate Neurodevelopmental Effects of Puberty Suppression in Transgender Youth, Transgender Health 246-257 (2020).

that "the effects of pubertal suppression warrant further study" and the "full consequences of suppressing endogenous puberty are not yet understood."[148]

These criticisms are misapplied, because the Chen article is not a substantive study of the effects of puberty blockers. It is, instead, a consensus parameter, which is an article that uses a structured methodology to consult experts to develop a research agenda for future studies. It is expected that the Chen piece would focus on what is not yet known, or what is not completely known, because it is attempting to identify research topics and approaches. Notably, and contrary to the June 2 Report's claims, Chen et al. recognize that existing evidence suggests that puberty blockers improve mental health functioning.

More generally, the June 2 Report's misleading characterization of Chen et al. reflects a basic lack of knowledge about scientific research. All research is flawed, including all RCTs: there simply is no perfect study in any area of medicine. The task of the scientist is to be rigorous in assessing what we know and to work to improve knowledge, incrementally, by conducting additional studies that build on earlier work. Thus, it is commonplace for authors to conclude medical research studies by calling for further research. Chen et al's statements are not indictments of puberty blockers – they are conventional acknowledgments of the value of further study that drives scientific inquiry and innovation.

The June 2 Report also contains a misleading account of the study by DeSanctis et al. The DeSanctis article reviews the literature on the use of puberty blockers (GnRHa's) for children diagnosed with central precocious puberty. De Sanctis finds that blockers are generally "safe and well-tolerated in children and adolescents" and that most drug reactions were mild.[149] The June 2 Report misleadingly and without foundation cites the De Sanctis piece as "[raising] questions about whether off-label use to treat a psychological condition [gender dysphoria] is worth the risks."[150] This attribution is bizarre, because De Sanctis et al. actually *support* the use of puberty blockers (by finding them safe and with only rare side effects) and do not offer any evidence at all to suggest that the risks are higher in the treatment of gender dysphoria.

As a final example, the June 2 Report criticizes a 2019 preliminary study by Kuper et al. without acknowledging the existence of a 2020 study by Kuper et al.[151] The earlier study presented data on the mental health of adolescents when initially presenting for care; only the later study presented full data that demonstrated the benefit of treatment.

C. The June 2 Report mistakenly claims that puberty blockers and hormones are experimental because they are used "off-label" and not approved by the FDA. In fact,

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[148] June 2 Report, p. 15.
[149] Vincenzo De Sanctis, et al., Long-Term Effects and Significant Adverse Drug Reactions (ADRs)Associated with the Use of Gonadotropin-Releasing Hormone Analogs (GnRHa) for Central Precocious Puberty: a Brief Review of Literature, 90(3) Acta Biomed. 345-359 (2019).
[150] June 2 Report, p. 16.
[151] June 2 Report, p. 16. The earlier Kuper et al. study is Laura E. Kuper et al., Baseline Mental Health and Psychosocial Functioning of Transgender Adolescents Seeking Gender-Affirming Hormone Therapy, 40(8) J. Dev. Behav. Pediatr. 589-596 (2019). The later study is Laura E. Kuper et al., Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy, 145(4) Pediatrics e20193006 (2020).

> off-label use, when supported by scientific evidence, as is the case here, is extremely common in medical practice and especially in pediatrics.

The June 2 Report repeatedly notes that the FDA has not approved the use of puberty blockers and hormones for the treatment of gender dysphoria in minors.[152] The report infers that lack of FDA approval renders a treatment unauthorized and experimental, but this is false.

Once again, the June 2 Report is (mis)using technical language in a way that is likely confusing to non-experts. The term "off-label" has a very specific meaning: a drug is off-label if the FDA has not specifically approved a particular medication for a particular use in a specific population. The off-label use of medications for children is quite common and often necessary, because an "overwhelming number of drugs" have no FDA-approved instructions for use in pediatric patients.[153]

The lack of FDA approval does not imply that the use of medications should be restricted. There is a consensus in the medical community that off-label use reflects a product of burdensome and expensive regulatory processes. Pharmaceutical companies often lack financial incentives to support research required for FDA approval for specific use in children.[154]

The American Academy of Pediatrics, recognizing these facts, specifically authorizes the off-label use of drugs:

> The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, *the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use.* Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient.[155]

Off-label use is so common in pediatrics that off-label drugs are prescribed in 20% of patient visits.[156] Combined hormonal contraceptives or progesterone-only contraceptive methods, which are approved on-label for contraception, are also used off-label to treat heavy menstrual bleeding, which could be due to a bleeding disorder, a delay in normal pubertal maturity or variety of other conditions; they are also used off-label for premenstrual dysphoria disorder and polycystic ovarian syndrome.

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[152] June 2 Report, pp. 8, 14, 15, 19.
[153] Boulware et al, supra note 27, quoting Kathleen A. Neville, et al., American Academy of Pediatrics Committee on Drugs, Off-label use of drugs in children, 133(3) Pediatrics 563-7 (2014) ("AAP Committee on Drugs")
[154] AAP Committee on Drugs (2014), supra note 66.
[155] Id. (emphasis added). See also Lenneke Schrier, et al., Off-label Use of Medicines in Neonates, Infants, Children, and Adolescents: a Joint Policy Statement by the European Academy of Paediatrics and the EuropeanSociety for Developmental Perinatal and Pediatric Pharmacology , 179(5) Eur. J. Pediatr 839-845 (2020).
[156] Diya Hoon, et al., Trends in Off-Label Drug Use in Ambulatory Settings: 2006-2015, 144(4) Pediatrics 1-10 (2019) (emphasis added).

A host of familiar examples provide illustrations of day-to-day, off-label use in pediatrics.[157] The use of steroids for croup is a life-saving treatment that is off-label. The medication helps toddlers get through severe, potentially airway-obstructing illnesses safely. Ondansetron (Zofran) is used off-label for nausea and vomiting to prevent fluid loss, as children are particularly vulnerable to severe dehydration.

Off-label use is also common in pediatric compassionate care, and frequently the on-label use is very different from the off-label use. Gabapentin, for example, is used on-label for the treatment of seizures but used off-label for neuropathic or mixed pain. Ketamine and fentanyl are used on-label in anesthesia but off-label for pain relief, for example, to manage chronic pain in palliative care and in patients with cancer.

In neonatal medicine, off-label medications are routinely used to treat the smallest and most fragile babies. Caffeine is used off-label to treat apnea (i.e., idiopathic respiratory arrest) of prematurity and phenobarbital is used off-label to treat neonatal seizures. More routinely, in general pediatric care, pantoprazole is a proton pump inhibitor (PPI) used to treat acid reflux. It is used off-label in neonates with gastroesophageal reflux disease who do not respond to traditional first-line treatments. It is used successfully to help infants gain adequate weight in the first four to six months of life if they do not respond to using different types of bottles, slow flow nipples, or more frequent and lower volume feedings.

In addiction medicine, routine medications like supplemental nicotine patches are off-label; they are not approved for use in those younger than 18 but are used successfully in vaping/smoking cessation, so much so that the AAP has issued guidelines on how to use and dose them. Buproprion is used on-label as an antidepressant and off-label for smoking cessation. Buprenorphine (suboxone) is used on-label in those 16 or older with opioid use disorder but used off-label in those who are younger; this medication prevents overdose death and allows those struggling with addiction to safely recover.

In psychiatry, some of the most commonly-prescribed medications for youth are off label. For example, selective serotonin reuptake inhibitors (SSRIs) are used to treat major depressive disorder and generalized anxiety in adolescents and have been shown to be effective, even though several of these ncluding sertraline and escitalopram) are off-label.[158] Other common examples include clonidine, which is FDA-approved for attention deficit hyperactivity disorder (ADHD) but is also used off-label for anxiety, insomnia, and post-traumatic stress disorder (PTSD).[159]

Finally, the June 2 Report also notes that testosterone is a controlled substance and is subject to risk of abuse, but, once again, this is misleading. The inclusion of testosterone on the schedule of controlled substances reflects the misuse of the drug by some individuals and

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[157] These examples are drawn from the list of off-label uses in AAP Committee on Drugs (2014) and reflect our clinical experience in major hospitals and clinics.
[158] For AACAP guidelines, see Boris Birmaher and David Brent, Practice Parameter for the Assessment and treatment of Children and Adolescents with Depressive Disorders, 46(110 J. Am. Acad. Child and Adolescent Psychiatry P1503-1526 (2007).
[159] Rama Yasaei and abdolreza Saadabadi, Clonidine, National L ibrary of Medicine (2022), at https://www.ncbi.nlm.nih.gov/books/NBK459124/[visited July 4, 2022].

communities (e.g., weight lifters and athletes who may use the drug to build muscle). The classification does not in any way imply that physicians should not dispense the drug if medically necessary. No special license is necessary for prescribing the medication, which is routinely prescribed to cisgender men with testosterone deficiency as well as to transgender men.

D. The June 2 Report falsely claims that medical care for gender dysphoria is provided to a large percentage of children who will come to regret their treatment. In fact, patients with gender dysphoria have vanishingly low rates of regret regarding their medical treatment.

The June 2 Report attempts to cast doubt on medical treatment for gender dysphoria by repeating the debunked claim that most transgender teens ultimately reject their transgender identity. Below, we analyze two related claims made in the report and show why both are refuted by sound evidence.

First, the report claims that "the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex."[160] This is false. We have refuted this claim in detail in prior work (addressing similar claims made to support medical treatment bans in Texas and Alabama). The key point is that *adolescents with gender dysphoria rarely find that their dysphoria resolves without treatment.*[161] Because medical treatment for gender dysphoria begins only in adolescence, and only if medically necessary for gender dysphoria, medical treatment is thus provided only to a group known to be quite stable in their gender identity.

The authoritative WPATH and Endocrine Society clinical practice guidelines contain measures to ensure that medical treatment is administered only when medically necessary.[162] As part of the process of diagnosis and treatment, clinicians take care to explain to the youth and their parents the risks and the benefits of medical treatment as well as the risks and benefits of no medical interventions.

Second, the June 2 report claims, without citation, that "roughly 8% [of transgender people] decide to return to their natal sex" for reasons ranging "from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria.[163] The 8% figure is not large, but it is nevertheless an overstatement of the percentages found in the scientific literature: solid studies show very low percentages of regret (typically under 1%) among transgender people who receive medical treatment for gender dysphoria.

The June 2 report offers as general evidence for its claims about regret only a 2021 study by Littman.[164] But the Littman study cannot establish how prevalent it is for transgender individuals to reject their transgender identity. Indeed, the Littman study does not even purport

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[160] June 2 Report, p. 14.
[161] Boulware et al., supra note 27, at 17-19.
[162] WPATH (2012) and Endocrine Society (2017), supra note 5.
[163] Id.
[164] Lisa Littman, Individuals Treated for Gender Dysphoria with Medical and/or Surgical Transition Who Subsequently Detransitioned: A Survey of 100 Detransitioners, 50 Archives of Sexual Behavior 3353-3369 (2021).

to show the percentage of transgender people who "detransition." Instead, it simply asked 100 people who self-identified as "detransitioners" about their reasons. Using Littman's study as evidence of widespread regret is akin to saying that giant pandas (an endangered species) are common because, if we search, we can find 100 of them.

Furthermore, the Littman study used a biased sampling and survey methodology: survey was anonymous; its participants were solicited from (among other venues) anti-transgender social media groups.

Finally, the June 2 Report makes a flagrant error in conflating "detransition" with "regret."[165] In addition, the Littman study is unscientific in describing a likely very diverse group of people as "detransitioners." She defines detransition as "discontinuing medications, having surgery to reverse the effects of transition, or both." Littman's definition is highly misleading, because transgender people may have many reasons to discontinue medication. One might continue to live socially in a gender role that is not the one assigned at birth and yet, by Littman's criteria, be counted as a "detransitioner." In our clinical practice, we have seen youth who discontinued hormone therapy because the effects had addressed their dysphoria; these patients were nonbinary, but Littman's method would mistakenly count them as "detransitioners."

By contrast, the June 2 report disregards a very large and far more nuanced and important 2021 study by Turban et al., which shows that transgender people who do return to live as the sex assigned at birth may not permanently do so and are, by their own report, influenced largely by "external factors, such as pressure from family, nonaffirming school environments, and sexual assault."[166] The study found that only a minority of survey participants "reported that detransition was due to internal factors, including psychological reasons, uncertainty about gender identity, and fluctuations in gender identity." Indeed, as the authors note, these psychological experiences "*did not necessarily reflect regret* regarding past gender affirmation, and were presumably temporary, as all of these respondents subsequently identified as transgender/gender diverse, an eligibility requirement for study participation."[167]

The June 2 Report also ignores a recent study, Olson et al. (2022), who find that after an average of 5 years of social transition, only 2.5% of youth identified as cisgender.[168]

Studies that actually focus on regret consistently find that transgender people only rarely regret their medical treatments.[169] For example, Bustos et al. (2021) found regret expressed by one

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[165] See generally Jack L. Turban, et al., Factors Leading to "Detransition" Among Transgender and Gender Diverse People in the United States: A Mixed-Methods Analysis, 8(4) LGBT Health 273-280 (2021) (noting that "the term 'detransition' has at times been conflated with regret, particularly with regard to medical and surgical affirmation").
[166] Id.
[167] Id.
[168] Kristina R. Olson, et al., Gender Identity Five Years After Social Transition, Pediatrics (preprint, May 2022) .
[169] Valeria P. Bustos, et al., Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence, 9(3) Plastic and Reconstructive Surgery- Global Open e3477 (2021); Sara Danker, et al., Abstract: A Survey Study of Surgeons' Experience with Regret and/or Reversal of Gender-Confirmation Surgeries, 6(9 Supp.) Plastic and Reconstructive Surgery 189 (2018); Chantal M. Wiepjes, et al., The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets, 15(4) J. Sex Med.582-590 (2018); see also Yolanda L.S. Smith, et al., Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals, 35(1) Psychological Medicine 89-99 (2005).

percent or fewer of transgender patients who underwent gender-affirming surgery, and Danker et al. (2018) report a rate of far less than 1%, as do Wiepjes et al. (2015).[170]

> E. The June 2 Report repeats discredited claims that "social contagion" is leading teens to become transgender. The issue, although sensationalized in the June 2 Report, is ultimately irrelevant to medical treatment, which is provided only after a multidisciplinary assessment and after a finding that gender dysphoria is persistent and medical treatment is warranted.

The June 2 Report claims that "social factors (e.g., peer influences and media) may be contributing factors to gender dysphoria,"[171] citing as evidence a single, discredited study by Littman. We have addressed this study at length in other work and note that

> WPATH, among other authorities, has taken a skeptical view of Littman's claim, and the study has been criticized for serious methodological errors, including the use of parent reports instead of clinical data and the recruitment of its sample of parents from anti-transgender websites. The journal of publication required an extensive correction of the original Littman article because of its misstatements. Such a correction in reputable, peer-reviewed academic journals is taken only when a panel of experts, in retrospect, came to recognize the methodological flaws of the original study and concluded that it would be unscientific to allow the originally published findings to stand."[172]

Littman's sensationalist hypothesis has been widely covered in the press, but no clinical studies have found that rapid-onset gender dysphoria exists. Further, no professional organization has recognized "rapid-onset gender dysphoria" as a distinct clinical condition or diagnosis.

Most recently, an April 2022 study of 173 youth presenting at Canadian gender clinics *found no evidence of rapid-onset dysphoria or social contagion.* The researchers posited that if "rapid onset" gender dysphoria were a real phenomenon, then teens who had more recently begun identifying as transgender would (per the Littman hypothesis) also be more likely to report online support and engagement in their gender identity. They might also (per Littman's hypothesis) be more likely to struggle with mental health concerns.

An April 2022 study of 173 youth found no such correlations, strongly undercutting the "rapid-onset" hypothesis endorsed by the June 2 report. The researchers controlled for age and sex assigned at birth and looked for correlations with recent gender knowledge (defined as less than one to two years having passed since "you realized your gender was different from what other people called you"). Recent gender knowledge was *not* significantly associated with depressive symptoms, psychological distress, past diagnoses with mental health issues or neurodevelopmental disorders, or self-harm. Nor was it associated with having gender-supportive online friends, general support from online friends or transgender friends, or gender support from parents.[173]

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[170] Id.
[171] June 2 Report, p. 12.
[172] Boulware et al., supra note 27, at 20-21 (internal citations omitted).
[173] Greta R. Bauer, et al., 243 J. Pediatrics 224 -227 (2022).

Data do substantiate that younger people today are more likely to identify as transgender than are older people, but this does not substantiate the idea of social contagion. The increase may be due to the increasing social acceptance of gender diversity (i.e., older people grew up in a more transphobic social environment). In fact, adolescent presentation of transgender identity is often observed and should not be pathologized. In the largest U.S. sample of transgender adults, over half reported first starting to realize that they were transgender in adolescence (57% ages 11-20) and roughly half (47%) started to disclose their identity during this time frame.[174]

Further, the data do not show a massive wave of transgender identity even among teens. A 2022 study by the Williams Institute found that, using an expansive definition of "transgender," about 0.5% of adults now identify as transgender, while 1.4% of youth aged 13-17 do, or about 300,000 young people.[175] This is not a large percentage or a large absolute number.

Underlying the June 2 Report's claim about social contagion is a set of imagined stereotypes – that teenagers do not known their own gender identity and readily change their gender identity based on peer influence and social media. But these stereotypes contradict the scientific understanding of gender identity formation. Studies of so-called "conversion" or "reparative" therapy, for example, finds that transgender identity is highly resistant to change even in the face of concerted efforts by medical authorities versed in psychological methods. Studies find that conversion therapy is ineffective in altering gender identity and is psychologically damaging.[176]

> F. The June 2 Report claims that inappropriate medical care is provided to adolescents with gender dysphoria who also have anxiety, depression, and other mental health conditions. These assertions are unsupported by scientific evidence and disregard evidence-based clinical practice guidelines that provide sound guidance for treating complex cases.

The June 2 Report speculates that because "a high proportion" of youth receiving medical care for gender dysphoria also have a behavioral health disorder, "available research raises questions as to whether the [individuals'] distress is secondary to pre-existing behavioral health disorders and not gender dysphoria."[177] In simpler terms, *the June 2 Report speculates that perhaps gender dysphoria is not real but is, rather, an imagined by-product of underlying mental illness.* A close examination shows that this claim has no foundation in science; it rests on unexamined and harmful stereotypes and unaccountably dismisses the scientific knowledge and clinical skill of child and adolescent psychologists and psychiatrists.

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[174] Sandy E. James, et al., The Report of the 2015 U.S. Transgender Survey, National Center for Transgender Equality (2015).
[175] Jody L. Herman, et al., How Many Adults and Youth Identify as Transgender in the United States?, U.C.L.A. School of Law, Williams Institute (2022).
[176] A survey of the scientific literature by the U.S. Department of Health and Human Services finds that "no ne of the existing research supports the premise that mental or behavioral health interventions can alter gender identity or sexual orientation." Substance Abuse and Mental Health Services Administration, Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth, U.S. Department of Health and Human Services, HHS Publication No. (SMA) 15-4928 (2015), p. 1.
[177] June 2 Report, p. 6.

First, the June 2 Report implicitly posits a causal hypothesis that behavioral health disorders cause gender dysphoria. This hypothesis is entirely devoid of scientific evidence. Indeed, the scientific evidence strongly suggests that the direction of causation runs the other way. It is well-established that being transgender leads to mental health concerns because of the social stress and discrimination of being transgender in a society that is strongly oriented to cisgender identity and disapproving of transgender identity.[178] In our society, transgender individuals experience a great deal of discrimination, hostility, and physical violence. Quite simply, it is unsafe to be transgender in this current hostile climate.[179] Accumulation of existential fear and threatening experiences can manifest as physical and mental conditions. Thus, one would expect – and studies confirm – that transgender people, on average, have worse physical and mental health than cisgender people.

Although the effects of gender minority stress are well-known, the June 2 Report makes no mention of the literature. Instead, it indulges in speculation based, apparently, on the stereotyping of transgender people as confused and dysfunctional. The June 2 Report posits that individuals with mental health concerns cannot be trusted to understand their own gender identity. This is a highly prejudicial stance and one that disregards the key role of psychologists and psychiatrists, who have developed sensitive and effective approaches to treating adolescents with gender dysphoria and mental health concerns.[180]

Second, the co-occurrence of psychological distress among individuals with gender dysphoria provides no reason for denying care. Any population of individuals – cisgender or transgender – will include some with mental health concerns, and the WPATH and Endocrine Society guidelines recognize that there is a higher prevalence of anxiety, depression and post-traumatic stress disorder among transgender youth than among cisgender youth. In response, the guidelines set out practices that include a careful psychological assessment of each adolescent as part of the process for determining whether medical treatment for gender dysphoria is appropriate and likely to have benefits that outweigh risks.

The Endocrine Society guidelines specifically recommend that mental health professionals should be able to diagnose gender dysphoria and distinguish it from other "conditions that have similar features (*e.g.*, body dysmorphic disorder)." In addition, the mental health provider should be prepared to diagnose psychiatric conditions, provide or refer for treatment, and to "psychosocially assess the person's understanding, mental health, and social conditions that can

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[178] Rylan J. Testa, et al., Development of the Gender Minority Stress and Resilience Measure, 2(1) Psychology of Sexual Orientation and Gender Diversity 65-77 (2015); Rylan J. Testa, et al., Suicidal Ideation in Transgender People: Gender Minority Stress and Interpersonal Theory Factors, 126(1) J. Abnormal Psychology 125-36 (2017); Alexandrai M. Delozier, et al., Health Disparities in Transgender and Gender Expansive Adolescents: A Topical Review from a Minority Stress Framework, 45(8) J. Pediatric Psychology 842-847 (2020); Jessica Hunter, et al., Gender Minority Stress in Trans and Gender Diverse Adolescents and Young People, 26(4) Clinical Child Psychology and Psychiatry 1182-1195 (2021).

[179] See, e.g., Rebecca L. Stotzer, Violence Against Transgender People: A Review of United States Data, 14(3) Aggression and Violent Behavior 170-179 (2009).

[180] See John F. Strang, et al., Initial Clinical Guidelines for Co-Occurring Autism Spectrum Disorder and Gender Dysphoria or Incongruence in Adolescents, 47(1) J. Clinical Child & Adolescent Psychology 105-115 (2016).

impact gender-affirming hormone therapy."[181] In our clinical practice, we also ensure that youth and their caregivers have the information and support necessary to fully understand the risks, benefits, and outcomes of treatment. That is, we not only provide assessment but also fill in any gaps in understanding and support the decision-making process.

Our experience in clinical practice reflects these guidelines. Any consultation for medical treatment for gender dysphoria includes a mental health assessment. Further, the treatment plan for each adolescent is then individualized to reflect the risks and benefits of treatment and the risks and benefits of no treatment. Consistent with the WPATH guidelines, as clinicians, we ensure that the mental health concerns are not interfering with our ability to assess gender dysphoria and youth assent to treatment.

Third, the June 2 Report implicitly claims that any mental health disorder impairs a minor's ability to provide informed assent and, somehow, also invalidates the informed consent of their guardian. Experts in child and adolescent psychiatry, child psychology, and adolescent medicine have established that youth can make complex medical decisions. Further, the literature specifically demonstrates that transgender youth with co-occurring mental health conditions can competently participate in decision-making.[182] With guidance from mental health providers, parents, and physicians, teens can be part of a decision process that helps them explore their identity and make nuanced decisions about the benefits and risks of medical treatment.[183] Indeed, these processes of exploration and decision-making are central goals of, and central tasks for, trained mental health providers who work with teens.

> G. The June 2 Report speculates, without evidence, that psychotherapy alone is as effective as medical treatment for gender dysphoria. This claim contradicts the findings of solid scientific studies, which show that medical care is more effective than psychotherapy alone.

The June 2 Report argues, without scientific evidence, that youth with gender dysphoria should not be offered medical treatment but instead should only receive psychotherapy, an approach that it mistakenly terms "watchful waiting."[184]

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[181] Endocrine Society (2017), supra note 5.
[182] Lieke J. Vrouenraets, et al., Assessing Medical Decision-Making Competence in Transgender Youth, 148(6) Pediatrics e2020049643 (2021).
[183] Beth A. Clark and Alice Virani, "This wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy, 18 J. Bioethical Inquiry 151-164(2021); Vrouenrats, et al., supra note 95; Megan S. O'Brien, Critical Issues for Psychiatric Medication Shared Decision Making with Youth and Families, 92(3) Families in Society 310-316 (2011); Mary Ann McCabe, Involving Children and Adolescents in Medical Decision Making: Developmental and Clinical Considerations 21(4) J. Pediatric Psychology 505-516 (1996).
[184] For example, at p. 12, the June 2 Report asks, "[S]hould conventional behavioral health services be utilized without proposing treatments that pose irreversible effects [i.e., drug therapies]? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects {i.e., the watchful waiting approach)?" At p. 20, the June 2 Report misuses the term "watchful waiting" to describe the denial of medical care to adolescents with gender dysphoria, and the report miscites its own purported expert report. The Cantor document discusses "watchful waiting" meaning the denial of social transition to prepubertal children, not the denial of medical treatment to adolescents. Cantor document, p. 10-11.

The report offers no actual evidence for this denial of standard medical care. Its recommendation rests, instead, on an unfounded and mistaken criticism of the existing literature. The Cantor document, attached to the AHCA report as Appendix C, states that several studies "successfully identified evidence of [mental health] improvement [due to medical treatment for gender dysphoria], *but because patients received psychotherapy along with medical services, which of those treatments caused the improvement is unknowable.*"[185]

This statement is false. Medical treatment for gender dysphoria has been shown to lead to positive effects on mental health that are not associated with psychotherapy alone. Costa et al. in 2015 found that puberty blockers improve psychosocial functioning in teens with gender dysphoria, compared to teens who receive psychotherapy but not blockers.[186] Costa's study ewas designed to include a control group of teens with gender dysphoria who did not receive blockers.

In a 2022 study, Tordoff et al find that puberty blockers and hormone therapy are associated with significant improvements in depression and suicidality in a population of transgender and nonbinary youths aged 13 to 20.[187] The authors showed the independent effects of medications such as puberty blockers and hormones on depression, anxiety, and gender dysphoria. They controlled for temporal trends and other confounding factors, expressly including whether the teen received "ongoing mental health therapy other than for the purpose of a mental health assessment to receive a gender dysphoria diagnosis."[188] Put simply, Tordoff et al. clearly found that youth with gender dysphoria reported better outcomes if they received puberty blockers, even after controlling for the effects of psychotherapy.

Similarly, in a 2020 study, Laura Kuper et al. found that gender-affirming hormone therapy made a large improvement in adolescents' body-related distress and led to small to moderate improvement in symptoms of depression and anxiety.[189] Kuper et al. specifically collected data on psychotherapy and the use of psychiatric medications and expressly controlled for both. Thus, Kuper et al.'s study shows that hormone treatment for gender dysphoria is effective above and beyond the benefits of psychotherapy and psychiatric medications.

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[185] Cantor document, p. 13.
[186] Costa et al., supra note 56.
[187] Diana M. Tordoff et al., Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care, 5(2) JAMA Network Open e220978 (2022).
[188] Id.
[189] Laura E. Kuper, et al., Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy, 145(4) Pediatrics e20193006 (2020).

TAB 183-28

From: FL-Rules@dos.state.fl.us
Sent: Thursday, July 7, 2022 1:43 PM EDT
To: Cole.Giering@ahca.myflorida.com
Subject: One-time User Comment From FLRules.com

FLRules.com one-time comment:

Name: Scott VanDeman
Email: svandeman@fcaap.org
Title: Comments from American Academy of Pediatrics and Florida Chapter, American Academy of Pediatrics
Comment: July 7, 2022

Tom Wallace
Deputy Secretary for Medicaid
Florida Agency for Health Care Administration
2727 Mahan Drive
Mail Stop #8
Tallahassee, FL 32308

Dear Director Wallace,

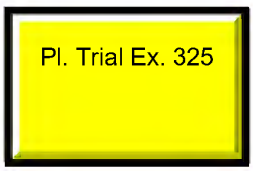
The American Academy of Pediatrics (AAP), a nonprofit organization representing 67,000 pediatricians dedicated to the health, safety and well-being of all children and the Florida Chapter of American Academy of Pediatrics, Inc (FCAAP), a nonprofit organization representing more than 2,600 pediatricians committed to serving all children across the state, thank you for the opportunity to provide comments on the Florida Agency for Health Care Administration's proposed rule to prohibit gender-affirming care in the state's Medicaid program.

We write to express our grave concerns with the proposed rule. Denying evidence-based, medically necessary standards of care to transgender adolescents constitutes a broad and sweeping discriminatory action by the State of Florida and its Medicaid program.

Gender-affirming care is the widely accepted standard of care for treating transgender adolescents with gender dysphoria. Gender-affirming care is endorsed and recommended by the American Academy of Pediatrics; the Florida Chapter of the American Academy of Pediatrics, Inc; the American Medical Association; the American College of Obstetricians and Gynecologists; the American College of Physicians; the American Psychiatric Association; the American Psychological Association; the American Academy of Family Physicians; the American Academy of Child and Adolescent Psychiatry; the Endocrine Society; the Society for Adolescent Health and Medicine; the Pediatric Endocrine Society; the World Professional Association for Transgender Health (WPATH); and many more members of the medical community.

Gender-Affirming Care is the Standard of Care
Gender-affirming care is developmentally appropriate care that seeks to understand and appreciate a child's or adolescent's gender identity and experience through a safe and nonjudgmental partnership that includes general pediatricians, pediatric specialists, mental health providers, children and adolescents and their families. While gender-affirming care is irrefutably the standard of care, it must, like all other areas of medicine, be individualized to meet the needs of each and every unique patient.

WPATH and the Endocrine Society have developed well-researched and evidence-based standards of care and clinical guidelines for the care of children and adolescents with gender dysphoria. WPATH's Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, Version 7 and the Endocrine Society's Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline (both are herein referenced as "standards of care") are in fact the gold standard, contrary to the State of



Florida's assertion, among the medical community for caring for children and adolescents with gender dysphoria.

For a model of care to be considered the standard of care for a specific diagnosis, the care must be "treatment that is accepted by medical experts as a proper treatment for a certain type of disease and that is widely used by healthcare professionals." The State of Florida's attempt to argue that gender-affirming care is not the standard of care, as referenced in its Florida Medicaid: Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria report and its "Florida Fact-Checked" version of the HHS Office of Population Affairs Guidance on gender-affirming care, is entirely inconsistent with the well-recognized and established definition of standard of care, and represents a purposeful mischaracterization of available evidence as well as the position of the medical community.

Instead of supporting the standard of care for transgender adolescents, the state is seeking to rely only on "watchful waiting." This outdated model is based on long-refuted binary notions of gender and assumes without evidence that gender identity becomes fixed at a certain age and will result in direct harm to gender dysphoric children and adolescents who are denied access to well-evidenced multidisciplinary care. Notably, "watchful waiting" is based on studies with flawed methodology, validity concerns, and limited follow-up of transgender adolescents. Thus, "watchful waiting" is not recommended by any major medical association in the United States.

Gender Dysphoria
Gender dysphoria is a formal diagnosis under The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) in which there is a pronounced incongruence between someone's gender identity or expression and sex assigned at birth. For the diagnosis, the patient must exhibit 2 of the following for at least 6 months:
? A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
? A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
? A strong desire for the primary and/or secondary sex characteristics of the other gender
? A strong desire to be of the other gender (or some alternative gender different from one's assigned gender)
? A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender)
? A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)
In an apparent attempt to undermine the validity of the diagnosis of gender dysphoria, the state, under "Etiology of Gender Dysphoria," implies that mental and physical health conditions are the primary cause of gender dysphoria and that psychological support is all that is needed to provide care for gender dysphoric youth. However, the preponderance of the evidence indicates that gender dysphoria is indeed a primary diagnosis in which mental health issues are often exacerbated by lack of access to appropriate gender affirming care. The state disqualifies its own arguments by stating: "At the moment, none of these studies provides a definitive cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative." To be clear, there is no evidence that mental or physical health conditions cause gender dysphoria. As such, mischaracterizing the diagnosis in an effort to prohibit gender-affirming care is disingenuous at best and would result in direct harm to transgender children and adolescents.

Included in the state's document is the suggestion that mental health care should be the first line of care for youth diagnosed with gender dysphoria. On this, we agree. In fact, the evidence-based standards of care for gender-dysphoria, as referenced above, recommend mental health evaluation and care as the first step for affected children and adolescents. Indeed, research demonstrates that transgender children and adolescents experience stigma and discrimination, which adversely affects their mental health. Children and adolescents diagnosed with gender dysphoria often have to hide their gender identities to avoid bullying and harassment and face greater risks of homelessness, physical violence in the home and in the community, and substance use. However, the state conflates the association of mental health diagnoses, trauma, and attachment issues with causality for gender dysphoria in an effort to discredit the primary diagnosis. In reality, the mental health issues faced by those with gender dysphoria are often the direct result of a lack of access to care or not being supported in their gender identity.

In further attempting to undermine the well-established diagnosis of gender dysphoria, the state seeks to incorporate

the concept of "rapid onset gender dysphoria." The manuscript from which the term "rapid onset gender dysphoria" originates has been widely criticized. An expert review emphasized the following issues:

? "This study of parent observations and interpretations serves to develop the hypotheses that rapid-onset gender dysphoria is a phenomenon and that social influences, parent-child conflict, and maladaptive coping mechanisms may be contributing factors for some individuals. Rapid-onset gender dysphoria (ROGD) is not a formal mental health diagnosis at this time. This report did not collect data from the adolescents and young adults (AYAs) or clinicians and therefore does not validate the phenomenon. Additional research that includes AYAs, along with consensus among experts in the field, will be needed to determine if what is described here as rapid-onset gender dysphoria (ROGD) will become a formal diagnosis. Furthermore, the use of the term, rapid-onset gender dysphoria should be used cautiously by clinicians and parents to describe youth who appear to fall into this category. The term should not be used in a way to imply that it explains the experiences of all gender dysphoric youth nor should it be used to stigmatize vulnerable individuals."
? "…the study design of this research falls under descriptive research: as such, it did not assign an exposure, there were no comparison groups, and the study's output was hypothesis-generating rather than hypothesis-testing."

The Coalition for the Advancement & Application of Psychological Science, which includes the American Psychiatric Association, the American Psychological Association, the Society for a Science of Clinical Psychology, the Society of Clinical Child and Adolescent Psychology, the Society of Pediatric Psychology, and many more international, national, and state psychological and psychiatric associations, published a position statement on the concept of rapid onset gender dysphoria, stating:

? …it has not been subjected to rigorous peer-review processes that are standard for clinical science. Further, there is no evidence that ROGD aligns with the lived experiences of transgender children and adolescents.
? Research on gender identity development in children and adolescents continues to evolve and these advances will likely influence diagnosis and empirically-based standards of care, as well as the legislative landscape impacting trans people's access to care and legal protections. The available research is clear that transgender people are subjected to marginalization, stigmatization, and minority stress, which have significant detrimental effects on health and well-being. Terms, such as ROGD, that further stigmatize and limit access to gender-affirming and evidence-based care violate the principles upon which CAAPS was founded and public trust in clinical science.

Mental Health Care
Under the evidence-based standards of care, mental health care is indeed the first step in the care of children and adolescents diagnosed with gender dysphoria. The evidence-based standards of care recommend that a child or adolescent diagnosed with gender dysphoria be seen and evaluated by a qualified mental health professional trained in child and adolescent developmental psychopathology, competent in diagnosing and treating the ordinary problems of children and adolescents and meeting the same competency requirements as mental health professionals working with adults. Under the evidence-based standards of care, a qualified mental health professional has a responsibility to:

? Directly assess gender dysphoria in children and adolescents (see general guidelines for assessment, below).
? Provide family counseling and supportive psychotherapy to assist children and adolescents with exploring their gender identity, alleviating distress related to their gender dysphoria, and ameliorating any other psychosocial difficulties.
? Assess and treat any coexisting mental health concerns of children or adolescents (or refer to another mental health professional for treatment). Such concerns should be addressed as part of the overall treatment plan.
? Refer adolescents for additional physical interventions (such as puberty-suppressing hormones) to alleviate gender dysphoria. The referral should include documentation of an assessment of gender dysphoria and mental health, the adolescent's eligibility for physical interventions (outlined below), the mental health professional's relevant expertise, and any other information pertinent to the youth's health and referral for specific treatments.
? Educate and advocate on behalf of gender dysphoric children, adolescents, and their families in their community (e.g., day care centers, schools, camps, other organizations). This is particularly important in light of evidence that children and adolescents who do not conform to socially prescribed gender norms may experience harassment in school (Grossman, D'Augelli, & Salter, 2006 Grossman, D'Augelli, Howell, & Hubbard, 2006); Sausa, 2005), putting them at risk for social isolation, depression, and other negative sequelae (Nuttbrock et al., 2010).

? Provide children, youth, and their families with information and referral for peer support such as support groups for parents of gender-nonconforming and transgender children (Gold & MacNish, 2011; Pleak, 1999; Rosenberg, 2002).

The evidence-based standards of care clearly recommend that mental health providers who care for children and adolescents with gender dysphoria diagnose and treat any other mental health conditions the child or adolescent is experiencing. Thus, the state's implication that mental health providers are not addressing existing mental health concerns prior to beginning gender-affirming medical care is wholly inaccurate. Prior to puberty, mental health professionals, pediatricians, and other health care providers "work together to destigmatize gender variance, promote the child's self-worth, facilitate access to care, educate families, and advocate for safer community spaces where children are free to develop and explore their gender" without medical interventions.

Medical Care

The state begins its literature review on gender dysphoria and puberty suppression by attempting to argue that a majority of children and adolescents will cease showing signs of gender dysphoria and conform to their sex assigned at birth. Herein lies a distinction between prepubertal children and adolescents that the state fails to consider, or outright ignores.

In its "Florida Fact-Checked" version of the HHS Gender Affirming Care document, the state notes that "most children identifying as transgender will detransition following the onset of puberty." Additionally, in the ACHA GAPMS report, the state makes a similar argument, including "neither organization explains that a majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that puberty suppression can have side effects." By definition, a child is defined as "a young person especially between infancy and puberty," while adolescence is defined as "the period of life when a child develops into an adult: the period from puberty to maturity terminating legally at the age of majority." The key difference between children and adolescents being the onset of puberty. By referencing "children" it is "Florida Fact- Checked" document and "young adolescents" in the ACHA GAPMS report, the state erroneously conflates the 2 terms. However, the definitions of these terms are different and cannot be used interchangeably.

Furthermore, the state relies on a study that "offers data on the percentage of children who opt not to transition after experiencing gender dysphoria." Similar claims made in other states that have attempted to ban gender-affirming care have been thoroughly debunked by a recent expert review from faculty from Yale University and the University of Texas Southwestern. The report from Yale examined in detail the misrepresentation of the Steensma et al study, explaining that:

? "...the Steensma study was not designed to (and the lead author has acknowledged) does not provide a basis for calculating what percentage of prepubertal children diagnosed with gender dysphoria persist with that diagnosis into adolescence. Rather, the Steensma study was designed only to study the characteristics of those who persisted.60 Among other limitations, in Steensma (2013), former patients who opted to not participate in the study (either refused to participate or did not respond to an offer to participate) were categorized as "desisters," i.e., patients whose gender dysphoria resolved without transition or treatment. Patients can fail to respond to a study request for many reasons, including having moved away, receiving treatment elsewhere, or being uninterested in participating in a study. Thus, SEGM misuses the Steensma data by counting nonresponding patients as having "desisted" in experiencing gender dysphoria.61 Indeed, in published correspondence, Steensma emphasizes that the 2013 study should not be used to calculate the percentages of "persisters" and "desisters."62 The misrepresentation of Steensma on the SEGM website constitutes a major violation of the scientific method and the accepted conventions of research."

Some prepubertal children's diagnosis of gender dysphoria will indeed not continue in adolescence, and as such, there are no recommended medical interventions for prepubertal children. For prepubertal children, gender exploration is a natural part of child development. However, for children diagnosed with gender dysphoria persisting at the onset of puberty (adolescence), research demonstrates that gender dysphoria will continue. ; Under gender-affirming care, adolescents diagnosed with gender dysphoria, after careful and exhaustive mental health evaluation and care , may progress to gender-affirming medical care under the evidence-based standards of care.

Pubertal Blockers

Under the evidence-based standards of care, gender-affirming medical care is a highly individualized model of care. Prior to beginning gonadotrophin-releasing hormone agonists (GnRH, herein referred to as puberty blockers) as a component of a multidisciplinary approach to caring for adolescents diagnosed with gender dysphoria, adolescents must meet stringent criteria under the evidence-based standards of care from WPATH, including:

? The adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed);
? Gender dysphoria emerged or worsened with the onset of puberty;
? Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment.
? The adolescent has given informed consent and, particularly when the adolescent has not reached the age of medical consent, the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process. Any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment."

The Endocrine Society lays out additional criteria that must be met prior to undergoing puberty blockers as a component of gender-affirming medical care:

? (the adolescent) has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
? (the adolescent) has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
? And a pediatric endocrinologist or other clinician experienced in pubertal assessment
o agrees with the indication for GnRH agonist treatment,
o has confirmed that puberty has started in the adolescent (Tanner stage =G2/B2),
o has confirmed that there are no medical contraindications to GnRH agonist treatment.

In the ACHA GAPMS report and the "Florida Fact- Checked" document, the state asserts that there is no credible evidence demonstrating puberty blockers benefit adolescents diagnosed with gender dysphoria. However, the state either unknowingly or willingly ignores the body of evidence that supports this practice. Medication to suppress puberty has been used to treat precocious puberty for decades. The identical therapeutics are also used in adolescents diagnosed with gender-dysphoria and perhaps more importantly represent a very reasonable balance of risk and benefit when considering the totality of the available data and clinical experience. The pubertal blocker phase of gender-affirming care importantly allows the patient to delay the development of secondary sex characteristics. By pausing the progression of secondary sex characteristics, adolescents are provided time to explore their gender identity, access and/or continue mental health support, and assess and define their treatment goals, in conjunction with their families.

Contrary to the state's assertion that the evidence supporting use of puberty blockers is "weak," a large body of evidence supports their use in adolescents diagnosed with gender dysphoria. For example, recent research examined 272 adolescents who were referred to a gender clinic, but had not yet began undergoing gender-affirming medical care, including puberty blockers, and 178 adolescents who had already began receiving gender-affirming care using puberty blockers with 651 cisgender adolescents. The researchers found that adolescents with gender dysphoria had worse psychological health compared with their cisgender adolescent peers and that after receiving puberty blockers as part of gender-affirming care, the adolescents with gender dysphoria had similar or better psychological health than their cisgender peers. Another recent study found that transgender adults who wanted and were able to access puberty blockers as adolescents were less likely to have lifetime suicidal ideation compared to transgender adults who were not able to access puberty suppression medication as adolescents. In a 2-year follow-up study, researchers found that the use of puberty blockers led to improvements in overall functioning and decreased instances of depression.

The state further asserts that "puberty suppression causes side effects, some of which have the potential to be permanent." However, experts point out that "recent studies suggest that puberty-blocking medication has

negligible or small effects on bone development in adolescents, and any negative effects are temporary and reversible. The most recent studies show that puberty-blocking drug therapy either has no effect on bone mineral density (BMD), a proxy measure of bone strength, or is associated with a very small decrease." Overall, the studies that have examined the use of puberty blockers, as a component of gender-affirming care, demonstrate that the use of these medications is evidence-based and provides for an appropriate risk/benefit ratio for adolescents diagnosed with gender dysphoria.

In addition, the state fixates on the argument that puberty blockers are used off-label, not approved by the Federal Drug Administration (FDA), and that no randomized clinical trials (RCT) have been completed on the use of puberty blockers to treat gender dysphoria. These arguments lack any basis. First, in pediatric medicine, "the purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient." The use of off-label medication in pediatric medicine is supported by clinical evidence and data. In suggesting that puberty blockers cannot be used to treat gender dysphoria simply because they have not been approved by the FDA for such purposes, the state fails to understand the relationship between the FDA and the practice of medicine:

? Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not in the approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects. Use of a marketed product in this manner when the intent is the "practice of medicine" does not require the submission of an Investigational New Drug Application (IND), Investigational Device Exemption (IDE) or review by an Institutional Review Board (IRB). However, the institution at which the product will be used may, under its own authority, require IRB review or other institutional oversight.

The use of off-label medication in pediatric medicine is not experimental, nor does it constitute anything other than the practice of evidence-based medicine. Off-label medication use for pediatric patients is commonplace and there is no basis to prohibit puberty blockers because of their off-label use in pediatrics.

The state's argument that puberty blockers have not undergone RCTs and therefore should be disqualified for use treating adolescents diagnosed with gender dysphoria is also severely flawed. As explained by Armand H. Antommaria, MD, PhD, FAAP, HEC-C, Director of the Ethics Center, the Lee Ault Carter Chair of Pediatric Ethics, and an Attending Physician in the Division of Hospital Medicine at Cincinnati Children's Hospital Medical Center:

? …it may, at times, be unethical to conduct randomized trials. For randomized trials to be ethical, clinical equipoise must exist; there must be uncertainty about whether the efficacy of the intervention or the control is greater. Otherwise, it would be unethical to knowingly expose trial participants to an inferior intervention or control. Trials must also be feasible; it would also be unethical to expose individuals to the risks of trial participation without the benefit of the trial generating generalizable knowledge. A randomized trial that is unlikely to find enough people to participate because they believe they might be randomized to an inferior intervention would be unethical because it could not produce generalizable knowledge due to an inadequate sample size.

Furthermore, a group of leading bioethicists echo Dr Antommaria's explanation: "Randomized control trials also are only ethical when there is clinical "equipoise," which means they are only appropriate when there is genuine uncertainty about whether the intervention will be more effective than the control." There is no uncertainty about the use of puberty blockers to treat adolescents diagnosed with gender dysphoria -- the evidence fully supports this intervention as a component of gender-affirming care. Studies other than RCTs are, in fact, utilized regularly in the practice of medicine and are preferable in some instances.

Gender-Affirming Hormone Therapy
As a component of gender-affirming care, adolescents who have received extensive mental health care and puberty blockers may progress to hormone therapy. As with every component of gender-affirming care, the use of hormone therapy is a highly individualized decision, and any decisions are made in concert with the adolescent, their family, and mental health and medical care providers. Under the evidence-based standards of care for receiving hormone

therapy, the following criteria must be met:

? A qualified MHP (mental health professional) has confirmed:
o the persistence of gender dysphoria,
o any coexisting psychological, medical, or social problems that could interfere with treatment (e.g., that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
o the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
? And the adolescent:
o has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
o has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
? And a pediatric endocrinologist or other clinician experienced in pubertal induction:
o agrees with the indication for sex hormone treatment,
o has confirmed that there are no medical contraindications to sex hormone treatment.

The state remarks in its Fact-Checked document that it is "misleading" to state that hormone therapy is partially reversible. This is purposefully misleading. The evidence-based standards of care acknowledge that some forms of hormone therapy are reversible and that some are not reversible. Initiating hormone therapy is not a decision that is made lightly and there are stringent criteria that must be met, as referenced above. Furthermore, experts at Yale University explain that hormone therapy has a wide range of uses in adolescents:

? Estrogen and testosterone are often used off-label to treat adolescents with intersex conditions. Common hormonal medications used off-label include norethindrone, a progesterone analogue used off-label for the treatment of heavy menstrual bleeding in those with polycystic ovarian syndrome, bleeding disorder, and anovulatory bleeding of early puberty. It is also used to treat endometriosis, which is a painful inflammatory condition. Many forms of combined hormonal contraception, as well as a testosterone-blocking medication (spironolactone), are used off-label to treat acne. Other examples include clonidine, a blood pressure medication used off-label for the treatment of ADHD, migraine headaches, disorders of behavioral regulation, and insomnia; and propranolol, a blood pressure medication used off-label for the treatment of performance anxiety.

As referenced in the preceding paragraph, the off-label use of hormone therapy for adolescents diagnosed with gender dysphoria "does not imply an improper, illegal, contraindicated, or investigational use. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient." Decision-making to initiate this form of gender-affirming care takes place at the clinical level, using the evidence-based standards of care and the best available evidence. By attempting to argue that hormone therapy is somehow more dangerous to adolescents with gender dysphoria than to cisgender adolescents undergoing to same treatment for a different medical condition, the state makes it abundantly clear that this is not about the health and well-being of adolescents; it is rather a misguided attempt to discriminate against adolescents with gender dysphoria.

In the GAPMS report, the state cites a study by Dutra et al that "examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that the use of estrogen or testosterone can increase risks for cardiovascular disease." To use this as a basis for the state's argument to prohibit gender-affirming care for adolescents diagnosed with gender dysphoria would mean that the state would need to prohibit the use of hormone therapy in Florida's population at large. Additionally, in making this argument the state fails to consider the intent of hormone therapy -- to align one's body with one's gender identity. The experts at Yale University also clarify this misrepresentation or misunderstanding:

? The medical result is that transgender individuals move toward the typical medical profile of their identified gender. And so transgender women, like cisgender women, have lower risks of cardiovascular disease than

cisgender men.111 Transgender women, like cisgender women, have a slightly higher risk of venous thromboembolism than cisgender men. In fact, transgender women have a lower risk of venous thromboembolism than cisgender women, and the overall risk is extremely low (less than 1%) for all transgender individuals, both women and men.112 The risk of venous thromboembolism in transgender women and non-pregnant cisgender women is less than the risk in pregnancy, which is the highest estrogenic physiologic state known.

? It is also critical to note that the medical impact of gender-affirming treatment is generally the same in transgender people as in cisgender people who take the same hormone medications. For example, physicians commonly prescribe hormonal contraceptives containing ethinyl estradiol (a synthetic estrogen) to adolescents for reasons including birth control, management of irregular or painful menstrual periods, and acne. In other words, similar doses of exogenous sex hormones are commonly administered to cisgender individuals for a host of reasons and are well tolerated.

Research shows that hormone therapy, as a component of gender-affirming care, is beneficial to caring for adolescents diagnosed with gender dysphoria. A recent study in the Journal of Adolescent Health examined data from transgender or nonbinary adolescents and young adults between 13-24 and found that the provision of hormone therapy in those under 18 resulted in lower levels of depression and suicide attempts compared to adolescents who were unable to access hormone therapy. Another recent study demonstrated that the provision of puberty blockers and hormone therapy reduced depression and suicidality over the course of 1 year.

Additionally, the evidence cited in the evidence-based standards of care reinforces the sound basis for the provision of hormone therapy in adolescents diagnosed with gender dysphoria. Under the evidence-based standards of care, there are specific criteria for gender-affirming surgical interventions. The state's focus on gender-affirming surgery and its attempt to classify it as common is a blatant misrepresentation intended to politicize the issue and cast doubt on the evidence-based standards of care.

Risks

Unlike the state's assertion on its "Florida Fact-Checked" document that "no reliable evidence shows that gender dysphoria significantly increases the risk of suicide," there is in fact evidence to support this. In a study of more than 1,000 transgender adolescents, transgender adolescents had higher odds of all suicide outcomes compared to cisgender adolescents, and were at greater risk for suicidal ideations and attempts compared to their cisgender peers. Additionally, in the first large scale (N = 120,670) study examining the relationship between transgender adolescents and suicide, the authors found that between 30-51% of transgender adolescents reported engaging in suicidal behavior, compared to between 10-18% of their cisgender peers.

As noted in the earlier section on mental health, adolescents with gender dysphoria face increased bullying, discrimination, harassment, and a lack of social acceptance. To add to these daily, ongoing issues, adolescents with gender dysphoria are at greater risk for suicide and other mental health conditions. Curiously, the State of Florida appears to agree that transgender adolescents (and other LGBTQ adolescents) face more serious mental health concerns than their cisgender peers, as it maintains a web site, Youth Suicide Prevention under the FL Department of Health, explaining the protective factors and risks associated with suicide in adolescents (the state refers to this population as teens). In identifying these protective factors and risks associated with suicide in adolescents, the state readily admits that "It is important to know that some youths experience an increased amount of risk. Youths are those who identify as LGBTQ, American Indian/Alaska Native, youth in the child welfare and juvenile justice systems or military service members can have higher incidence of suicidal behavior." The state cannot have it both ways; it cannot argue that gender dysphoria doesn't increase the risk of suicide, as noted it its "Florida Fact-Checked" document (ignoring the evidence that patently refutes this argument), and then readily acknowledge via its youth suicide prevention web site that transgender adolescents are at increased risk of suicide.

As referenced in an earlier section of this comment letter, access to and the provision of puberty blockers and hormone therapy as part of gender-affirming care works and is the gold standard according to the medical community to alleviate mental health conditions and risks associated with gender dysphoria in adolescents.

Medicaid is a Critical Source of Health Care for Children, including Transgender Adolescents

Medicaid is a vital source of health insurance for children (for data reporting purposes below, the term "children" is inclusive of "adolescents") in Florida and across the United States. Nationally, children make up the single largest group of enrollees in Medicaid and the Children's Health Insurance Program (CHIP); more than 40 million—or 53%

of all US children—rely on Medicaid and CHIP coverage, including with special health care needs and those from low-income families. In Florida, over 2.8 million children were enrolled in Medicaid or CHIP as of February 2022. Medicaid also provides comprehensive prenatal care, enabling millions of healthy pregnancies and births, thereby helping millions of children obtain a healthy start. In states that have expanded Medicaid coverage to low-income adults, this coverage not only provides many documented benefits to those adults, but also has added benefits for children and adolescents, including an increased likelihood that they are covered, improved access to needed care, improved financial security for the family, higher preventive care use, and other benefits. ;

The direct benefits of Medicaid coverage for children and adolescents are many. In addition to improved access to care and health outcomes, those with Medicaid coverage miss less school, do better in school, are more likely to graduate and attend college, become healthier adults, earn higher wages, and pay more in taxes. Together with CHIP, Medicaid has been instrumental in driving down the rate of uninsurance among children, which stands at 5.7% nationally and 7.6% in Florida (2019).
Medicaid is not a benefit exclusive to cisgendered individuals. Indeed, Medicaid is of vital importance to transgender individuals, as it is estimated that almost 1/3 of all transgender persons will fall below the poverty line, more than twice the rate of the general population. Both cisgender and transgender individuals enrolled in Medicaid rely on the program to cover their necessary medical care. However, the State of Florida, in promulgating this rule, is discriminating against Medicaid's transgender enrollees by seeking to arbitrarily ban a whole category of treatments which is exclusively utilized by transgender individuals.

Unlike many private health insurance plans, Medicaid guarantees that benefits for children are designed specifically for them. The Early and Periodic Screening, Diagnosis and Treatment (EPSDT) provision of federal Medicaid law is a cornerstone Medicaid protection and the definitive gold standard of pediatric health care benefits. EPSDT guarantees that all Medicaid-eligible children are screened to assess and identify health issues early and ensures the provision of medically necessary health services to address those identified health conditions. EPSDT is designed to attend to a broad range of child health needs, including preventive care; physical and mental health; oral, hearing and vision care; habilitative care; and social and emotional development. EPSDT ensures that the medically necessary health care needs of the individual child determine what services and treatments Medicaid ultimately covers for that child. Such decisions of medical necessity are based on the expertise of the pediatrician or other treating clinician, who, through years of education, clinical training, and practice, takes into consideration the widely accepted evidence-based standards of care for the condition being treated.

This regulation as proposed would usurp this process of expert clinical decision-making made in the context of the physician-patient relationship; instead, it seeks to codify a discriminatory ban on widely accepted evidence-based standards of care for transgender adolescents and other individuals. As described in detail above, these standards of care are evidence-based and recommended by the medical community. Presented under the guise of an alternative care standard, this proposed prohibition on specific treatments for gender dysphoria not only ignores the prevailing consensus of numerous medical organizations, but also seeks to jettison the role of the treating clinician in determining medically necessary care for an individual. In every way, this proposed ban is a discriminatory gutting of the practice of medicine for transgender adolescents and other individuals, seeking to stifle the physician-patient relationship and replace it with the state's entirely ideological interest in ending gender affirming care in Florida's Medicaid program. In so doing, this proposed rule ignores the health and well-being of children, adolescents, and other individuals in Florida, both now and in the future, who could benefit from these treatments, and places their health interests as secondary to that of the state. This proposed rule counters medical consensus, discriminates against transgender adolescents, obstructs the physician-patient relationship, subverts Medicaid's EPSDT protection that places medical judgment central to coverage determinations, and, if finalized as proposed, would leave transgender adolescents and other individuals enrolled in Florida Medicaid with nowhere to turn for their much-needed health care.

The consequences of such actions are likely to be many. As detailed throughout this letter, the mental and physical health and well-being of transgender children and adolescents often rely on their abilities to access much needed mental and physical health care—care that is in keeping with the widely recognized evidence-based standards of care for gender dysphoria. In proposing this rule, Florida ignores broad consensus among the medical community as to what those evidence-based standards of care are, and instead seeks, for its own discriminatory reasons, to impose alternate standards and an outright ban of specific treatments for transgender adolescents in the state's Medicaid program. As pediatricians who care for the health and well-being of all children in Florida and across the United

States, we call for the Florida Medicaid program to return to the evidence-based standards of care widely accepted among the medical community, and for this discriminatory ban to be rescinded. Only by doing so will the health and well-being of transgender children and adolescents in Florida be preserved.

Sincerely,

Moira Szilaygi, MD, PhD, FAAP
President, American Academy of Pediatrics

Lisa Gwynn, DO, MBA, MSPH, FAAP
President, Florida Chapter of the American Academy of Pediatrics, Inc

**Please note: A sourced version of this letter containing footnotes is being provided in PDF format via email.

TAB 183-37

RICK SCOTT
GOVERNOR

ELIZABETH DUDEK
SECRETARY

BREAST PUMP
GAPMS DETERMINATION REPORT WITH RECOMMENDATION

Date: May 18, 2015

To: Justin Senior, Deputy Secretary for Medicaid

From: Bureau of Medicaid Policy

Subject: **Breast Pump Coverage**

PURPOSE

In order for a breast pump to be covered under the Florida Medicaid program, it must meet medical necessity criteria as defined in 59G-1.010(166),[A1] Florida Administrative Code. (F.A.C.), and funded through the General Appropriations Act of Chapter 216, Florida Statutes (F.S.).

Pursuant to the criteria set forth in 59G-1.010(166)(a)(3), F.A.C., breast pumps must be consistent with generally accepted professional medical standards (GAPMS) as determined by the Medicaid program, and not experimental or investigational.

In accordance with the determination process established in 59G-1.035,[A2] F.A.C., this GAPMS Determination Report with Recommendation is submitted for review to the Deputy Secretary for Medicaid.

The Deputy Secretary for Medicaid will make the final determination as to whether breast pumps are consistent with generally accepted professional medical standards and not experimental or investigational.

RECOMMENDATION

This report recommends breast pumps as a health service that is consistent with generally accepted professional medical standards. It is further recommended that the following devices be covered:

1. A rent-to-purchase electric breast pump may be considered medically necessary when a nursing mother is experiencing prolonged separation from her infant because of work, school, or a medical reason.

2. Electric hospital grade breast pump rental may be considered medically necessary when a newborn recipient has one of the following conditions:
   - Prematurity (less than 37 weeks gestation),
   - Neurologic disorder,
   - Genetic abnormalities (e.g., Down Syndrome),

Pl. Trial Ex. 333

- Anatomic and mechanical malformation (e.g., cleft lip and palate),
- Congenital malformations requiring surgery (e.g., respiratory, cardiac, gastrointestinal, central nervous system)

An electric hospital grade breast pump rental may also be considered medically necessary when the nursing mother has been diagnosed with and is receiving treatment for mastitis or related infection of the breast.

Coverage of an electric hospital grade breast pump rental would be limited to no more than a three month period. Exceptions can be made on a case by case basis, based upon medical necessity.

REPORT WITH RECOMMENDATION

This report with recommendation is presented as the summary assessment considering the factors identified in 59G-1.035 F.A.C., based on the collection of information from sources of reliable evidence. The intent is to provide a brief analysis with justification in support of the final recommendation.

The analysis described in this report includes:

- Background information and pertinent current Medicaid policies
- An overview of the health service
- Information submitted by the requestor
- Confirmation of clearance from the government regulatory body
- Evidence based clinical practice guidelines
- Coverage policies from commercial and other state Medicaid insurers.

HEALTH SERVICE SUMMARY

Breast Pumps – Device Summary

There are three basic types of breast pumps:

- Manual pumps
- Battery-powered pumps
- Electric pumps

These pumps may be offered with single or double pumping actions. Table 1 provides information on different types and descriptions of breast pumps that are available.

Pumping Type	How it works	Types of Breast Pumps
Single	Extracts milk from one breast at a time.	Most manual breast pumps are single pumps. Most battery-powered pumps are single pumps.
Double	Can be used to extract milk from both breasts at the same time.	Some electric pumps are double pumps.

Table 1

GOVERNMENT REGULATORY BODY APPROVAL

Medical devices (including breast pumps) are regulated by the United States Food and Drug Administration (FDA). Breast pumps are often used by breastfeeding women to extract ("express") their breast milk. Breast pumps can also be used to maintain or increase a woman's milk supply, relieve engorged breasts and plugged milk ducts, or pull out flat or inverted nipples so a nursing baby can latch-on to its mother's breast more easily. Many women find it convenient, or even necessary, to use a breast pump to express and store their breast milk once they have returned to work, are traveling, or are otherwise separated from their baby. A breast pump can be used as a supplement to breastfeeding and some pumps are designed to mimic the suckling of a nursing baby. A number of breast pumps have been reviewed and approved by the FDA (U.S. Food and Drug Administration, 2015).[A3]

CLINICAL OUTCOMES

The benefits of breastfeeding are widely acknowledged, and as such, breastfeeding is the infant feeding method recommended by numerous organizations, including the Association of Women's Health, Obstetric and Neonatal Nurses[A4]; the World Health Organization[A5]; the Dietitians of Canada and Breastfeeding Committee for Canada[A6]; the American Dietetic Association[A7]; and the American Academy of Pediatrics (AAP).[A8]

The American Academy of Family Physicians[A9] and most all of the organizations listed above recommends that all babies, with rare exceptions, be breastfed and/or receive expressed human milk exclusively for the first six months of life.

The AAP[A8] reports that breastfeeding is associated with reductions in middle ear infections, gastrointestinal infections, sudden infant death syndrome, and adolescent and adult obesity rates. Therefore, the AAP also recommends exclusive breastfeeding for the first 6 months after birth, and then continued breastfeeding for one year or longer, as other foods are introduced. These benefits are further supported by literature published by the Institute of Child Health and Human Development.

The Institute of Child Health and Human Development (ICHHD)[A10] also proposes certain benefits of breastfeeding for the nursing mother, including:

- Less blood loss following childbirth and improved healing
- Improved postpartum weight loss
- Lower likelihood of experiencing postpartum depression, which is seen more often in new mothers who do not breastfeed
- Less chance of developing certain health conditions, such as rheumatoid arthritis, cardiovascular disease, and certain cancers (for example, breast cancer)
- Physical and emotional benefits of breastfeeding directly from a mother's breast due to skin-to-skin contact with her infant

EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES

Both the ICHHD and in an issue paper regarding Medicaid coverage of lactation services, the Department of Health and Human Services, Centers for Medicare & Medicaid Services, provides that improving the health of the population and reducing preventable causes of poor health, such as obesity, is a priority; and current research indicates that breastfeeding or using

expressed milk for the first 6 to 12 months of life is highly beneficial for both the mother and infant in reducing these and other preventable health conditions. [A11]

On January 20, 2011, the United States Surgeon General released "The Surgeon General's Call to Action to Support Breastfeeding." This report indicates that there is a 32% higher risk of childhood obesity and a 64% higher risk of type 2 diabetes for children who are not breastfed. This report also provides recommended actions to remove some of the obstacles faced by women who want to breastfeed their babies; pointing out the health and economic benefits of breastfeeding, and offering opportunities for women to be supported in the workplace for breastfeeding including access to high-grade electric breast pumps. [A12]

In July, 2014, the National Center for Chronic Disease Prevention and Health Promotion's Division of Nutrition, Physical Activity, and Obesity, which is a division of the Centers for Disease Control and Prevention, published a Breastfeeding Report Card. Florida is within approximately two percentage points of national averages for the number of babies being breastfed with three quarters of all babies born being breastfed at some point, and around half still being breastfed at six months (Table 2). [A13]

Centers for Disease Control and Prevention National Immunization Survey (July 2014)					
Breastfeeding Rates	Ever Breastfed (%)	Breastfeeding at 6 months (%)	Breastfeeding at 12 months (%)	Exclusive breastfeeding at 3 months (%)	Exclusive breastfeeding at 6 months (%)
U.S. National	79.2	49.4	26.7	40.7	18.8
Florida	77.0	48.7	26.9	38.9	18.3

Table 2

An effective electric breast pump is an important tool for the management of breastfeeding challenges such as providing human milk to sick or premature infants. A breast pump is also, in Western culture, critical for breastfeeding mothers who return to work. Obtaining an effective electric breast pump can be difficult for uninsured or impoverished women because of the expense, complicated insurance reimbursements, and scarcity of providers that supply breast pumps to the inner-city community (Chamberlain, McMahon, Philipp, and Merewood, 2006).[A14]

Mothers who work outside the home initiate breastfeeding at the same rate as mothers who stay at home. However, the breastfeeding continuance rate declines sharply in mothers who return to work. While the work environment may be less than ideal for the breastfeeding mother, obstacles can be overcome. Electric piston pumps may be the most suitable type for mothers who work outside the home for more than 20 hours per week; however, when a mother is highly motivated, any pump type can be successful in any situation (Biagioli, 2003). [A15]

COVERAGE POLICY [A16]

Affordable Care Act

The Affordable Care Act (2010) requires most health insurance plans to cover the cost of a breast pump as part of women's preventative health services. These rules apply to health insurance marketplace plans and all other private health insurance plans, except for grandfathered plans. State Medicaid programs are not required by the Affordable Care Act to provide lactation services including breast pumps. [A11]

Florida Women, Infants, and Children (WIC)
Florida's Special Supplemental Nutrition Program covers breast pumps under certain circumstances. However, funding for breast pumps statewide is limited. Of the available pumps, local WIC offices use a priority system to determine who will receive a breast pump, as the resource is limited.

Medicare
Medicare does not cover breast pumps or breast pump supplies.

Aetna
Aetna covers the rental of breast pumps under its DME benefit when either of the following criteria is met:

- The newborn is detained in the hospital after the mother is discharged
- The infant is diagnosed with a congenital disorder that interferes with feeding

Florida Blue (Commercial Insurer Blue Cross/Blue Shield)
Florida Blue covers the following:

- One electrical or manual breast pump per member, per delivery (hospital grade electric breast pumps are excluded except when medically necessary during an inpatient hospital stay)

Minnesota Medicaid
Minnesota Medicaid covers breast pumps when ordered by the treating provider for any nursing mother experiencing separation from her infant because of work, school, illness or any other medical reason.

New York Medicaid
New York Medicaid covers hospital or professional grade breast pump under the following circumstances impacting the newborn:

- Prematurity (including multiple gestation),
- Neurologic disorders,
- Genetic abnormalities (e.g., Down's Syndrome),
- Anatomic and mechanical malformations (e.g., cleft lip and palate),
- Congenital malformations requiring surgery (e.g., respiratory, cardiac, gastrointestinal, CNS),
- Prolonged infant hospitalization.

Oregon Medicaid
Oregon Medicaid covers breast pumps taking into consideration the medical appropriateness for the infant and/or mother.

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FISCAL

Reimbursement rates for electric and hospital grade breast pumps are variable, based on research and review of other states coverage polices (Table 3).

Table 1: Other States' Medicaid Rates

	Electric Pump	Electric Hospital-Grade Pump[1]
Alaska	$1.27	$91.50
Connecticut	$118.75	
Idaho	$394.34	
Illinois	$119.74	
Maryland	$87.90	$56.21
Michigan	$134.32	$61.82
Minnesota	$256.14	$51.31
New Mexico	$49.25	
New York	$173.47	$38.61
Oregon	$80.92	
Texas	$152.88	$39.15
Washington	$65.60	$80.52
Average Mean[2]	**$124.00**	**$58.07**

Table 3

In conducting the fiscal analysis for coverage breast pumps under Florida Medicaid, we utilized the average reimbursement rates, as reflected above for each device.

Electric Breast Pump Purchase
In 2013, Florida Medicaid reimbursed for 111,619 births. In Florida, while 77% of newborns born in 2013 were reported to have ever been breastfed, only about 49% are still being breastfed at six months of age (Table 2). This signals that while a large percentage (the majority) of women in Florida have attempted to breastfeed their newborn/infant, only about half continue to do so for as long as recommended. Therefore, assuming 50% of these newborns were breastfed and there was a need to utilize an electric breast pump, the total cost for Florida Medicaid is expected to be $6,920,378.

Hospital Grade Breast Pumps Rentals
During state fiscal year 2013-2014, there were approximately 60,000 infants diagnosed with prematurity (less than 37 weeks gestation), a neurologic disorder, genetic abnormalities (e.g., Down Syndrome), an anatomic and/or mechanical malformation (e.g., cleft lip and palate), and congenital malformations requiring surgery (e.g., respiratory, cardiac, gastrointestinal, central nervous system).

[1] Per month rental rate
[2] Removed outlier rates

Assuming 50% of these newborns' mothers desired to breastfeed, but due to the child's condition required a hospital grade breast pump, the total cost for Florida Medicaid is expected to be $5,226,300 (based on a maximum rental period of three months). The estimated annual fiscal impact of covering both electric and hospital grade breast pumps is $12,146,678. The cost of this may be partially offset in the short-term by reductions in middle ear and gastrointestinal infections and in the long-term by reduced rates of obesity with its associated chronic disease costs (e.g. diabetes).

GENERALLY ACCEPTED PROFESSIONAL MEDICAL STANDARDS RECOMMENDATION

This report recommends breast pumps as a health service that is consistent with generally accepted professional medical standards. It is further recommended that the following devices be covered:

1. A rent-to-purchase electric breast pump may be considered medically necessary when a nursing mother is experiencing prolonged separation from her infant because of work, school, or a medical reason.

2. Electric hospital grade breast pump rental may be considered medically necessary when a newborn recipient has one of the following conditions:
   - Prematurity (less than 37 weeks gestation),
   - Neurologic disorder,
   - Genetic abnormalities (e.g., Down Syndrome),
   - Anatomic and mechanical malformation (e.g., cleft lip and palate),
   - Congenital malformations requiring surgery (e.g., respiratory, cardiac, gastrointestinal, central nervous system).

   An electric hospital grade breast pump rental may also be considered medically necessary when the nursing mother has been diagnosed with and is receiving treatment for mastitis or related infection of the breast.

   Coverage of an electric hospital grade breast pump rental would be limited to no more than a three month period. Exceptions can be made on a case by case basis, based upon medical necessity.

✓ **Concur** ____ **Do Not Concur**

Comments:

_____

_____

_____

Signature
Deputy Secretary for Medicaid (or designee)

5/28/15
Date

Attachments

A1. 59G-1.010(166), F.A.C., "Medically Necessary"
A2. 59G-1.035, F.A.C., "Determining Generally Accepted Professional Medical Standards"
A3. FDA. 501(k) Devices: Megna Breast Pumps K142479. U.S. Food and Drug Administration. February 2015.
FDA. 501(k) Devices. Ardo Carum and Calypso Powered Breast Pumps K141742 . U.S. Food and Drug Administration. October 2014
FDA. 501(k) Devices. Expresse and Premier Powered Breast Pumps K973501. U.S. Food and Drug Administration. December 1997
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A5. World Health Organization. Media Centre: Infant and young child feeding Fact Sheet N342. February 2014. http://www.who.int/mediacentre/factsheets/fs342/en/
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A13. Centers for Disease Control and Prevention. *Breastfeeding Report Card United states/2014.* National Center for Chronic Disease Prevention and Health Promotion, Division of Nutrition, Physical Activity, and Obesity. 2014. www.cdc.gov
A14. Chamberlain, L.B., McMahon, M., Philipp, B.L., Merewood, A., Breast pump access in the inner city: a hospital-based initiative to provide breast pumps for low-income women. *Journal of Human Lactation*. 2006. 22(1);94-98
A15. Biagioli, Frances, Returning to work while breastfeeding. *American Family Physician.* 2003. 68(11);2199-2207
A16. *Hardcopy*

TAB 184-21

U.S. Department of Justice

Civil Rights Division

Assistant Attorney General
950 Pennsylvania Ave, NW - RFK
Washington, DC 20530

March 31, 2022

Dear State Attorneys General:

The U.S. Department of Justice (the Department) is committed to ensuring that transgender youth, like all youth, are treated fairly and with dignity in accordance with federal law. This includes ensuring that such youth are not subjected to unlawful discrimination based on their gender identity, including when seeking gender-affirming care. We write to remind you of several important federal constitutional and statutory obligations that flow from these fundamental principles.

People who are transgender are frequently vulnerable to discrimination in many aspects of their lives, and are often victims of targeted threats, legal restrictions, and anti-transgender violence.[1] The Department and the federal government more generally have a strong interest in protecting the constitutional rights of individuals who are lesbian, gay, bisexual, transgender, queer, intersex, nonbinary, or otherwise gender-nonconforming,[2] and in ensuring compliance with federal civil rights statutes. The Department is also charged with the coordination and enforcement of federal laws that protect individuals from discrimination in a wide range of federally-funded programs and activities.[3]

Intentionally erecting discriminatory barriers to prevent individuals from receiving gender-affirming care implicates a number of federal legal guarantees. State laws and policies that prevent parents or guardians from following the advice of a healthcare professional regarding what may be medically necessary or otherwise appropriate care for transgender minors may infringe on rights protected by both the Equal Protection and the Due Process Clauses of the Fourteenth Amendment. The Equal Protection Clause requires heightened scrutiny of laws that discriminate on the basis of sex[4] and prohibits such discrimination absent an "exceedingly

[1] *See, e.g.*, Michelle M. Johns et al., Ctrs. for Disease Control and Prevention, *Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students—19 States and Large Urban School Districts, 2017*, Morbidity and Mortality Weekly Report 68: 67-71 (2019), https://www.cdc.gov/mmwr/volumes/68/wr/mm6803a3.htm?s_cid=mm6803a3_w (finding that transgender youth reported higher levels of violence victimization compared to their cisgender peers).
[2] *See, e.g.*, Exec. Order No. 13,988, § 1, 86 Fed. Reg. 7023 (Jan. 20, 2021); Pamela S. Karlan, Principal Deputy Assistant Attorney General, Civ. Rts. Div., U.S. Dep't of Justice, Memorandum, *Application of Bostock v. Clayton County to Title IX of the Education Amendments of 1972* (Mar. 26, 2021), https://www.justice.gov/crt/page/file/1383026/download.
[3] Exec. Order No. 12,250, § 1-201, 45 Fed. Reg. 72,995 (Nov. 2, 1980).
[4] *See, e.g.*, *Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 610-13 (4th Cir. 2020), *as amended* (Aug. 28, 2020), *reh'g en banc denied*, 976 F.3d 399 (4th Cir. 2020), *cert. denied*, 2021 WL 2637992 (June 28, 2021); *Whitaker* v.

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persuasive" justification.[5] Because a government cannot discriminate against a person for being transgender "without discriminating against that individual based on sex,"[6] state laws or policies that discriminate against transgender people must be "substantially related to a sufficiently important governmental interest."[7]

A law or policy need not specifically single out persons who are transgender to be subject to heightened scrutiny. When a state or recipient of federal funds criminalizes or even restricts a type of medical care predominantly sought by transgender persons, an intent to disfavor that class can "readily be presumed."[8] For instance, a ban on gender-affirming procedures, therapy, or medication may be a form of discrimination against transgender persons, which is impermissible unless it is "substantially related" to a sufficiently important governmental interest.[9] This burden of justification is "demanding."[10] Such a law or policy will not withstand heightened scrutiny when "the alleged objective" differs from the "actual purpose" underlying the classification.[11] In addition, the Due Process Clause protects the right of parents "to seek and follow medical advice" to safeguard the health of their children.[12] A state or local government must meet the heavy burden of justifying interference with that right since it is well established within the medical community that gender-affirming care for transgender youth is not only appropriate but often necessary for their physical and mental health.[13]

In addition to these constitutional guarantees, many federal statutes require recipients of federal financial assistance to comply with nondiscrimination requirements as a condition of receiving those funds. Relevant statutes include:

- **Section 1557 of the Affordable Care Act**[14] protects the civil rights of people—including transgender youth—seeking nondiscriminatory access to healthcare in a range of health

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Kenosha Unified Sch. Dist. No. 1 Bd. of Educ., 858 F.3d 1034, 1051 (7th Cir. 2017), *cert. dismissed*, 138 S. Ct. 1260 (2018); *see also* Brief for the United States as Amicus Curiae Supporting Plaintiffs-Appellees, *Brandt v. Rutledge*, No. 21-2875 (8th Cir. Jan. 21, 2022); En Banc Brief for the United States as Amicus Curiae Supporting Plaintiff-Appellee, *Adams v. School Board of St. John's County*, No. 18-13592 (11th Cir. Nov. 26, 2021); Brief for the United States as Amicus Curiae Supporting Plaintiffs-Appellees, *Corbitt v. Taylor*, No. 21-10486 (11th Cir. Aug. 2, 2021).

[5] *United States v. Virginia*, 518 U.S. 515, 531 (1996) ("Parties who seek to defend gender-based government action must demonstrate an 'exceedingly persuasive justification' for that action.") (quoting *Mississippi Univ. for Women v. Hogan*, 458 U.S. 718, 724 (1982)).

[6] *Bostock v. Clayton Cnty.*, 140 S. Ct. 1731, 1741 (2020).

[7] *Grimm*, 972 F.3d at 608 (quoting *City of Cleburne v. Cleburne Living Ctr.*, 473 U.S. 432, 441 (1985) (internal quotations omitted)).

[8] *Bray v. Alexandria Women's Health Clinic*, 506 U.S. 263, 270 (1993) ("Some activities may be such an irrational object of disfavor that, if they are targeted, and if they also happen to be engaged in exclusively or predominantly by a particular class of people, an intent to disfavor that class can readily be presumed.").

[9] *Virginia*, 518 U.S. at 533.

[10] *Id.*

[11] *Miss. Univ.*, 458 U.S. at 730.

[12] *Parham v. J.R.*, 442 U.S. 584, 602 (1979).

[13] *See, e.g.*, *Brandt v. Rutledge*, 551 F. Supp. 3d 882, 891, 893 (E.D. Ark. 2021).

[14] 42 U.S.C. § 18116.

programs and activities.[15] Categorically refusing to provide treatment to a person based on their gender identity, for example, may constitute prohibited discrimination under Section 1557. As the U.S. Department of Health and Human Services has stated, restricting an individual's ability to receive medically necessary care, including gender-affirming care, from their health care providers solely on the basis of their sex assigned at birth or their gender identity may also violate Section 1557.[16]

- **Title IX of the Education Amendments of 1972**[17] prohibits sex discrimination, including sex-based harassment, by recipients of federal financial assistance that operate education programs and activities.[18] Policies and practices that deny, limit, or interfere with access to the recipient's education program or activity because students are transgender minors receiving gender-affirming care may constitute discrimination on the basis of sex in violation of Title IX.

- The **Omnibus Crime Control and Safe Streets Act of 1968**[19] prohibits sex discrimination in certain law enforcement programs and activities receiving federal financial assistance.[20] If a law enforcement agency takes a transgender minor who is receiving gender-affirming care into custody or arrests the child's parents on suspicion of child abuse because the parents permitted such medical care, that agency may be violating the statute's nondiscrimination provision.

- **Section 504 of the Rehabilitation Act of 1973**[21] protects people with disabilities, which can include individuals who experience gender dysphoria.[22] Restrictions that prevent, limit, or interfere with otherwise qualified individuals' access to care due to their gender

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[15] *See, e.g.*, Notification of Interpretation and Enforcement of Section 1557 of the Affordable Care Act and Title IX of the Education Amendments of 1972, reprinted at 86 Fed. Reg. 27,984 (May 25, 2021).
[16] U.S. Dep't Health & Hum. Servs., *Notice and Guidance on Gender Affirming Care, Civil Rights, and Patient Privacy* (Mar. 2, 2022), https://www.hhs.gov/sites/default/files/hhs-ocr-notice-and-guidance-gender-affirming-care.pdf.
[17] 20 U.S.C. § 1681, *et seq*.
[18] *See* Karlan, *supra* note 2; *see also Doe v. Snyder*, --- F.4th ---, 2022 WL 711420, at *9 (9th Cir. Mar. 10, 2022); *Grimm*, 972 F.3d at 619.
[19] 34 U.S.C. § 10101, *et seq*.
[20] *See* 34 U.S.C. § 10228(c)(1); *see also* Kristen Clarke, Assistant Attorney General, Civ. Rts. Div., U.S. Dep't of Justice, Memorandum, *Interpretation of Bostock v. Clayton County regarding the nondiscrimination provisions of the Safe Streets Act, the Juvenile Justice and Delinquency Prevention Act, the Victims of Crime Act, and the Violence Against Women Act* (Mar. 10, 2022), https://www.justice.gov/crt/page/file/1481776/download.
[21] 29 U.S.C. § 794. Additionally, Title II of the Americans with Disabilities Act extends disability civil rights protections with respect to all programs, services and activities of state and local governments, regardless of the receipt of federal financial assistance. *See* 42 U.S.C. § 12132.
[22] *See, e.g.*, *Doe v. Penn. Dep't of Corrections*, No. 1:20-cv-00023-SPB-RAL, 2021 WL 1583556, at *12 (W.D. Pa. Feb. 19, 2021), report and recommendation adopted in relevant part, 2021 WL 1115373 (W.D. Pa. March 24, 2021); *Lange v. Houston Cnty.*, 499 F. Supp. 3d 1258, 1270 (M.D. Ga. 2020); *Doe v. Mass. Dep't of Correction*, No. 1:17-cv-12255-RGS, 2018 WL 2994403 at *6 (D. Mass. June 14, 2018); *Blatt v. Cabela's Retail, Inc.*, No. 5:14-CV-04822, 2017 WL 2178123 (E.D. Pa. May 18, 2017).

dysphoria, gender dysphoria diagnosis, or perception of gender dysphoria may violate Section 504.

All persons should be free to access the services, programs, and activities supported by federal financial assistance without fear that they might face unlawful discrimination for doing so. Courts have held that many nondiscrimination statutes contain an implied cause of action for retaliation based on the general prohibition against intentional discrimination, and agencies have made this clear in regulations.[23] Thus, any retaliatory conduct may give rise to an independent legal claim under the protections described above.

* * *

Thank you for your continued commitment to improving the well-being of children and their families. The Department is always available to help ensure that state and local governments, many of which are recipients of federal financial assistance, meet their obligations under federal law. Please feel free to contact the Department's Civil Rights Division for assistance if you have further questions.

Sincerely,

Kristen Clarke
Assistant Attorney General
Civil Rights Division
U.S. Department of Justice

[23] *See, e.g.*, *Jackson v. Birmingham Bd. of Ed.*, 544 U.S. 167, 173 (2005) ("Retaliation against a person because that person has complained of sex discrimination is another form of intentional sex discrimination…"). Examples of agency regulations that prohibit retaliation include 24 C.F.R. § 1.7(e) (Dep't of Housing and Urban Development); 34 C.F.R. § 100.7(e) (Dep't of Education); 38 C.F.R. § 18.7(e) (Dep't of Veterans Affairs); and 45 C.F.R. § 80.7(e) (Dep't of Health and Human Services). Other relevant regulations can be found in the Civil Rights Division's Title VI Legal Manual. Civ. Rts. Div., U.S. Dep't of Justice, *Title VI Legal Manual*, Section VIII, https://www.justice.gov/crt/book/file/1364106/download.

TAB 193-5

Mission:
To protect, promote & improve the health of all people in Florida through integrated state, county & community efforts.

Ron DeSantis
Governor

Joseph A. Ladapo, MD, PhD
State Surgeon General

Vision: To be the **Healthiest State** in the Nation

Treatment of Gender Dysphoria for Children and Adolescents

April 20, 2022

The Florida Department of Health wants to clarify evidence recently cited on a fact sheet released by the US Department of Health and Human Services and provide guidance on treating gender dysphoria for children and adolescents.

Systematic reviews on hormonal treatment for young people show a trend of low-quality evidence, small sample sizes, and medium to high risk of bias. A paper published in the International Review of Psychiatry states that 80% of those seeking clinical care will lose their desire to identify with the non-birth sex. One review concludes that "hormonal treatments for transgender adolescents can achieve their intended physical effects, but **evidence regarding their psychosocial and cognitive impact is generally lacking**."

According to the Merck Manual, "gender dysphoria is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the sex assigned at birth."

Due to the lack of conclusive evidence, and the potential for long-term, irreversible effects, the Department's guidelines are as follows:

- Social gender transition should not be a treatment option for children or adolescents.
- Anyone under 18 should not be prescribed puberty blockers or hormone therapy.
- Gender reassignment surgery should not be a treatment option for children or adolescents.
    - Based on the currently available evidence, "encouraging mastectomy, ovariectomy, uterine extirpation, penile disablement, tracheal shave, the prescription of hormones which are out of line with the genetic make-up of the child, or puberty blockers, are all clinical practices which run an **unacceptably high risk of doing harm**."
- Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider.

These guidelines do not apply to procedures or treatments for children or adolescents born with a genetically or biochemically verifiable disorder of sex development (DSD). These disorders include, but are not limited to, 46, XX DSD; 46, XY DSD; sex chromosome DSDs; XX or XY sex reversal; and ovotesticular disorder.

The Department's guidelines are consistent with the federal Centers for Medicare and Medicaid Services age requirement for surgical and non-surgical treatment. These guidelines are also in line with the guidance, reviews, and recommendations from Sweden, Finland, the United Kingdom, and France.

Parents are encouraged to reach out to their child's health care provider for more information.

Florida Department of Health
Office of the State Surgeon General
4052 Bald Cypress Way, Bin A-00 • Tallahassee, FL 32399-1701
PHONE: 850/245-4210 • FAX: 850/922-9453
FloridaHealth.gov

TAB 193-6

Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

June 2022

Ron DeSantis, Governor
Simone Marstiller, Secretary

DX
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Contents

Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term "gender" in reference to the construct of male and female identities and the term "sex" when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).[1]

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one's gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as "the distress that may accompany the incongruence between one's experienced or expressed gender and one's assigned gender." As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having "a strong desire to be of the other gender or an insistence that one is the other gender" or "a strong preference for cross-gender roles in make-believe or fantasy play." The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include "a strong desire to be the other gender" or "a strong desire to be rid of one's primary and/or secondary sexual characteristics." The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition "is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

[1] The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money's theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money's ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth." Additionally, the Merck Manual further states that "gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold" (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.[2]

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman's study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V's criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA's definition. They further asserted that the APA intended to "reduce pathologization" by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA's definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V's criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one's gender as a disorder. In addition, the APA considers gender as part of one's identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

[2] Following the release of the Florida Department of Health's guidelines for treating gender dysphoria, Merck removed its definition for "gender dysphoria" from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the "effort to reduce stigma" (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one's gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies "a marked incongruence between one's experienced/expressed gender and natal sex, of at least 6 months' duration" as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for "marked." This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH's *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)[3], behavioral health professionals are supposed to "find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment." WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

[3] The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as "gender affirming" surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a "standard of care" and that its grades for available services are low or very low (Endocrine Society, 2017).[4]

[4] Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient's overall behavioral health and that providing a "surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it" (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.[5]
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

[5] Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozlowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozlowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozlowska et al also cite other studies that indicate a high correlation between gender dysphoria and "adverse childhood events" and further assert that the condition "needs to be conceptualized in the context of the child's lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway" (Kozlowska et al, 2021).

For their study, Kozlowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child's developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozlowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of "adverse childhood events" such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported "instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures." These results led Kozlowska et al to conclude that gender dysphoria can be "associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion." The study also cites that treatment requires "a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child's presentation" (Kozlowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual's gravitation to the opposite sex documented over multiple years) but rather exposure to "social and peer contagion." Littman uses this term in the context of definitions cited in academic literature, stating that "social contagion is the spread of affect or behaviors through a population" and that "peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others." Examples of the latter's negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that "online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria." The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozlowska et al's study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman's research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a "maladaptive coping mechanism" for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman's study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential “gateway drug” for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who “wished they were the other sex” were more likely to become desisters and that those who “believed that they were the other sex” persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrect Gender Dysphoria Scale and Children's Global Assessment Scale)[6] to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

[6] Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is "variable." The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	**Reversible or Irreversible**
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017[7]

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

[7] This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as "irreversible" in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are "gender affirming." This decision mirrors the DSM-V's interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an "affirmation and acceptance of who they (i.e., patient) have always been" (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP's endorsement of "gender affirming" treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP's position is based on research that does not support intervention but rather supports "watchful waiting" because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites "gender affirming" interventions as the only effective method. To conclude, he states the organization is "advocating for something far in excess of mainstream practice and medical consensus" (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP's endorsement as a basis for "gender affirming" treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals' gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.[8] WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

[8] Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a "cure" to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al's study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).[9] Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden's overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al's conclusions were "too strong" and that further analysis by the authors revealed that the new "results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

[9] Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison" (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al's findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al's research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient's perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the "lifesaving" potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline "Almost half of LGBTQ youths 'seriously considered suicide in the past year'" (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that "there is great uncertainty about the effects" of sex reassignment treatments and that the "evidence alone is not sufficient to support" using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on "gender affirming" treatments. The authors noted this research had a "critical risk of bias" and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that "transgender youth who socially transitioned at early ages" will continue "to identify that way." While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their "assigned gender at birth," the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V's diagnostic criteria for gender dysphoria and that the children's families supported the decisions to transition. Instead, the authors relied on a child's chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study's publication under the headline "Few Transgender Children Change Their Minds After 5 Years" (New York Times, 2022). Such a title can add to the public's perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments "constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety." The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that "children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function" (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a "case-by-case" basis.[10] CMS specifically noted that the decision memo is not a National Coverage Determination and that "no national policy will be put in place for the Medicare program" (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that "the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up." In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo's criteria (CMS, 2017).

The basis for Medicare's decision is that the "clinical evidence is inconclusive" and that "robust" studies are "needed to ensure that patients achieve improved health outcomes." In its review of available literature, CMS sought to answer whether there is "sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria." After evaluating 33 studies that met inclusion criteria, CMS's review concludes that "not enough high-quality evidence" is available "to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively." Additionally, out of the 33 studies, just 6 provided "useful information" on the procedures' effectiveness, revealing that their authors "assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies" that "did not demonstrate clinically significant changes or differences in psychometric test results" following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).[11]

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).[12]

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[10] The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.
[11] Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.
[12] The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery. [13] The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

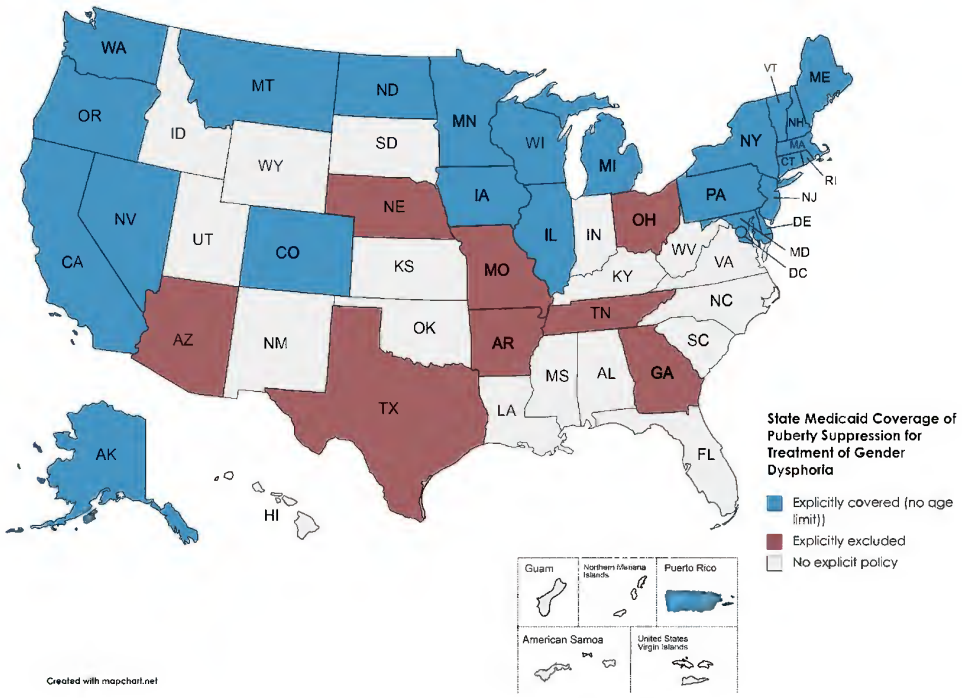
- "Social gender transition should not be a treatment option for children or adolescents."
- "Anyone under 18 should not be prescribed puberty blockers or hormone therapy."
- "Gender reassignment surgery should not be a treatment option for children or adolescents."
- "Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider."

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment's ability to improve mental health (DOH, 2022).

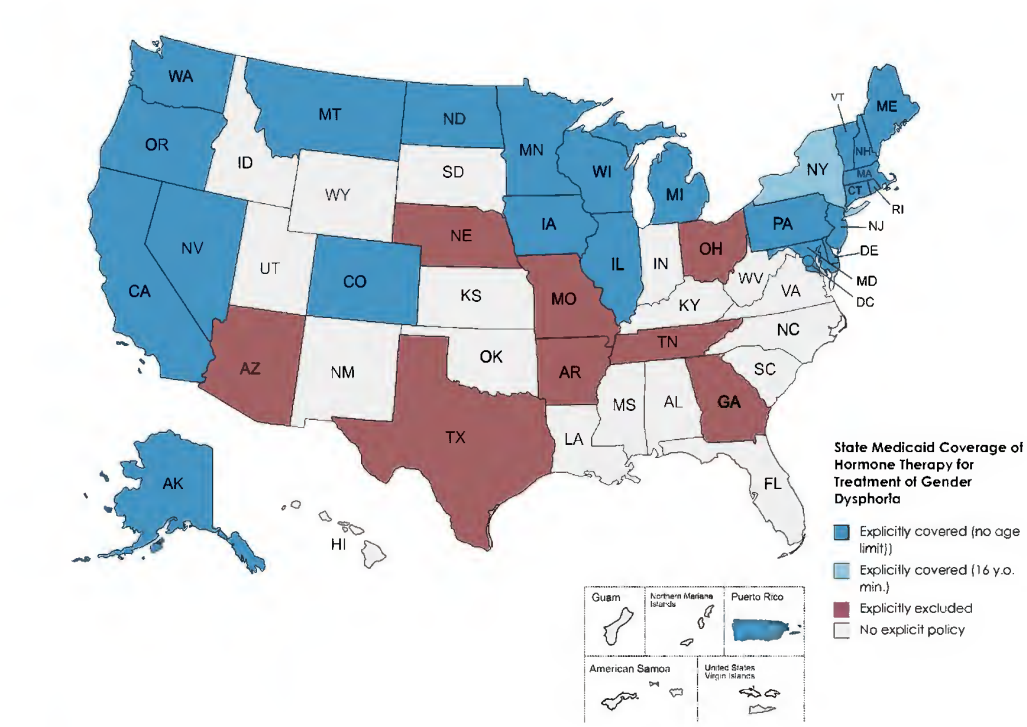
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

[13] Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida's public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

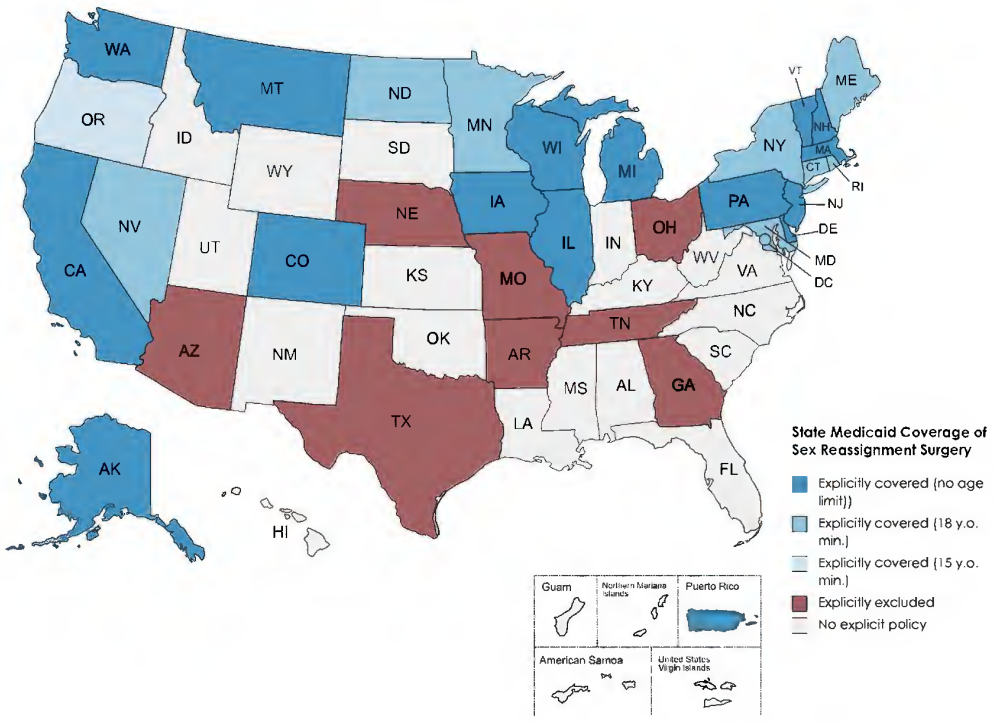
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

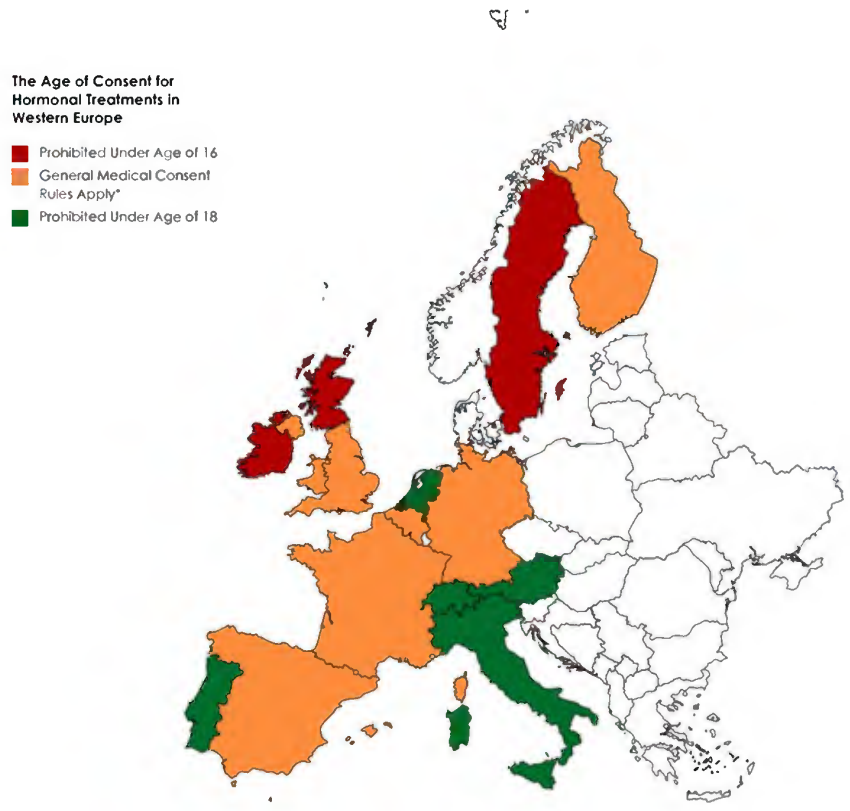
Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that "the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits." With the exception of youths who exhibited "classic" signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors "is an experimental practice" and that "no irreversible treatment should be initiated." The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.'s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

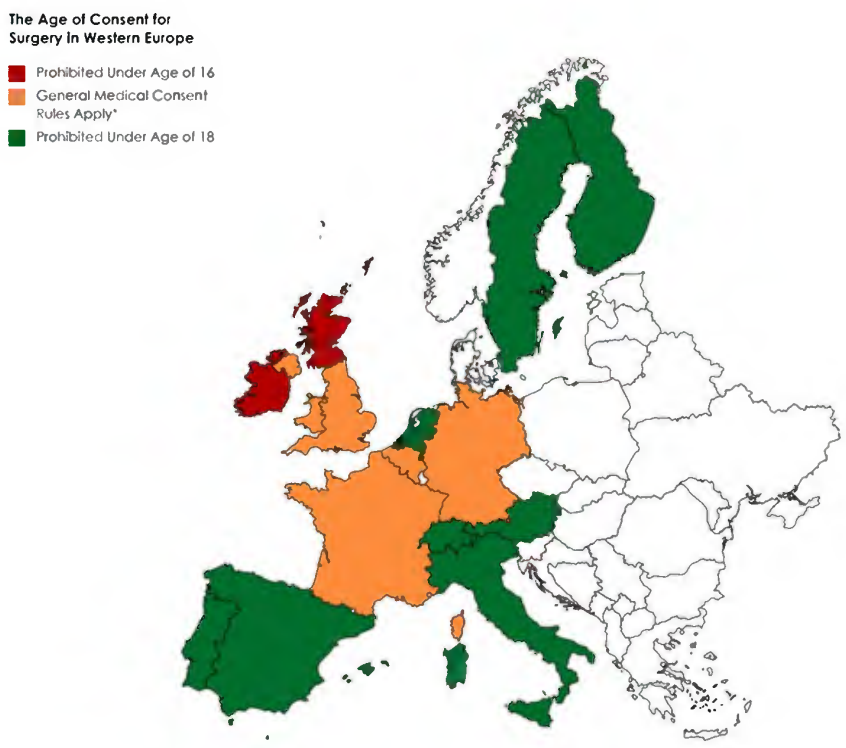
Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

✓ **Concur** ____ **Do not Concur**

Comments:

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Tom Wilson
Deputy Secretary for Medicaid (or designee)

6/2/22
Date

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

ATTACHMENT A

RON DESANTIS
GOVERNOR

SIMONE MARSTILLER
SECRETARY

April 20, 2022

Tom Wallace
Deputy Secretary for Medicaid
Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308

Dear Deputy Secretary Wallace:

On April 20, 2022, the Florida Department of Health released guidance on the treatment of gender dysphoria for children and adolescents.[1] The Florida Medicaid program does not have a policy on whether to cover such treatments for Medicaid recipients diagnosed with gender dysphoria. Please determine, under the process described in Florida Administrative Code Rule 59G-1035, whether such treatments are consistent with generally accepted professional medical standards and not experimental or investigational. Pursuant to Rule 59G-1035(5), I look forward to receiving your final determination.

Sincerely,

Simone Marstiller
Secretary

[1] *See* https://www.floridahealth.gov/newsroom/2022/04/20220420-gender-dysphoria-press-release.pr.html (last visited Apr. 20, 2022).

ATTACHMENT B

59G-1.035 Determining Generally Accepted Professional Medical Standards.

(1) Definitions.

(a) Generally accepted professional medical standards – Standards based on reliable scientific evidence published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations' recommendations.

(b) Health service(s) – Diagnostic tests, therapeutic procedures, or medical devices or technologies.

(c) Relevant – Having a significant and demonstrable bearing on the matter at hand.

(2) Pursuant to the criteria set forth in subparagraph 59G-1.010(166)(a)3., Florida Administrative Code (F.A.C.), the Agency for Health Care Administration (hereafter referred to as Agency) will determine when health services are consistent with generally accepted professional medical standards and are not experimental or investigational.

(3) Health services that are covered under the Florida Medicaid program are described in the respective coverage and limitations handbooks, policies, and fee schedules, which are incorporated by reference in the F.A.C. The public may request a health service be considered for coverage under the Florida Medicaid program by submitting a written request via e-mail to HealthServiceResearch@ahca.myflorida.com. The request must include the name, a brief description, and any additional information that supports coverage of the health service, including sources of reliable evidence as defined in paragraph 59G-1.010(84)(b), F.A.C.

(4) To determine whether the health service is consistent with generally accepted medical standards, the Agency shall consider the following factors:

(a) Evidence-based clinical practice guidelines.

(b) Published reports and articles in the authoritative medical and scientific literature related to the health service (published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations).

(c) Effectiveness of the health service in improving the individual's prognosis or health outcomes.

(d) Utilization trends.

(e) Coverage policies by other creditable insurance payor sources.

(f) Recommendations or assessments by clinical or technical experts on the subject or field.

(5) Based upon the information collected, a report with recommendations will be submitted to the Deputy Secretary for Medicaid (or designee) for review. The Deputy Secretary for Medicaid (or designee) will make a final determination as to whether the health service is consistent with generally accepted professional medical standards and not experimental or investigational.

(6) In order for the health service to be covered under the Florida Medicaid program, it must also meet all other medical necessity criteria as defined in subsection 59G-1.010(166), F.A.C., and funded through the General Appropriations Act or Chapter 216, F.S.

Rulemaking Authority 409.919 FS. Law Implemented 409.902, 409.906, 409.912, 409.913 FS. History–New 2-26-14, Amended 9-28-15.

ATTACHMENT C

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence

Romina Brignardello-Petersen, DDS, MSc, PhD
Wojtek Wiercioch, MSc, PhD

1. Introduction

We prepared this report to fulfill a request from the Florida Agency for Health Care Administration. This report contains three documents: 1. Main document (this document) summarizing the methodology used and the findings, 2. Methods document, which provides a detailed description of the systematic methodology used to find, prioritize, appraise, and synthesize the evidence, and 3. Results document, which describes the evidence available, the estimates of the effects of gender affirming therapies, and the certainty (also known as quality) of the evidence.

This document is organized in four parts. First, we describe the credentials and expertise of the health research methodologists conducting this evidence evaluation. Second, we summarize the methodology used. Third, we summarize the main findings. Finally, we briefly discuss strengths and limitations of our process and of the evidence.

2. Credentials and expertise

Two experts in health research methodology, who specialize in evidence synthesis to support decision making, prepared this report. Their relevant credentials and expertise are described below.

Dr. Romina Brignardello-Petersen: Assistant Professor at the Department of Health Research Methods, Evidence, and Impact, at McMaster University. Dr. Brignardello-Petersen obtained a DDS degree (University of Chile) in 2007, an MSc degree in Clinical Epidemiology and Health Care Research (University of Toronto) in 2012, and MSc in Biostatistics (University of Chile) in 2015, and a PhD in Clinical Epidemiology and Health Care Research (University of Toronto) in 2016. Dr. Brignardello-Petersen has worked in evidence synthesis projects since 2010, and her research has focused on the methodology for the development of Systematic Reviews and Clinical Practice Guidelines since 2012. Through January 2022, she has published 122 peer reviewed scientific articles (24 as a first author and 9 as a senior author). Dr. Brignardello-Petersen has acted as a research methodologist for several groups and organizations, including the World Health Organization, the Pan-American Health Organization, the American Society of Hematologists, the American College of Rheumatology, and the Society for Evidence Based Gender Medicine, among others. Her research program has been awarded over $2M CAD from the Canadian Institutes for Health Research. Dr. Brignardello-Petersen has no lived experience as a person or family member of a person with gender dysphoria, and her research interests are not in this area.

Dr. Wojtek Wiercioch: Postdoctoral Research Fellow at the Department of Health Research Methods, Evidence, and Impact, at McMaster University. Dr. Wiercioch obtained an MSc degree (2014, McMaster University) and a PhD degree (2020, McMaster University) in Health Research Methodology. Dr. Wiercioch has worked in evidence syntheses projects since 2011, and his research focuses on evidence synthesis, guideline development methodology, and the guideline development process. Through April

2022, he has published 86 peer-reviewed scientific articles. Dr. Wiercioch has acted as a guideline methodologist for several groups and organizations, including the World Health Organization, the American Society of Hematologists, the Endocrine Society (of America), and the American Association for Thoracic Surgeons, among others. Dr. Wiercioch has no lived experience as a person or family member of a person with gender dysphoria, and his research interests are not in this area.

3. Methods

We conducted an overview of systematic reviews. We used a reproducible approach to search, select, prioritize, appraise, and synthesize the available evidence, following high methodological standards. We describe full details of the methodology in an accompanying document.

In brief, we searched for systematic reviews published in English language in Epistemonikos, OVID Medline, and grey literature sources, through April 30, 2022. We selected systematic reviews which included studies on young individuals with a diagnosis of gender dysphoria, who received puberty blockers, cross-sex hormones, or surgeries; and in which authors reported data regarding outcomes important to patients: gender dysphoria, depression, anxiety, quality of life, suicidal ideation, suicide, adverse effects, and complications. Systematic reviews could have included any type of primary study design.

The two reviewers screened all titles and abstracts, followed by full text of potentially relevant systematic reviews. We then prioritized the most useful systematic review providing evidence for each of the outcomes, using pre-established criteria that considered date of publication, applicability, availability of outcome data, methodological quality of the systematic review, and usefulness of the data synthesis conducted in the systematic review (see methods document for details).

After abstracting data from the systematic reviews, we synthesized the best available evidence for each of the outcomes, and assessed the certainty (also known as quality) of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We conducted GRADE assessments using the information provided by the systematic review authors (risk of bias of primary studies, characteristics of included studies, results reported by the studies). We present the all the information about outcomes in GRADE summary of findings tables.

In addition, to evaluate the robustness of our conclusions, we systematically searched for and evaluated primary studies answering the questions of interest published after the authors of the included systematic reviews conducted their searches.

4. Results

We included 61 systematic reviews, from which 3 addressed the effects of puberty blockers, 22 addressed the effects of cross-sex hormones, 30 addressed the effects of surgeries, and 6 addressed the effects of more than one of these interventions. After our prioritization exercise, we included information from 2 systematic reviews on puberty blockers, 4 on cross-sex hormones, and 8 on surgeries.

4.1 Puberty blockers

For most outcomes (except suicidality), there is no evidence about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. There is very low certainty about the effects of puberty blockers on suicidal ideation.

The studies included in the systematic review reported outcomes among a group of people with gender dysphoria after receiving puberty blockers. Low certainty evidence suggests that after treatment with puberty blockers, people with gender dysphoria experience a slight increase in gender dysphoria, and an improvement in depression, and anxiety. Low certainty evidence also suggests that a moderate percentage of patients experience adverse effects. The findings must be interpreted considering that these studies did not have a comparison group, and that it is unknown if people with gender dysphoria that do not use puberty blockers experience similar or different outcomes.

4.2 Cross sex hormones

For almost all outcomes (except breast cancer) there is no evidence about the effect of cross sex hormones compared to not using cross sex hormones. In other words, no studies compared the outcomes between a group of people with gender dysphoria using cross sex hormones and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use cross-sex hormones experience more improvement in gender dysphoria, depression, anxiety, quality of life, and suicidality than those with gender dysphoria who do not use cross-sex hormones. There is low certainty evidence suggesting that cross-sex hormones may not increase the risk of breast cancer.

The studies included in the systematic reviews reported changes in the outcomes among a group of patients with gender dysphoria after the use of cross-sex hormones. Low certainty evidence suggests that after treatment with cross-sex hormones, people with gender dysphoria experience an improvement in gender dysphoria, depression, anxiety, and suicidality. There is very low certainty evidence about the changes in quality of life. There is moderate certainty evidence suggesting a low prevalence of venous thromboembolism after treatment with cross-sex hormones. The findings must be interpreted considering that these studies did not have a comparison group, and that it is unknown if people with gender dysphoria that do not use cross-sex hormones experience similar or different outcomes.

4.3 Surgeries

There were no systematic reviews and studies reporting on gender dysphoria, depression, anxiety, and suicidality. Therefore, the effects of surgeries on these outcomes (when compared to a group of patients with gender dysphoria who do not undergo surgery), or the changes in these outcomes (improvements or deterioration) among patients who undergo any gender-affirming surgery is unknown. Because of the lack of comparative studies, it is also unknown whether people with gender dysphoria who undergo surgeries experience more improvement in quality of life or less regret than those with gender dysphoria who do not undergo any surgeries. There is low certainty evidence suggesting that a low percentage of participants experience regret, and very low certainty evidence about changes in quality of life after surgery.

In assigned females at birth, low certainty evidence suggests that a high percentage of people are satisfied after chest surgery. There is very low certainty evidence, however, about satisfaction after bottom surgery, and about complications after both chest and bottom surgery. In assigned males at birth, low certainty evidence suggests a high percentage of people satisfied and a low percentage of people experiencing regret after vaginoplasty. There is very low certainty, however, about satisfaction with chest surgery and complications and reoperations after bottom surgery.

4.4 Evidence published after the systematic reviews selected

We found 10 relevant studies that were published after the systematic reviews were conducted. This evidence was not sufficient to importantly change the conclusions previously made.

5. Discussion

5.1 Summary of the evidence

In this report, we systematically summarized the best available evidence regarding the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria. We did not find evidence about the effect of these interventions on outcomes important to patients when compared to not receiving the intervention. We found low and very low certainty evidence suggesting improvements in gender dysphoria, depression, anxiety, and quality of life, as well as low rates of adverse events, after treatment with puberty blockers and cross-sex hormones.

5.2 Completeness and applicability

There are several gaps in the evidence regarding the effects of puberty blockers, cross-sex hormones, and surgeries in patients with gender dysphoria. Although we found some evidence for all the outcomes of interest, the evidence is suboptimal: several limitations included the lack of studies with a comparison group, and the risk of bias and imprecision, resulting in low or very low certainty evidence for all outcomes.

The applicability of the evidence may also be limited. Although we only rated down for indirectness when it was considered a serious problem (i.e., in evidence about the effects of surgeries, which was collected from people who were importantly older than the target population in this report), there are also potential applicability issues to consider in the evidence regarding the effects of puberty blockers and cross-sex hormones. It is not clear to what extent the people included in the studies were similar enough to the people seeking these treatment options today. For example, some of the included studies were conducted in people who had a diagnosis of gender dysphoria confirmed with strict criteria, as well as a supportive environment. It is important to take into account to what extent this may compromise the applicability of the results to people who are not in the same situation.

5.3 Strengths and limitations of the process for developing this report

We followed a reproducible process for developing this report. We used the highest methodological standards and the approach to evidence synthesis we generally use when supporting organizations in the development of their guidelines. This approach is based on prioritizing the sources of evidence most likely to be informative (i.e., to identify and use the evidence with the highest certainty level).

To follow the principles for evidence-based decision making, which require using the best available evidence to inform decisions, we summarized the best available evidence. Because knowing the best

available evidence necessitates being aware of all the available evidence, we based this report on systematic reviews of the literature. We chose the most trustworthy and relevant systematic reviews among many published reviews.

One potential limitation of the process is that, due to feasibility concerns, we relied on the information reported by the systematic reviewers. Most of the systematic reviews we used, unfortunately, were judged at moderate or low methodological quality, which may raise concerns about the trustworthiness of the evidence presented in this report. We believe, however, that the results and conclusions of this report would not be importantly different had the systematic reviews been conducted following higher methodological standards. Because there are no randomized controlled trials, well-conducted comparative observational studies, or very large case series (which include a large sample of consecutive patients who are representative of the whole population) addressing the effects of puberty blockers, cross-sex hormones, and surgeries; the certainty of the evidence about the effects of these interventions is likely to continue being low or very low, even if a few more studies are included (as observed after searching for primary studies published after the reviews were conducted) or some data points were reported inaccurately in the systematic reviews.

Also due to feasibility concerns, the scope of this report was limited to outcomes that are important to patients. Although some may question the decision of not including surrogate outcomes for which there is evidence available (e.g. bone density, blood pressure), decision makers should rarely consider these outcomes and should instead focus on outcomes that do matter to people and stakeholders (e.g., fractures, cardiovascular events).

5.4 Implications

The evidence evaluating the effects of puberty blockers, cross-sex hormones, and surgeries in people with gender dysphoria has important limitations. Therefore, decisions regarding their use should carefully consider other relevant factors. At a patient level, these factors include patients' values and preferences (how patients trade off the potential benefit and harms - what outcomes are more important to them), and resources needed to provide the interventions (and the availability of such resources). At a population level, in addition to these factors, it would be important to consider resources needed to implement the interventions, feasibility, acceptability by relevant stakeholders, and equity.

It is important to note that when there is low or very low certainty evidence, it is rarely appropriate to make decisions that will be applied to the majority of the patients (equivalent to strong recommendations). This implies, at the patient level, that shared decision making is a key part of the decision-making process. At a policy level, extensive debate may be needed.

6. Conclusions

Due to the important limitations in the body of evidence, there is great uncertainty about the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria. This evidence alone is not sufficient to support whether using or not using these treatments. We encourage decision makers to be explicit and transparent about which factors play an important role in their decision, and how they are weighed and traded off.

Methods

To ensure completeness and feasibility of the evidence review, we used an approach in which we prioritized the types of studies according to the design that was more likely to provide the best available evidence. First, we searched for systematic reviews of the literature. Second, we appraised all existing systematic reviews to select the most trustworthy (highest methodological quality, most up-to-date, most applicable) from which to draw conclusions. Third, we used the information presented in the systematic reviews to abstract information regarding the effects of the interventions of interest. Fourth, we assessed the certainty of the evidence (also known as quality of the evidence) abstracted from the selected systematic reviews. We planned to search for primary studies if systematic reviews were not found.

Information sources: We searched for existing systematic reviews in:

1. Epistemonikos (https://www.epistemonikos.org), an electronic database that focuses on systematic reviews. We used a comprehensive search strategy based on the population, using the terms “gender dysphoria”, “gender identity disorder” and “transgender”. We conducted this search on April 23, 2022.
2. OVID Medline. We used a search strategy based on the population and the interventions of interest, as well as an adaptation of a filter for systematic reviews from the Health Information Research Unit at McMaster University. We conducted this search on April 23, 2022.
3. Grey literature: we conducted a manual search in the websites of specific health agencies: National Institutes for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ), Canada’s Drug and Health Technology Agency (CADTH), and the website from the Society for Evidence-Based Gender Medicine (SEGM). We conducted these searches between April 27-30, 2022.

We used no date limits for the searches, but we did limit to systematic reviews published in English. Search strategies are available in Appendix 1.

Eligibility criteria: We included systematic reviews, which we defined as:

1. Reviews in which the authors searched for studies to include in at least one electronic database, and in which there were eligibility criteria for including studies and a methodology for assessing and synthesizing the evidence, or
2. Reviews in which the authors searched for studies to include in at least one electronic database, and although there was no description of eligibility criteria or methodology, the presentation of the results strongly suggested that the authors used systematic methods (e.g. flow chart depicting study selection, tables with the same information from all included studies, synthesis of data at the outcome level).

We screened systematic reviews using the following criteria for inclusion:

- ***Type of participants:*** Young individuals (< 25 years old) with a diagnosis of gender dysphoria/gender identity disorder. We included reviews in which authors used any label and diagnostic criteria for this condition. We included reviews in which the participants in the reported studies were older if it was the only evidence available for a specific question. We excluded reviews with mixed populations (i.e. with and without gender dysphoria) in which people without gender dysphoria constituted more than 20% of the total sample.

- ***Type of Interventions*:** Puberty blockers, cross-sex hormones, gender affirming surgeries. We included any type of puberty blockers and cross-sex hormones, provided with any regimen. We included the following surgeries: phalloplasty, vaginoplasty, and chest surgery (mastectomy or breast implants/augmentation). We only included these when they were performed for the first time (i.e., not revision surgeries).

- ***Type of comparison:*** When the systematic reviews included comparative studies, the comparator of interest was no intervention. Participants could have received psychotherapy or counselling as a cointervention (in both groups).

- ***Type of outcomes:*** Gender dysphoria, mental health outcomes (depression and anxiety), quality of life, suicidal ideation, suicide, adverse effects (for puberty blockers and cross-sex hormones only), and satisfaction, complications, reoperation, and regret (for surgeries only). We included any length of follow-up. We excluded surrogate outcomes such as blood pressure, bone mineral density, kidney or liver function test values, etc.

- ***Type of studies included in the systematic reviews:*** Any clinical study (studies in which the researchers recruited and measured outcomes in humans) regardless of study design. This included randomized clinical trials, comparative observational studies, and case series. Because we could not quantify effect measures, incidence, or prevalence, we excluded case reports.

We excluded systematic reviews published only in abstract format, and those that we could not retrieve in full text (no access through the McMaster University library, or open access online).

Selection process: The two reviewers screened all titles and abstracts independently and in duplicate, followed by screening of full texts of potentially eligible systematic reviews independently and in duplicate, using the systematic review online application Covidence (https://www.covidence.org). We solved disagreements by consensus.

To select the most useful systematic reviews among all of those that met the eligibility criteria, we used the following prioritization criteria:

1. Date of publication: we prioritized systematic reviews published within the last 3 years (2020-2022)

2. Match between eligibility criteria of the review and the question of interest: we prioritized reviews in which the authors specifically included the population, intervention, comparison, and outcomes of interest for this evidence review
3. Outcome data available: we prioritized systematic reviews in which the authors report outcome data
4. Methodological quality: we used a modified version of the items in AMSTAR 2.[1] We modified the items to ensure assessment of methodological rather than reporting quality (Table 1). We rated each systematic review as having high, moderate, low, or critically low methodological quality, according to the guidance from the developers of the tool.[1] We reached consensus on critical items that determined this rating (Table 1). We prioritized selection of systematic reviews with highest methodological quality.

For surgical interventions, in addition, we prioritized systematic reviews that covered all gender affirming surgeries (instead of focusing on a specific type of surgery).

We selected a systematic review specifically for each of the outcomes of interest. In other words, we chose the best systematic review to inform each outcome. Each systematic review, however, could inform more than one outcome.

Table 1: Items used to rate the methodological quality of the eligible systematic reviews

AMSTAR Item	Modification to measure methodological quality
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Does the review have a clear question and are the eligibility criteria for studies consistent with the question?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No modification needed
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No modification needed
4. Did the review authors use a comprehensive literature search strategy?	Did the authors search in at least 2 electronic databases, using a reproducible search strategy?
5. Did the review authors perform study selection in duplicate?	No modification needed
6. Did the review authors perform data extraction in duplicate?	No modification needed
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No modification needed
8. Did the review authors describe the included studies in adequate detail?	No modification needed
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No modification needed

10. Did the review authors report on the sources of funding for the studies included in the review?	Did the review authors consider conflicts of interest and how they may have affected the results of the primary studies?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Was the synthesis of evidence done appropriately? (outcome level, appropriate meta analysis or narrative synthesis)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Did authors use subgroup or sensitivity analysis to assess the effect of risk of bias in meta-analytic results? Likely not applicable to most cases
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Did the review authors incorporate an assessment of risk of bias at the outcome level when drawing conclusions?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Did the review authors incorporate an assessment of heterogeneity at the outcome level when drawing conclusions?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Did the authors address publication bias? (regardless of whether synthesis was using a meta-analysis or narrative)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Did the authors report conflicts of interest and did they manage any existing conflict of interest appropriately?

Shaded items were items considered critical.

Data abstraction: We abstracted outcome data from each of the systematic reviews. To ensure feasibility, we used the data as reported by the authors of the review and did not re-abstract data from the primary studies. One reviewer abstracted the data and a second reviewer checked the data for accuracy.

Data synthesis: Using the systematic reviews prioritized, we synthesized the evidence at the outcome level. Because of the higher likelihood of it resulting in higher certainty of evidence (details below) for each outcome, when there was comparative data (i.e. comparison of outcomes between an untreated and a treated group) and non-comparative data (i.e. changes from before to after treatment in one group, or only outcomes after treatment), we prioritized comparative data.

We prioritized numerical results (i.e. magnitudes of effect) and reported estimates and their 95% confidence intervals (CIs). When results were not reported in that way, we calculated the estimates and CIs when systematic review authors provided sufficient information. When necessary, we assumed moderate correlation coefficients for the changes between baseline and follow up (coefficient= 0.4). When this information was not available we reported narratively the effect estimates and ranges.

When a specific study reported the same outcome measured by more than one scale, we chose the scale presented first. We highlighted situations when the results obtained with other scales were importantly different.

When the same outcome was reported by more than one study but we could not pool the results, we created narrative syntheses.

Certainty of evidence: For each outcome, we assessed the certainty of the evidence (also known as quality of the evidence) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[2] The certainty of evidence can be rated as high, moderate, low, or very low (Table 2). For effects of interventions, the certainty of the evidence started as high and could be rated down due to serious concerns about risk of bias, inconsistency, indirectness, imprecision, and publication bias. For inferences about the effect of using a treatment versus no treatment, when there was no comparison group, we assessed risk of bias as very serious and rated down the certainty of the evidence 2 levels by default. We used the same principles when assessing the certainty of the evidence in estimates of prevalence or rates, but did not judge risk of bias as resulting in very serious concerns due to lack of a comparison group. For all assessments, we used the information presented by the authors of the systematic review (e.g. assessments of risk of bias of the included studies, effect estimates from studies).

Table 2: GRADE levels of certainty of the evidence

Certainty level	Definition
High ⊕⊕⊕⊕	We are very confident that the true result (effect estimate/ prevalence/ mean, etc.) lies close to that of the estimate of the result
Moderate ⊕⊕⊕◯	We are moderately confident in the result: the true result is likely to be close to the estimate of the result, bur there is a possibility that it is substantially different
Low ⊕⊕◯◯	Our confidence in the result is limited: the true result may be substantially different from the estimate of the result
Very low ⊕◯◯◯	We have very little confidence in the result: the true result is likely to be substantially different from the estimate of the result

Presentation of results: We created GRADE Summary of Findings tables in which we describe the evidence available for each of the outcomes, and the certainty of the evidence. These tables contain the following information:

- Outcomes: measurement method (including scales, if applicable) and follow-up
- Estimates of effect: absolute and relative estimates of effect, and their corresponding 95% CIs.
- Number of studies and participants providing evidence for the outcome
- GRADE certainty of the evidence, with a link to detailed explanations (provided at the bottom of the table) of why the certainty of the evidence was rated at a specific level
- A narrative statement about what happens with the outcome, based on the estimate of effect and certainty of evidence.

Searching for new evidence not included in the systematic reviews: To assess if newer evidence not included in the included systematic reviews would change the conclusions importantly, we searched for and assessed primary studies answering the questions of interest that were published after the authors of such systematic reviews conducted their searches. We defined an important change in conclusions as a change in the certainty of the evidence (from low/ very low/ not available to high/ moderate).

We searched OVID Medline from January 1, 2019 through May 12, 2022, for studies published in English. We included studies if they enrolled young individuals (< 25 years old, with at least 20% of the people being this age) with a diagnosis of gender dysphoria/gender identity disorder, who received puberty blockers, cross-sex hormones, or surgeries; and measured any of the outcomes of interest.

For outcomes that should be evaluated in a comparative manner (e.g., depression, anxiety, etc.), because they are the only type of study design that would change the conclusions importantly, we selected comparative clinical studies (studies in which the researchers recruited and measured outcomes in humans, and compared a group of people who received the intervention with another one who did not receive the intervention). This included randomized clinical trials, and comparative observational studies. For outcomes that can only occur when the treatment is administered, we included non-comparative observational studies (case series). For these to change conclusions, they should have a sufficiently large sample size, and therefore we excluded case series in which the researchers reported information from <100 people.

Two reviewers screened the potentially relevant articles at title and abstract and full text screening stage. We abstracted relevant study characteristics and outcome data, and assessed risk of bias of comparative studies using the most relevant domains of the Risk of Bias for non-Randomized studies of Interventions (ROBINS-I) tool[3] (table 3). For non-comparative studies, we used a list of custom items that captured the most important potential risk of bias concerns of case series (table 4). We judged the risk of bias of each study as the highest risk of bias of any of the domains assessed (e.g., one domain judged at critical risk of bias resulted in the study judged at critical risk of bias). We summarized this information at the study and judged whether it would have changed the conclusions importantly if added to the body of evidence from the systematic reviews.

Table 3: Domains used to assess risk of bias of comparative studies

Domain	Low	Critical
Confounding	Adjusted for all relevant confounding factors	No adjustment
Classification of intervention	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
Deviation from intended interventions	No cointerventions or cointerventions balanced between the groups	Cointerventions unbalanced between the groups

Missing data	More than 90% of patients who started the study provided outcome data	Less thank 50% of patients who started the study provided outcome data
Measurement of outcome	All outcomes measured in the same way in both groups	Outcomes measured differently in both groups

Each domain could be judged at low, moderate, serious, or critical risk of bias. In addition, information could be insufficient to make a judgment. The table describes the criteria used to judge a domain in the extreme categories.

Table 4: Domains used to assess risk of bias of non- comparative studies

Domain	Low	High
Representativeness of the sample	Included all consecutive patients	Highly selected sample based on specific characteristics related with the prognosis after treatment
Classification of the intervention	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
Deviation from intended interventions	No cointerventions outside what would be observed in practice (or in a small proportion of patients)	Most patients received co interventions that could influence the outcomes
Missing data	More than 90% of patients who started the study provided outcome data	Less thank 50% of patients who started the study provided outcome data
Measurement of outcome	Outcomes measured prospectively or from medical records	Outcomes reported by the patients and/ or needed to recall what happened a long time ago

Each domain could be judged at low, moderate, or high risk of bias. In addition, information could be insufficient to make a judgment. The table describes the criteria used to judge a domain in the extreme categories.

References

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj* 2017;358:j4008. doi: 10.1136/bmj.j4008 [published Online First: 2017/09/25]
2. Blashem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of the evidence. *Journal of clinical epidemiology* 2011;64:401-06.
3. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical research ed)* 2016;355:i4919. doi: 10.1136/bmj.i4919 [published Online First: 2016/10/14]

Search Strategies

Questions Covered:

PICO questions:

1. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **puberty blockers (gonadotrophin releasing hormone (GnRH) analogues)** compared to no puberty blockers?

2. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **cross-sex hormones** compared to no cross-sex hormones?

3. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of **gender-affirming surgeries** compared to no surgery?

Search Strategies:

Note: Population, puberty blocker, cross-sex hormones search blocks adapted from NICE (2020) evidence reviews. Gender-affirming search block adapted from Wernick *et al.* 2019. Systematic reviews filter adapted from McMaster University Health Information Research Unit (HIRU).

Databases: Medline, Epistemonikos
Grey Literature: CADTH, AHRQ, SEGM, NICE

Medline

OVERVIEW	
Interface:	Ovid
Databases:	OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Study Types:	Systematic Reviews
Search Run:	April 23, 2022

Search Strategy: search terms [number of results]

Population

1	exp "Sexual and Gender Minorities"/	12385
2	Gender Dysphoria/	774
3	Gender Identity/	20481
4	Gender Role/	197
5	"Sexual and Gender Disorders"/	81
6	Transsexualism/	4236
7	Transgender Persons/	5303
8	Health Services for Transgender Persons/	186

9 exp Sex Reassignment Procedures/ 1208
10 gender identity disorder.mp. 492
11 non-binary.mp. 566
12 transgender.mp. 9989
13 (gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).tw. 16428
14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw. 13749
15 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. 19665
16 (genderfluid or genderqueer or agender).mp. 130
17 ((correct or chosen) adj3 name).mp. 591
18 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. 135313
19 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw. 13749
20 (male-to-female or m2f or female-to-male or f2m).tw. 148579
21 or/1-20 342948

Cross-Sex Hormones

22 Hormones/ad, tu, th 4676
23 exp Progesterone/ad, tu, th 11265
24 exp Estrogens/ad, tu, th 29635
25 exp Gonadal Steroid Hormones/ad, tu, th 35375
26 (progesteron* or oestrogen* or estrogen*).tw. 223307
27 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. 1488
28 exp Estradiol/ad, tu, th 11197
29 exp Testosterone/ad, tu, th 8710
30 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. 86509
31 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. 100252
32 or/22-31 345895

Puberty Blockers

33 Gonadotropin-Releasing Hormone/ 28809
34 (pubert* adj3 block*).ti,ab. 141
35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. 20121
36 (GnRH adj2 analog*).ti,ab. 2878
37 GnRH*.ti,ab. 24390
38 "GnRH agonist*".ti,ab. 4749
39 Triptorelin Pamoate/ 1981
40 triptorelin.ti,ab. 821
41 arvekap.ti,ab. 1

42	("AY 25650" or AY25650).ti,ab.	1
43	("BIM 21003" or BIM21003).ti,ab.	0
44	("BN 52014" or BN52014).ti,ab.	0
45	("CL 118532" or CL118532).ti,ab.	0
46	Debio.ti,ab.	119
47	diphereline.ti,ab.	28
48	moapar.ti,ab.	0
49	pamorelin.ti,ab.	1
50	trelstar.ti,ab.	3
51	triptodur.ti,ab.	1
52	("WY 42422" or WY42422).ti,ab.	0
53	("WY 42462" or WY42462).ti,ab.	0
54	gonapeptyl.ti,ab.	0
55	decapeptyl.ti,ab.	225
56	salvacyl.ti,ab.	0
57	Buserelin/	2137
58	buserelin.ti,ab.	1395
59	onist.ti,ab.	0
60	("hoe 766" or hoe-766 or hoe766).ti,ab.	72
61	profact.ti,ab.	2
62	receptal.ti,ab.	31
63	suprecur.ti,ab.	5
64	suprefact.ti,ab.	25
65	tiloryth.ti,ab.	0
66	histrelin.ti,ab.	78
67	"LHRH-hydrogel implant".ti,ab.	1
68	("RL 0903" or RL0903).ti,ab.	1
69	("SPD 424" or SPD424).ti,ab.	1
70	goserelin.ti,ab.	1016
71	Goserelin/	1643
72	("ici 118630" or ici118630).ti,ab.	51
73	("ZD-9393" or ZD9393).ti,ab.	0
74	zoladex.ti,ab.	388
75	leuprorelin.ti,ab.	525
76	carcinil.ti,ab.	0
77	enanton*.ti,ab.	26
78	ginecrin.ti,ab.	0
79	leuplin.ti,ab.	15
80	Leuprolide/	3018
81	leuprolide.ti,ab.	2004
82	lucrin.ti,ab.	16
83	lupron.ti,ab.	183
84	provren.ti,ab.	0
85	procrin.ti,ab.	3
86	("tap 144" or tap144).ti,ab.	41
87	(a-43818 or a43818).ti,ab.	3
88	Trenantone.ti,ab.	2
89	staladex.ti,ab.	0

90 prostap.ti,ab. 6
91 Nafarelin/ 327
92 nafarelin.ti,ab. 263
93 ("76932-56-4" or "76932564").ti,ab. 0
94 ("76932-60-0" or "76932600").ti,ab. 0
95 ("86220-42-0" or "86220420").ti,ab. 0
96 ("rs 94991 298" or rs94991298).ti,ab. 0
97 synarel.ti,ab. 13
98 deslorelin.ti,ab. 306
99 gonadorelin.ti,ab. 237
100 ("33515-09-2" or "33515092").ti,ab. 0
101 ("51952-41-1" or "51952411").ti,ab. 0
102 ("52699-48-6" or "52699486").ti,ab. 0
103 cetrorelix.ti,ab. 520
104 cetrotide.ti,ab. 52
105 ("NS 75A" or NS75A).ti,ab. 0
106 ("NS 75B" or NS75B).ti,ab. 0
107 ("SB 075" or SB075).ti,ab. 1
108 ("SB 75" or SB75).ti,ab. 67
109 gonadoliberin.ti,ab. 151
110 kryptocur.ti,ab. 7
111 cetrorelix.ti,ab. 520
112 cetrotide.ti,ab. 52
113 antagon.ti,ab. 18
114 ganirelix.ti,ab. 160
115 ("ORG 37462" or ORG37462).ti,ab. 3
116 orgalutran.ti,ab. 26
117 ("RS 26306" or RS26306).ti,ab. 5
118 ("AY 24031" or AY24031).ti,ab. 0
119 factrel.ti,ab. 13
120 fertagyl.ti,ab. 12
121 lutrelef.ti,ab. 5
122 lutrepulse.ti,ab. 3
123 relefact.ti,ab. 10
124 fertiral.ti,ab. 0
125 (hoe471 or "hoe 471").ti,ab. 6
126 relisorm.ti,ab. 4
127 cystorelin.ti,ab. 19
128 dirigestran.ti,ab. 5
129 or/33-128 47108

Gender-affirming Surgeries

130 virilization/ 2309
131 (virilism or virili?ation or masculini?ation).mp. 5657
132 feminization/ 797
133 femini?ation.mp. 3420
134 (vaginoplasty or vaginoplasties).mp. 1022

135 exp Vagina/ or *Reconstructive Surgical Procedures/ 78841
136 (vaginoplasty or vaginoplasties).mp. 1022
137 (phalloplasty or phalloplasties).mp. 561
138 exp Penile Prosthesis/ 1636
139 "penile reconstruction".mp. 292
140 (vagina reconstruction or vaginal reconstruction).mp. 549
141 (genitoplasty or genitoplasties).mp. 263
142 transsexualism/su [Surgery] 1007
143 sex reassignment.mp. 1668
144 sex transformation.mp. 42
145 or/130-144 91560

Systematic Review Filter

147 meta-analysis/ 158633
148 (meta anal* or meta-anal* or metaanal*).ti,ab. 231876
149 ((systematic or evidence) adj2 (review* or overview*)).ti,ab. 279806
150 ((pool* or combined) adj2 (data or trials or studies or results)).ab. 65411
151 (search strategy or search criteria or systematic search or study selection or data extraction).ab. 70886
152 (search* adj4 literature).ab. 84593
153 or/146-152 521554

Combine Interventions and Population

154 32 or 129 or 145 459771
155 21 and 154 17838

Limit to Systematic Reviews in English Language

156 153 and 155 295
157 limit 156 to english language 288

Epistemonikos

OVERVIEW	
Interface:	https://www.epistemonikos.org/
Database:	Epistemonikos
Study Types:	Systematic Reviews
Search Run:	April 23, 2022
Search Strategy: search terms [number of results]	

Population

(title:((title:(gender dysphoria) OR abstract:(gender dysphoria)) OR (title:(gender identity disorder) OR abstract:(gender identity disorder)) OR (title:(transgender) OR abstract:(transgender))) OR abstract:((title:(gender dysphoria) OR abstract:(gender dysphoria)) OR (title:(gender identity disorder) OR abstract:(gender identity disorder)) OR (title:(transgender) OR abstract:(transgender))))

Limit to Systematic Reviews

*Limited by publication type "systematic review" [425]

Canadian Agency for Drugs and Technologies in Health (CADTH)

OVERVIEW	
Interface:	https://www.cadth.ca/
Database:	CADTH
Study Types:	Systematic Reviews, Health Technology Reviews
Search Run:	April 27, 2022
Search Strategy: search terms [number of results]	

"gender dysphoria" [10]
Limit to Health Technology Review [2]

"transgender" [9]
Limit to Health Technology Review [5]

"gender identity disorder" [1]

Agency for Healthcare Research and Quality (AHRQ)

OVERVIEW	
Interface:	https://search.ahrq.gov/
Database:	AHRQ
Study Types:	Evidence Based Practice (EPC) Centre Reports, Full Research Reports, Health Technology Assessments
Search Run:	April 29, 2022
Search Strategy: search terms [number of results]	
Search titles only. "gender identity disorder" "gender dysphoria" "transgender" [7]	

Society for Evidence-based Gender Medicine (SEGM)

OVERVIEW	
Interface:	https://segm.org/news
Database:	SEGM News
Study Types:	Systematic Reviews
Search Run:	April 30, 2022
Search Strategy: search terms [number of results]	
Find in page: "systematic" [5]	

National Institute for Health and Care Excellence (NICE)

OVERVIEW	
Interface:	https://www.nice.org.uk/
Database:	NICE
Study Types:	Systematic Reviews, Guidelines with Systematic Reviews
Search Run:	April 30, 2022
Search Strategy: search terms [number of results]	
gender dysphoria [1] *Limit to Guidance* [1] transgender [10] *Limit to Guidance* [7]	

gender identity disorder [9] *Limit* to *Guidance* [8]

Search Strategies – Individual Studies

Questions Covered:

PICO questions:

1. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **puberty blockers (gonadotrophin releasing hormone (GnRH) analogues)** compared to no puberty blockers?

2. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **cross-sex hormones** compared to no cross-sex hormones?

3. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of **gender-affirming surgeries** compared to no surgery?

Search Strategies:

Note: Population, puberty blocker, cross-sex hormones search blocks adapted from NICE (2020) evidence reviews. Gender-affirming search block adapted from Wernick *et al.* 2019.

Databases: Medline

Medline

OVERVIEW	
Interface.	Ovid
Databases:	OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Study Types:	Any
Search Run:	May 12, 2022

Search Strategy: search terms [number of results]		
Population		
1	exp "Sexual and Gender Minorities"/	12631
2	Gender Dysphoria/	781
3	Gender Identity/	20586
4	Gender Role/	204
5	"Sexual and Gender Disorders"/	81
6	Transsexualism/	4259
7	Transgender Persons/	5371
8	Health Services for Transgender Persons/	187
9	exp Sex Reassignment Procedures/	1211
10	gender identity disorder.mp.	492

11 non-binary.mp. 574
12 transgender.mp. 10079
13 (gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).ti,ab. 16546
14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).ti,ab. 9375
15 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).ti,ab. 19788
16 (genderfluid or genderqueer or agender).mp. 132
17 ((correct or chosen) adj3 name).mp. 591
18 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).ti,ab. 135744
19 (male-to-female or m2f or female-to-male or f2m).ti,ab. 149067
20 or/1-19 341083

Cross-sex Hormones

21 Hormones/ad, tu, th 4690
22 exp Progesterone/ad, tu, th 11270
23 exp Estrogens/ad, tu, th 29646
24 exp Gonadal Steroid Hormones/ad, tu, th 35401
25 (progesteron* or oestrogen* or estrogen*).ti,ab. 223689
26 ((cross-sex or crosssex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).ti,ab. 1507
27 exp Estradiol/ad, tu, th 11200
28 exp Testosterone/ad, tu, th 8722
29 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).ti,ab. 86670
30 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).ti,ab. 100411
31 or/21-30 346508

Puberty Blockers

32 Gonadotropin-Releasing Hormone/ 28845
33 (pubert* adj3 block*).ti,ab. 142
34 ((gonadotrophin or gonadotropin) and releasing).ti,ab. 20158
35 (GnRH adj2 analog*).ti,ab. 2879
36 GnRH*.ti,ab. 24437
37 "GnRH agonist*".ti,ab. 4763
38 Triptorelin Pamoate/ 1983
39 triptorelin.ti,ab. 822
40 arvekap.ti,ab. 1
41 ("AY 25650" or AY25650).ti,ab. 1
42 ("BIM 21003" or BIM21003).ti,ab. 0
43 ("BN 52014" or BN52014).ti,ab. 0
44 ("CL 118532" or CL118532).ti,ab. 0

45	Debio.ti,ab.	119
46	diphereline.ti,ab.	28
47	moapar.ti,ab.	0
48	pamorelin.ti,ab.	1
49	trelstar.ti,ab.	3
50	triptodur.ti,ab.	1
51	("WY 42422" or WY42422).ti,ab.	0
52	("WY 42462" or WY42462).ti,ab.	0
53	gonapeptyl.ti,ab.	0
54	decapeptyl.ti,ab.	225
55	salvacyl.ti,ab.	0
56	Buserelin/	2137
57	buserelin.ti,ab.	1396
58	onist.ti,ab.	0
59	("hoe 766" or hoe-766 or hoe766).ti,ab.	72
60	profact.ti,ab.	2
61	receptal.ti,ab.	31
62	suprecur.ti,ab.	5
63	suprefact.ti,ab.	25
64	tiloryth.ti,ab.	0
65	histrelin.ti,ab.	78
66	"LHRH-hydrogel implant".ti,ab.	1
67	("RL 0903" or RL0903).ti,ab.	1
68	("SPD 424" or SPD424).ti,ab.	1
69	goserelin.ti,ab.	1017
70	Goserelin/	1644
71	("ici 118630" or ici118630).ti,ab.	51
72	("ZD-9393" or ZD9393).ti,ab.	0
73	zoladex.ti,ab.	388
74	leuprorelin.ti,ab.	529
75	carcinil.ti,ab.	0
76	enanton*.ti,ab.	26
77	ginecrin.ti,ab.	0
78	leuplin.ti,ab.	15
79	Leuprolide/	3018
80	leuprolide.ti,ab.	2003
81	lucrin.ti,ab.	16
82	lupron.ti,ab.	183
83	provren.ti,ab.	0
84	procrin.ti,ab.	3
85	("tap 144" or tap144).ti,ab.	41
86	(a-43818 or a43818).ti,ab.	3
87	Trenantone.ti,ab.	2
88	staladex.ti,ab.	0
89	prostap.ti,ab.	6
90	Nafarelin/	327
91	nafarelin.ti,ab.	263
92	("76932-56-4" or "76932564").ti,ab.	0

93	("76932-60-0" or "76932600").ti,ab.	0
94	("86220-42-0" or "86220420").ti,ab.	0
95	("rs 94991 298" or rs94991298).ti,ab.	0
96	synarel.ti,ab.	13
97	deslorelin.ti,ab.	310
98	gonadorelin.ti,ab.	238
99	("33515-09-2" or "33515092").ti,ab.	0
100	("51952-41-1" or "51952411").ti,ab.	0
101	("52699-48-6" or "52699486").ti,ab.	0
102	cetrorelix.ti,ab.	520
103	cetrotide.ti,ab.	52
104	("NS 75A" or NS75A).ti,ab.	0
105	("NS 75B" or NS75B).ti,ab.	0
106	("SB 075" or SB075).ti,ab.	1
107	("SB 75" or SB75).ti,ab.	67
108	gonadoliberin.ti,ab.	152
109	kryptocur.ti,ab.	7
110	cetrorelix.ti,ab.	520
111	cetrotide.ti,ab.	52
112	antagon.ti,ab.	18
113	ganirelix.ti,ab.	161
114	("ORG 37462" or ORG37462).ti,ab.	3
115	orgalutran.ti,ab.	26
116	("RS 26306" or RS26306).ti,ab.	5
117	("AY 24031" or AY24031).ti,ab.	0
118	factrel.ti,ab.	13
119	fertagyl.ti,ab.	12
120	lutrelef.ti,ab.	5
121	lutrepulse.ti,ab.	3
122	relefact.ti,ab.	10
123	fertiral.ti,ab.	0
124	(hoe471 or "hoe 471").ti,ab.	6
125	relisorm.ti,ab.	4
126	cystorelin.ti,ab.	19
127	dirigestran.ti,ab.	5
128	or/32-127	47179

Surgery

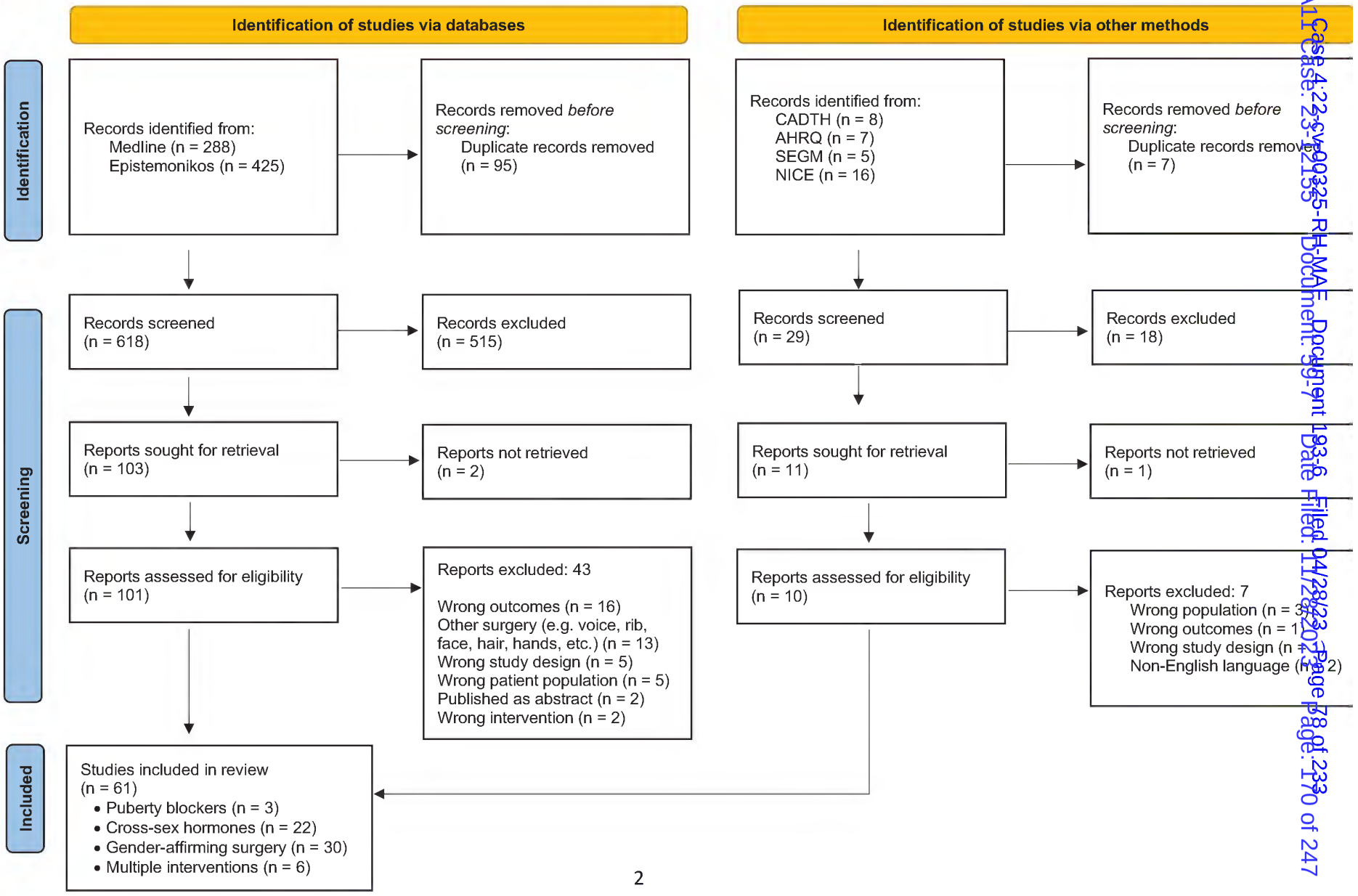
129	virilization/	2309
130	(virilism or virili?ation or masculini?ation).mp.	5664
131	feminization/	798
132	femini?ation.mp.	3425
133	(vaginoplasty or vaginoplasties).mp.	1032
134	(vaginoplasty or vaginoplasties).mp.	1032
135	(phalloplasty or phalloplasties).mp.	561
136	exp Penile Prosthesis/	1642
137	"penile reconstruction".mp.	292

138	(vagina reconstruction or vaginal reconstruction).mp.	550
139	(genitoplasty or genitoplasties).mp.	263
140	transsexualism/su [Surgery]	1007
141	sex reassignment.mp.	1674
142	sex transformation.mp.	42
143	or/129-142	14290
	Any intervention AND population	
144	31 or 128 or 143	386835
145	20 and 144	16516
	Limit to Humans	
146	animals/ not humans/	4972586
147	145 not 146	9281
148	limit 147 to humans	7901
	Limit to Publication Year 2019 to Current	
149	limit 148 to yr="2019 -Current"	1859

Results

Search results and eligible reviews: After screening 647 records found through our searches, we found 61 eligible systematic reviews. From these, 27 were published between 2020 and 2022 (Figure 1). Overall, 4% (1/27) of the reviews were judged to be of high methodological quality, 15% (4/27) were moderate methodological quality, 37% (10/27) were low methodological quality, and 44% (12/27) were critically low methodological quality.

We provide reasons for excluding systematic reviews in appendix 1.



Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 1: PRISMA flow diagram for the selection of systematic reviews. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Outcomes:

1. **Puberty blockers:** We found 4 systematic reviews assessing the effects of puberty blockers published between 2020 and 2022.[1-4] From these, we judged 2 as having moderate methodological quality, and 2 as having critically low methodological quality. Details of the assessment are provided in Figure 2.

   Table 1 summarizes the evidence about the effects of puberty blockers on the outcomes of interest. We used information from 2 systematic reviews.[2 3] For most outcomes (except suicidality), there is no evidence about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. There is very low certainty about the effects of puberty blockers on suicidal ideation (see details in Table 1).

   Studies, however, reported outcomes among a group of people with gender dysphoria after receiving puberty blockers. The findings are:
   - There is low certainty evidence suggesting that treatment with puberty hormones may slightly increase gender dysphoria severity (mean change score in the Utrecht Gender Dysphoria scale, 0.7 points [95% CI, -4.2 to 5.6], range 12-60, with higher scores reflecting more severe gender dysphoria)
   - There is low certainty evidence suggesting that treatment with puberty blockers may decrease depression (mean change score in the Beck Depression Inventory, -3.4 [95% CI, -5.7 to -1.0], range 0-63, with higher scores reflecting more severe depression)
   - There is low certainty evidence suggesting that treatment with puberty blockers may decrease anxiety (mean change score in the Trait Anxiety Scale, trait subscale, -1.5 [95% CI, -4.7 to -1.8], range 0-80, with higher scores reflecting more severe anxiety)
   - There is low certainty evidence suggesting a moderate percentage of patients reporting adverse events after treatment with puberty blockers (see Table 1 for details)
   - There is very low certainty evidence about how puberty blockers affect suicidality

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 2: AMSTAR assessment judgements for systematic reviews addressing puberty blockers

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
AHRQ 2021																	MODERATE
NICE 2020a																	MODERATE
Ramos 2020																	CRITICALLY LOW
Rew 2020																	CRITICALLY LOW

Figure legend:

Yes

Probably yes

Probably no

No

Not applicable

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no puberty blockers	**Risk / mean with puberty blockers**				
Gender dysphoria assessed with: difference (effect) in gender dysphoria proportion or severity	Not reported					The effects of puberty blockers on gender dysphoria are unknown
Gender dysphoria assessed with: mean change score in the Utrecht Gender Dysphoria Scale (12-60, higher scores reflect more gender dysphoria, 40 points or more indicate a diagnosis of gender dysphoria) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	0.7 (-4.2 to 5.6)	NA	41 (1 study)	⨁⨁◯◯ LOW[1]	The mean gender dysphoria score may increase by 0.7 points after puberty blockers
Depression assessed with: difference (effect) in depression proportion or severity	Not reported					The effects of puberty blockers on depression are unknown

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no puberty blockers	Risk / mean with puberty blockers				
Depression assessed with: mean change score in Beck Depression Inventory-II scale (0-63, higher scores represent more severe depression) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	-3.4 (-5.7 to -1.0)	NA	41 (1 study)	⨁⨁◯◯ LOW[1]	The mean depression score may decrease by 3.4 points after puberty blockers
Anxiety assessed with: difference (effect) in anxiety proportion or severity	Not reported					The effects of puberty blockers on anxiety are unknown
Anxiety assessed with: mean change score in STAI-Trait scale (0-80, higher scores represent more severe anxiety) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	-1.5 (-4.7 to 1.8)	NA	41 (1 study)	⨁⨁◯◯ LOW[1]	The mean anxiety score may decrease by 1.5 points after puberty blockers

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no puberty blockers	Risk / mean with puberty blockers				
Quality of life assessed with: any measure	Not reported					The effects of puberty blockers on quality of life are unknown
Suicidal ideation difference (effect) in suicidal ideation (Rew, 2020) Follow-up: cross-sectional survey	The authors report that "compared to youth who did not receive pubertal suppression, those who did showed lower lifetime rates of suicidal ideation".			89 (1 study)	⨁◯◯◯ VERY LOW[2]	We are very uncertain about the effect of puberty blockers on suicidal ideation
Adverse effects assessed with: proportion of patients reporting adverse effects (NICE, 2020a) Follow up: mean 2.3 years (range 0.0 to 11.3 years)	NA	11%[3] (2% to 29%)	NA	27 (1 study)	⨁⨁◯◯ LOW[4]	The proportion of patients reporting adverse effects after treatment with puberty blockers may be 11%

STAI-Trait: Trait Anxiety Scale. Range: 0-80
CI: Confidence interval
NA: Not applicable

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no puberty blockers	Risk / mean with puberty blockers				

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. Mean change rated down due to risk of bias and imprecision. According to the systematic review authors, the study had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size).
2. The authors of Rew 2020 narratively summarized the outcome of Turban *et al.* 2020; a cross-sectional online survey study. According to the systematic review authors, Turban et al. did not describe the study participants and the setting in detail and it was unclear whether outcomes were measured in a valid and reliable way. We therefore, downgraded the certainty of evidence by one level from low to very low due to high risk of bias.
3. The authors reported 3/27 (11%) participants treated with GnRHa developed side effects: 1 participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, 1 participant developed leg pains and headaches, which eventually resolved without treatment, 1 participant gained 19 kg within 9 months of initiating GnRH analogues.
4. Proportion of adverse effects rated down due to risk of bias and imprecision. According to the systematic review authors, the cohort study Khatchadourian *et al.* 2014 was assessed at high risk of bias due to incomplete reporting of its cohort. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size).

2. **Cross-sex hormones:** We found 9 systematic reviews assessing the effects of cross-sex hormones published between 2020 and 2022.[4-12] One of these, however, included both puberty blockers and cross-sex hormones combined in their evidence synthesis as was not prioritized.[5] From the 8 remaining reviews, we judged 1 as having high methodological quality, 2 as having moderate methodological quality, 2 as having low methodological quality, and 3 as having critically low methodological quality. Details of the assessment are provided in Figure 3. Because of its eligibility criteria related to study design, the systematic review judged at high methodological quality[7] did not include any studies and therefore we could not use it to inform any outcome.

   Table 2 summarizes the evidence about the effects of cross-sex hormones on the outcomes of interest. We used information from 4 systematic reviews.[6 9 11 12] For most outcomes (all except risk of breast cancer), there is no evidence about the effect of cross-sex hormones compared to not using cross-sex hormones. In other words, no studies compared the outcomes between a group of people with gender dysphoria using cross-sex hormones and another not using it. Therefore, it is unknown whether people with gender dysphoria who use cross-sex hormones experience more improvement in gender dysphoria, depression, anxiety, quality of life, and suicidality than those with gender dysphoria who do not use them. There is low certainty evidence suggesting that cross-sex hormones may not increase or decrease the risk of breast cancer (see details in Table 2).

   Studies, however, reported outcomes among a group of people with gender dysphoria after receiving cross-sex hormones. The findings are:
   - There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease gender dysphoria severity (mean change score in the Utrecht Gender Dysphoria scale, -42.4 points [95% CI, -44.1 to -40.1], range 12-60, with higher scores reflecting more severe gender dysphoria)
   - There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease depression (measured with different scales, see Table 4 for details) and the need for treatment for depression (change in percentage, -39%)
   - There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease anxiety (measured with different scales, see Table 4 for details) and the need for treatment for anxiety (change in percentage, -32%)
   - There is very low certainty about the change in quality of life after treatment with cross-sex hormones.
   - There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease suicidality degree (mean change score in the Ask Suicide-Screening questions scale, -0.84 points [95% CI, -1.30 to -0.44], range 0-4, with higher scores reflecting more severe suicidality) and the percentage of patients with need for treatment due to suicidality/self-harm (change in percentage, -31%). There is very low certainty evidence about the percentage of people with suicidal ideation and suicide attempts after treatment with cross-sex hormones.

- There is low certainty evidence suggesting a low prevalence of venous thromboembolism after treatment with cross-sex hormones (see Table 2 for details)

Figure 3: AMSTAR assessment judgements for systematic reviews addressing cross-sex hormones

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
AHRQ 2021																	MODERATE
Baker 2021																	MODERATE
Fledderus 2020																	CRITICALLY LOW
Haupt 2020																	HIGH
Karalexi 2020																	LOW
Kotamarti 2021																	CRITICALLY LOW
Mattawanon 2021																	CRITICALLY LOW
NICE 2021b																	MODERATE
Totaro 2021																	LOW

Figure legend:

Yes

Probably yes

Probably no

No

Not applicable

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Gender dysphoria assessed with: difference (effect) in gender dysphoria percentage or severity	Not reported					The effects of cross-sex hormones on gender dysphoria are unknown
Gender dysphoria assessed with: mean change score in the Utrecht Gender Dysphoria Scale (12-60, higher scores reflect more gender dysphoria, 40 points or more indicate a diagnosis of gender dysphoria) (NICE, 2020b) Follow up: 1 year	NA	-42.4 (-44.1 to -40.1)	NA	23 (1 study)	⨁⨁◯◯ LOW[1]	The mean gender dysphoria score may decrease by 42 points after cross-sex hormones
Depression assessed with: difference (effect) in depression percentage or severity	Not reported					The effects of cross-sex hormones on depression are unknown

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Depression assessed with: mean change score in depression scales (higher scores represent more severe depression) (NICE, 2020b) Follow up: 1 year	NA	The mean depression score reduction was 9.6 points when using the BDI-II scale (n=23) and 7.5 when using the CESD-R scale (n=50). The authors report that both reductions were statistically significant[2]	NA	73 (2 studies)	⨁⨁◯◯ LOW[1]	The mean depression score may decrease after cross-sex hormones
Depression assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants requiring treatment was reduced by 39% (from 54% at baseline), which was statistically significant	NA	52 (1 study)	⨁⨁◯◯ LOW[1]	The percentage of participants requiring treatment may be reduced by 39% after cross-sex hormones
Anxiety assessed with: difference (effect) in anxiety percentage or severity	Not reported					The effects of cross-sex hormones on anxiety are unknown

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Anxiety assessed with: mean change score in anxiety scales (higher scores represent more severe anxiety) (NICE, 2020b) Follow up: 1 year	NA	The mean anxiety score reduction was 16.5 points when using the STAI-State scale and 14.5 when using the STAI-Trait scale. The authors report that both reductions were statistically significant	NA	23 (1 study)	⨁⨁◯◯ LOW[1]	The mean anxiety score may decrease after cross-sex hormones
Anxiety assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants requiring treatment was reduced by 32% (from 48% at baseline), which was statistically significant	NA	52 (1 study)	⨁⨁◯◯ LOW[1]	The percentage of participants requiring treatment may be reduced by 32% after cross-sex hormones
Quality of life assessed with: difference (effect) in quality of life improvement	Not reported					The effects of cross-sex hormones on quality of life are unknown

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Quality of life assessed with: mean change score in QLES-Q-SF score (higher scores represent better quality of life) (NICE, 2020b) Follow up: 1 year	NA	The mean quality of life score improved, but the differences were not statistically significant. The magnitudes were not reported	NA	50 (1 study)	⨁◯◯◯ VERY LOW[3]	We are very uncertain about the quality of life change after cross-sex hormones
Suicide/ suicidal ideation assessed with: difference (effect) in suicide or suicidal ideation	Not reported					The effects of cross-sex hormones on suicide/ suicidal ideation are unknown
Suicidality assessed with: change in score from ASQ instrument (higher scores represent greater degree of suicidality) (NICE, 2020b) Mean follow up: 1 year	NA	-0.84 (-1.30 to -0.44)	NA	39 (1 study)	⨁⨁◯◯ LOW[1]	Suicidality scores may decrease by 0.84 points after cross-sex hormones

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Suicidal ideation assessed with: percentage of participants with suicidal ideation measured with PHQ-9 (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants with suicidal ideation decreased by 6% (from 10% at baseline). The authors did not conduct a statistical analysis	NA	50 (1 study)	⨁◯◯◯ VERY LOW[3]	We are very uncertain about the change in percentage of patients in suicidal ideation after cross-sex hormones
Suicide attempts assessed with: not reported (NICE, 2020b) Follow up: not reported	NA	The percentage of people with lifetime suicide attempts was 15%, those with attempts 3 months before treatment was 2%, and those with attempts at follow up was 5%	NA	130 (1 study)	⨁◯◯◯ VERY LOW[3]	We are very uncertain about the percentage of people with suicide attempts after cross-sex hormones
Suicidality/ self-harm assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants requiring treatment was reduced by 31% (from 35% at baseline), which was statistically significant	NA	52 (1 study)	⨁⨁◯◯ LOW[1]	The percentage of participants requiring treatment may be reduced by 31% after cross-sex hormones
Venous thromboembolism assessed with: Risk of VTE	Not reported					The effects of cross-sex hormones on the risk of VTE are unknown

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	**Risk/ mean with cross-sex hormones**				
Venous thromboembolism assessed with: Prevalence among assigned males at birth (Totaro, 2021) Mean follow up: 4.1 years	NA	**20 per 1,000** (10 to 30)	NA	11,542 (18 studies)	⨁⨁⨁◯ MODERATE[4]	The prevalence of VTE among assigned males at birth is probably 2% after cross-sex hormones
Venous thromboembolism assessed with: Prevalence among assigned females at birth (Kotamarti, 2021) Mean follow up: 5.7 years	NA	**6 per 1,000** (CI not reported)[5]	NA	4,218 (8 studies)	⨁⨁⨁◯ MODERATE[6]	The prevalence of VTE among assigned females at birth is probably 0.6% after cross-sex hormones
Breast cancer assessed with: Risk of breast cancer (Fledderus, 2020) Follow up: not reported	Two studies compare the risk of beast cancer between assigned females at birth using versus not using testosterone, and found no differences (0 vs 1 case [total n= 130], and 1 vs 6 [total n=1579]). A third study compared assigned females at birth with non transgender women and found a lower risk in the former (magnitude not reported)		NA	2,938 (3 studies)	⨁⨁◯◯ LOW[7]	The risk of breast cancer may not increase or decrease due to the use of cross-sex hormones

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no cross-sex hormones	Risk/ mean with cross-sex hormones				

ASQ: Ask Suicide-Screening Questions. Range 0-4
BDI-II: Beck Depression Inventory. Range: 0-63
CESD-R: Center for Epidemiological Studies Depression Scale. Range: 0-60
CI: Confidence interval
NA: Not applicable
PHQ-9: Patient Health Questionnaire (PHQ) Modified for Teens. For suicidal ideation, it is a single question (yes/no)
QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire. Range: 15-75
STAI: State-Trait Anxiety Inventory. Range: 0-80

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. Mean change rated down due to risk of bias and imprecision. According to the systematic review authors, the studies had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size)
2. Similar results when this outcome was measured using the Patient Health Questionnaire (PHQ) Modified for Teens in one of the same studies
3. Rated down due to risk of bias, imprecision, and indirectness. According to the systematic review authors, the studies had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size). Finally, 30% of the participants did not have a diagnosis of gender dysphoria.
4. Prevalence rated down due to risk of bias. According to the systematic review authors, only 6 out of the 18 studies (representing 16.5% of the weight of the studies) were at low risk of bias.

5. A meta-analysis of independent studies reported in this systematic review suggested that the prevalence of VTE in non-transgender females at birth was 1.7% (based on 7 studies and 18,748 persons)
6. Prevalence rated down doe to risk of bias. According to the systematic review authors, all studies had at least one domain judged as problematic.
7. Risk rated down 2 levels because of risk of bias. The researchers did not account for confounding in any of the studies.

3. **Surgeries:** We found 15 systematic reviews assessing the effects of gender-affirming surgeries published between 2020 and 2022. We judged 8 as having low methodological quality and 7 as having critically low methodological quality. Details of the assessment are provided in Figure 4. We present the results regarding the effects of surgeries in three parts. First, we describe the effects of all surgeries on mental health outcomes in all patients. Second, we describe the effects of all surgeries on surgical outcomes in assigned females at birth (transgender males). Finally, we describe the effects of all surgeries on surgical outcomes in assigned males at birth (transgender females).

3.1 Effects of surgeries on mental health outcomes: Table 3 summarizes the evidence about the effects of all surgeries on mental health outcomes in all patients. We used information from 2 systematic reviews.[13 14] There were no systematic reviews and studies reporting on gender dysphoria, depression, anxiety, and suicidality. Therefore, the effects of surgeries on these outcomes (when compared to a group of patients with gender dysphoria who do not undergo surgery), or the changes in these outcomes (improvements or deterioration) among patients who undergo surgeries is unknown.

The systematic reviews addressed quality of life and depression, but none of the included studies included a comparison group. Thus, it is unknown whether people with gender dysphoria who undergo surgeries experience more improvement in quality of life or less regret than those with gender dysphoria who do not undergo surgeries.

Studies, however, reported the following outcomes among a group of people with gender dysphoria after undergoing surgeries. The findings are:

- There is low certainty evidence suggesting that the percentage of people who experience regret after surgery is low (1%)
- There is very low certainty evidence about how surgeries affect quality of life (see Table 3 for details)

Figure 4: AMSTAR assessment judgements for systematic reviews addressing gender-affirming surgery

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
Bustos SS 2021																	LOW
Bustos VP 2021																	LOW
Bustos VP 2021b																	LOW
Dunford 2021																	LOW
Eftekhar, 2020																	LOW
Falcone 2021																	CRITICALLY LOW
Hu, 2022																	CRITICALLY LOW
Huayllani 2021																	CRITICALLY LOW
Jolly 2021																	LOW
Nassiri 2020																	CRITICALLY LOW
Oles 2022																	LOW
Oles 2022b																	LOW
Salibian 2021																	CRITICALLY LOW
Sijben 2021																	CRITICALLY LOW
Tay 2021																	CRITICALLY LOW

Figure legend:

Yes

Probably yes

Probably no

No

Not applicable

Table 3: All surgeries compared to no surgeries in young people (<21 years old) with gender dysphoria

Patient or population: young people (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries
Outcomes: Mental health and regret

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Gender dysphoria assessed with: any measure	Not reported					The effects of surgery on gender dysphoria, the changes in gender dysphoria severity after surgery, and the prevalence of gender dysphoria after surgery are unknown
Depression assessed with: any measure	Not reported					The effects of surgery on depression, the changes in depression severity after surgery, and the prevalence of depression after surgery are unknown
Anxiety assessed with: any measure	Not reported					The effects of surgery on anxiety, the changes in anxiety severity after surgery, and the prevalence of anxiety after surgery are unknown
Suicidality assessed with: any measure	Not reported					The effects of surgery on suicidality, the changes in anxiety severity after surgery, and the prevalence of anxiety after surgery are unknown
Quality of life assessed with: difference (effect) in quality of life	Not reported					The effects of surgery on quality of life are unknown
Quality of life assessed with: change in quality of life	Not reported					The change in quality of life after surgery is unknown

Quality of life assessed with: mean score in the Short Form-36 Scale (0-100, higher scores reflect better quality of life) (Eftekhar Ardebili, 2020) Follow up: cross-sectional	NA	59.17 (48.59 to 69.74)[1]	NA	633 (5 studies)	⨁◯◯◯ VERY LOW[2]	We are very uncertain about the quality of life after surgeries
Regret assessed with: difference (effect) in percentage of people with regret	Not reported					The effects of surgery on regret are unknown
Regret assessed with: percentage of people with regret (Bustos, 2021) Mean follow up: 4 years	NA	1% (0 to 2%)[3]	NA	7928 (27 studies)	⨁⨁◯◯ LOW[4]	The percentage of people who experience regret is low

CI: Confidence interval
NA: Not applicable

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. Similar scores for assigned males at birth and assigned females at birth.
2. Mean score rated down for risk of bias and inconsistency. According to the systematic review authors, all studies had concerns related to risk of bias. In addition, the smaller studies showed better quality of life than the larger study.
3. Similar percentage for assigned males at birth and assigned females at birth, and for different types of surgeries (all pooled percentages below 2%).
4. Percentage rated down due to risk of bias and indirectness. According to the authors, many of the studies had moderate or high risk of bias. The mean age of the participants at the time of surgery was higher than the target population. Because it was considered to not have an important effect on the pooled estimate, we did not rate down for statistical heterogeneity

3.2 **Effects of surgeries on assigned females at birth:** Table 4 summarizes the evidence about the effects of all surgeries on surgical outcomes among assigned at birth females. We used information from 3 systematic reviews.[13-17] Due to the nature of the outcomes (i.e. they can only be experienced by people who undergo surgeries), there cannot be studies comparing the outcomes between a group of people with gender dysphoria who undergo surgeries and another who does not.

Studies, therefore, assessed the outcomes among a group of people with gender dysphoria after surgery. The findings are:

- There is low certainty evidence suggesting that the percentage of people who are satisfied after chest surgery is high (92%)
- There is very low certainty evidence about the rate of surgical complications after chest surgery
- There is very low certainty evidence about the percentage of people who are satisfied, and the rate of surgical complications after bottom surgeries (see Table 4 for details)

Table 4: All surgeries compared to no surgeries in assigned females at birth (<21 years old) with gender dysphoria

Patient or population: assigned females at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Chest surgery						
Satisfaction assessed with: percentage of people who reported being satisfied (Bustos VP, 2020b) Range of follow up: 6 weeks to 46 months[1]	NA	92% (88% to 96%)[2]	NA	733 (14 studies)	⨁⨁◯◯ LOW[3]	The percentage of people who reports being satisfied may be 92%
Surgical complications assessed with: rate of complications across patients (Oles, 2022) Range of follow up: 8 weeks to 1 year	NA	16.8% Range (5.5% to 80.0%)	NA	1255 (7 studies)	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the rate of surgical complications
Reoperation assessed with: rate of reoperation across patients (Oles, 2022) Range of follow up: 8 weeks to 1 year	NA	6.2% Range (0.7% to 11.2%)	NA	1214 (6 studies)	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the rate of reoperation
Bottom surgery						

Table 4: All surgeries compared to no surgeries in assigned females at birth (<21 years old) with gender dysphoria

Patient or population: assigned females at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Satisfaction assessed with: percentage of people who reported being satisfied (Oles, 2022b) Range of follow up: 6 weeks to 46 months	NA	89.6% (45% to 100%)[5]	NA	1458 (27 studies)	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the percentage of people who reports being satisfied
Surgical complications-Major assessed with: percentage of people experiencing major complications (Oles, 2022b) follow up: not reported	NA	The percentage was - 2.3% (range 0 to 20%) experiencing total flap loss - 19.5% (range 0 to 72%) experiencing prosthesis issues - 24.5% (range 0 to 86%) experiencing urethral issues	NA	3177 (42 studies)[6]	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the percentage of people who experience major surgical complications
Surgical complications-Minor assessed with: percentage of people experiencing major complications (Oles, 2022b) follow up: not reported	NA	The percentage varied from 9.3% (range 0% to 45.5%) experiencing donor site issues, to 24% (range 10 to 93%) experiencing urethral issues[7]	NA	4466 (52 studies)[8]	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the percentage of people who experience minor surgical complications

Table 4: All surgeries compared to no surgeries in assigned females at birth (<21 years old) with gender dysphoria

Patient or population: assigned females at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Reoperation assessed with: rate of reoperation across patients (Oles, 2022b) follow up: not reported	NA	27.6% Range (2.5% to 40%)	NA	1624 (15 studies)	⨁◯◯◯ VERY LOW[4]	We are very uncertain about the percentage of people who undergo reoperations

CI: Confidence interval
NA: Not applicable

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. Studies used different scales to assess satisfaction
2. The percentage was similar when the analysis was done by type of surgery and by follow up time (< 1 year vs 1 year or more). Another systematic review (Oles, 2022) also investigated this outcome, and reported a very similar percentage of satisfaction (91.8%, range 73% to 100%)
3. Percentage of patients satisfied rated down due to risk of bias and indirectness. According to the systematic review authors, several studies were judged at moderate and high risk of bias. In addition, the median of the mean age of patients included in the studies was 28 years
4. Rated down due to risk of bias, inconsistency/ imprecision, and indirectness. Even though the review authors did not assess risk of bias, these studies were included in other systematic reviews in which the authors judged several of them at high risk of bias. The studies report inconsistent results (some high and other low rates). The patients are older than the target population.
5. Results for phalloplasty. Similar results for metoidioplasty (91.3%).

6. People and studies for urethral complications. 2671 people (37 studies) for prosthesis issues, and 1548 people (22 studies) for total flap loss.
7. Percentage of wound dehiscence 9.8% (range, 2.9% to 75%), percentage of infection/ partial necrosis 10.3% (range, 0 to 45.8%), percentage of prosthesis issues 14.2% (range, 1.6 to 41.9%), percentage of incontinence 15.3% (range, 5.4% to 59.1%)
8. People and studies for infection/ partial necrosis. 2389 people (31 studies) for urethral issues, 1736 people (17 studies) for wound dehiscence, 1080 (10 studies) for prosthesis issues, 1053 people (8 studies) for donor site issues, 131 people (3 studies) for incontinence

3.3 **Effects of surgeries on assigned males at birth**: Table 5 summarizes the evidence about the effects of all surgeries on surgical outcomes among assigned at birth males. We used information from 3 systematic reviews.[16 18 19] Due to the nature of the outcomes (i.e. they can only be experienced by people who undergo surgeries), there cannot be studies comparing the outcomes between a group of people with gender dysphoria who undergo surgeries and another who does not.

Studies, therefore, assessed the outcomes among a group of people with gender dysphoria after surgery. The findings are:

- There is low certainty evidence suggesting that the percentage of people who are satisfied after vaginoplasty is high (91%)
- There is very low certainty evidence about the percentage of people who are satisfied, the rate of complications, and the rate of reoperations after chest surgery (see Table 5 for details)
- There is low certainty evidence suggesting that the percentage of people who have regret after vaginoplasty is low (2%)
- There is very low certainty evidence about the rate of complications and the rate of reoperations after vaginoplasty (see Table 5 for details)

Table 5: All surgeries compared to no surgeries in assigned males at birth (<21 years old) with gender dysphoria

Patient or population: assigned males at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Chest surgery						
Satisfaction assessed with: percentage of people who reported being satisfied (Oles 2022) Range of follow up: 12 months to 17 years	NA	Range 75% (80/107) to 95% (33/35)[1]	NA	142 (2 studies)	⨁◯◯◯ VERY LOW[2]	We are very uncertain about the percentage of people who report being satisfied
Surgical complications assessed with: rate of complications across patients (Oles 2022) Range of follow up: 2 weeks to 16 years	NA	The complication rates were: - 3.8% (range 0% to 5.5%) of capsular contracture - 2.2% of major hematoma - 2.2% of implant extrusion[3]	NA	432 (5 studies)	⨁◯◯◯ VERY LOW[2]	We are very uncertain about the rate of surgical complications
Reoperation assessed with: rate of reoperation across patients (Oles 2022) Range of follow up: Not reported	NA	8.6% Range (4.4% to 10.4%)	NA	291 (2 studies)	⨁◯◯◯ VERY LOW[2]	We are very uncertain about the rate of reoperation
Bottom surgery						

Table 5: All surgeries compared to no surgeries in assigned males at birth (<21 years old) with gender dysphoria

Patient or population: assigned males at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Satisfaction assessed with: percentage of people who reported being satisfied for overall outcomes (Bustos SS, 2021) Range of follow up: 1 week to 11.3 years	NA	91% (81% to 98%)[4]	NA	1230 (12 studies)	⨁⨁◯◯ LOW[5]	The percentage of people who report being satisfied with overall outcomes may be 91%
Regret assessed with: percentage of people who reported regret (Bustos SS, 2021) Range of follow up: 2 months to 24.1 years	NA	2% (1% to 3%)	NA	1137 (15 studies)	⨁⨁◯◯ LOW[6]	The percentage of people who report regret may be 2%
Surgical complications assessed with: rate of complications across patients (Bustos SS, 2021) Range of follow up: 3 weeks to 24.1 years	NA	The complication rates were: - 1% (95% CI, <0.1% to 2%) of fistula - 11% (95% CI, 8% to 14%) of stenosis and/or strictures - 4% (95% CI, 1% to 9%) of tissue necrosis - 3% (95% CI, 1% to 4%) of prolapse[7]	NA	4196 (42 studies)[3]	⨁◯◯◯ VERY LOW[8]	We are very uncertain about the rate of surgical complications

Table 5: All surgeries compared to no surgeries in assigned males at birth (<21 years old) with gender dysphoria

Patient or population: assigned males at birth (<21 years old) with gender dysphoria
Intervention: surgeries
Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens
	Risk / mean with no surgery	Risk/ mean with surgery				
Reoperation assessed with: rate of reoperation across patients (Tay, 2021) Range of follow up: 6 weeks to 14.8 months	NA	One study reported a surgical revision rate of 9% (1/11 patients), and a second study reported that 13% (19/145) patients required repeat surgery due to complications.	NA	156 (2 studies)	⨁◯◯◯ VERY LOW[9]	We are very uncertain about the percentage of people who undergo reoperations

CI: Confidence interval
NA: Not applicable

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. Another systematic review, Sijben 2021, reported satisfaction from 3 additional studies: 82% (113/138) were satisfied or very satisfied, 93% (32/34) were happier and more satisfied with their chest, and 79% (28/36) were very satisfied with the overall cosmetic result (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
2. Rated down due to risk of bias, indirectness (the included studies were not restricted to youth or young adults), and imprecision (too few participants included, not meeting optimal information size).

3. Another systematic review, Sijben 2021, reported similar ranges for rates of complication requiring reoperation from 7 studies (835 patients): capsular contraction (range 0.0-5.6%), asymmetry (3.6%), hematoma (range 0.0-2.9%), infection (range 0.0-0.9%), striae distensae (0.7%), implant rupture (0.7%), abscess (0.4%), scarring (0.0%), hypersensitivity (0.0%), and numbness (0.0%) (very low certainty of evidence due to risk of bias, imprecision, and indirectness)
4. Bustos SS *et al.* 2021 additionally reported on satisfaction for functional (87%, 95% CI 77% to 94%) and aesthetic (90%, 95% CI 84% to 94%) outcomes. Another systematic review and meta-analysis, Oles 2022b, similarly reported that 92.3% (range 23.1% to 100%) of patients (2410/2601) were satisfied after vaginoplasty (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
5. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), and indirectness as the included studies were not restricted to youth or young adults. We did not rate down for imprecision or inconsistency despite high I^2 values as a satisfaction rate of 80% or above was deemed as a minimum threshold for clinical importance.
6. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), and indirectness as the included studies were not restricted to youth or young adults.
7. Another systematic review, Oles 2022b, similarly reported the percentage of patients experiencing complications from 51 studies, ranging from 2.4% to 12.0% (range 0% to 88%) for minor complications (intraoperative injury, wound dehiscence, superficial necrosis, infection, urinary issues, vaginal prolapse, stenosis, and bleeding) and 1.6% to 2.1% (range 0% to 31%) for major complications (flap/graft necrosis and infection) after genitoplasty (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
8. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), imprecision and inconsistency, with wide confidence intervals and I^2 values ranging from 65.8% to 94.3%, and indirectness as the included studies were not restricted to youth or young adults.
9. Rated down due to risk of bias, indirectness (the age range of patients in the included studies was 24 to 39 years; the studies included were restricted to those that investigated the use of peritoneum in neovagina construction), and imprecision (too few participants included, not meeting optimal information size).

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Results from search for studies not included in the systematic reviews: After screening 1854 records found through our searches, we found 10 eligible studies (figure 5). From these, 8 were comparative observational studies[20-27] and 2 were non- comparative[28 29]. We provide reasons for excluding studies in appendix 2.

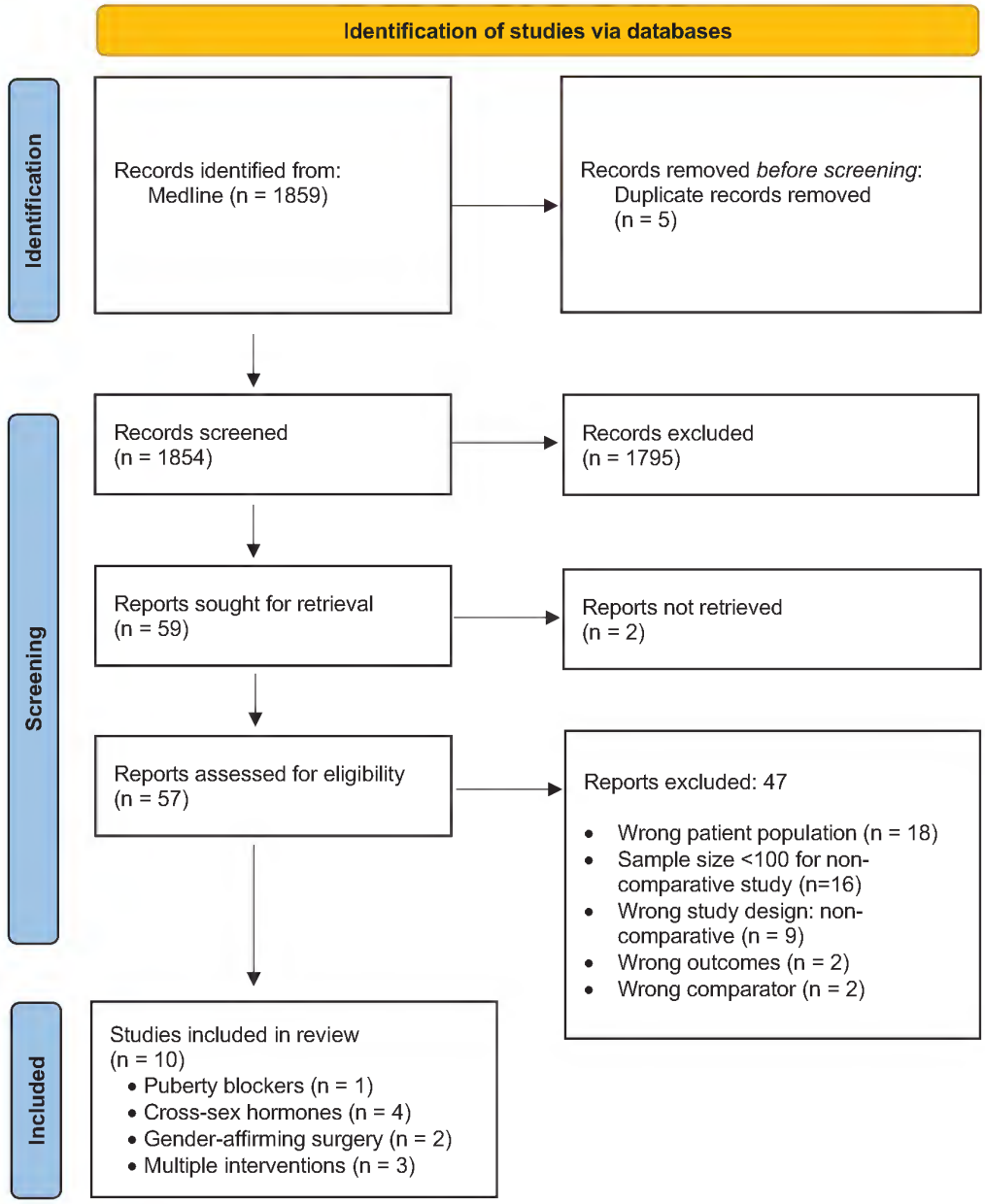

Figure 5: PRISMA flow diagram for the selection of primary studies. *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

None of the studies were judged as likely to importantly change the conclusions obtained from the systematic reviews (Tables 6 and 7). The main limitations of the comparative studies were risk of bias concerns (Figures 6 and 7) due to confounding, classification of intervention, and missing data; as well as small sample sizes. Although non-comparative studies were at lower risk of bias, because their results were consistent with those of the included evidence, they were also judged as unlikely to change the conclusions importantly.

Table 6: Characteristics of eligible comparative observational studies

Study ID	Sample size*	Study design	Intervention	Comparator	Outcomes measured	Likely to change conclusions	Reasons
VanDerMiesen, 2020	450	Retrospective cohort study	Puberty blockers	Waiting for puberty blockers	Self-harm/ suicidality, internalizing behaviors	No	Reports a small benefit on suicidality and moderate on internalizing behaviours, but high risk of bias
Becker-Hebly, 2021	75	Prospective cohort study	1. Puberty blockers 2. Cross-sex hormones 3. Surgery	No medical intervention yet; psychosocial intervention only	Health-related quality of life	No	Critical risk of bias (missing data due to low response rate, and confounding). Reports small benefit in mean change score for mental and physical dimension QoL as compared to no medical treatment. Imprecision; the 95% CIs for mean change scores are wide.
Green, 2021	3235	Cross-sectional study	Cross-sex hormones	Would like to take cross-sex hormones	Depression, suicidality	No	Critical risk of bias, no follow up of patients (measurement of current outcomes and not adjusting for baseline)
Tordoff, 2022	84	Prospective cohort study	1. Puberty blockers 2. Cross-sex hormones	No intervention	Depression, anxiety, suicidal thoughts	No	Moderate risk of bias, small sample size
Turban, 2022	9341	Cross-sectional study	Cross-sex hormones	Desired but never accessed gender affirming hormones	Suicidal ideation, suicidal attempt	No	Critical risk of bias, no follow up of patients (measurement of current outcomes and not adjusting for baseline)
Grannis, 2021	47	Cross-sectional study	Cross-sex hormones	No intervention yet	Anxiety, depression	No	Critical risk of bias, no follow up of patients, small sample size
Fontanari, 2020	350	Cross-sectional study	1. Cross-sex hormones 2. Cross-sex hormones or surgery	1. Waiting for cross-sex hormones 2. No intervention	Anxiety, depression, gender distress	No	Critical risk of bias (confounding, self-reported classification of interventions). Online cross-sectional survery reported small benefit in anxiety and depression mean scores, and little to no effect on gender distress with cross-sex hormones and/or surgery. Non-randomized comparative study provides very low certainty evidence due to

							very serious risk of bias and serious imprecision (95% CIs include little to no effect)
Castelo-Branco, 2021	205	Cross-sectional study	Cross-sex hormones	No intervention	Anxiety, depression	No	Critical risk of bias due to confounding (non-adjusted analysis). Reported no difference observed in anxiety and depression mean scores (Symptom Checklist-90-Revised scale) between groups. Non-randomized comparative study provides low certainty evidence.

*Considered the number of participants relevant to the questions of this report, not all people included in the studies

Table 7: Characteristics of eligible non- comparative observational studies

Study ID	Sample size	Intervention	Outcomes measured	Likely to change conclusions	Reasons
Bordas, 2021	813	FtM bottom surgery	Surgical complications, satisfaction	No	Reports rate of complications (10.5%) and satisfaction (79% totally satisfied, 20% mainly satisfied) within range of effects reported by studies already included in systematic reviews. Unlikely to reduce imprecision and inconsistency within body of evidence (3177 and 1458 people, respectively) of non-comparative studies (42 and 27, respectively) to increase certainty of evidence
Elias, 2022	110	FtM top surgery	Complications	No	Reports rate of complications (16%) and revision surgery (5%), which is consistent with the rates reported in the studies included. Unlikely to increase the certainty of evidence

Figure 6: Risk of bias judgements for comparative studies

Study ID	Intervention	Confounding	Classification of the intervention	Deviations from intended interventions	Missing data	Measurement of outcome	Overall
Becker-Hebly, 2021	Puberty blockers, cross-sex hormones, or surgery						CRITICAL
Castelo-Branco, 2021	Cross-sex hormones						CRITICAL
Fontanari, 2020	Cross-sex hormones, cross-sex hormones or surgery						CRITICAL
Grannis, 2021	Cross-sex hormones						CRITICAL
Green, 2021	Cross-sex hormones						CRITICAL
Tordoff, 2022	Puberty blockers, cross-sex hormones						MODERATE
Turban, 2022	Cross-sex hormones						CRITICAL
Van Der Miesen, 2020	Puberty blockers						SERIOUS

Figure legend:

Low

Moderate

Serious

Critical

Unclear

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Figure 7: Risk of bias judgements for non-comparative studies

Study ID	Intervention	Representativeness of sample	Classification of intervention	Deviation from intended interventions	Missing data	Measurement of outcome	Overall
Bordas, 2021	FtM bottom surgery						LOW
Elias, 2022	FtM top surgery						MODERATE

Figure legend:

Low

Moderate

High

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29. Elias N, Rysin R, Kwartin S, et al. Breaking the Binary: The Approach to Chest Masculinizing Gender-Affirming Surgery in Trangender Men. *The Israel Medical Association journal : IMAJ* 2022;24(1):20-24.

ID	Study	Reason
#534	Abu-Ghname 2020	Wrong population: non transgender men
#434	Aires 2022	Wrong interventions: Other type of surgery: glottoplasty
#514	Angus 2021	Wrong outcomes: It does not include any outcome of interest. Includes: serum total testosterone concentration, body fat redistribution, breast development, and facial/body hair reduction
#318	Baddredine 2022	Wrong intervention. Continuing vs stopping estrogen during perioperative period of vaginoplasty
#40	Baram 2019	Wrong outcomes: only clinical outcomes are sperm count, testicular histology, hormone levels, etc.
#145	Barcelos 2022	Wrong outcomes: sexual satisfaction, desire, and function outcomes only
#60	Boczar 2021	No outcome data
#386	Bouman 2014	Wrong population: unclear that more than 80% are transgender
#208	Bustos 2021	Wrong intervention: niple areola reconstruction
#54	Connelly 2021	Wrong outcomes: Blood pressure
#43	Coon 2022	Wrong intervention: facial gender surgery
#34	D'Angelo 2018	Wrong design: narrative review
#165	Delgado-Ruiz 2019	Wrong outcomes: bone density
#355	Escandon 2022	Other type of surgery: facial surgery
#129	Fighera 2019	Wrong outcomes: bone mass
#597	Hembree 2017	Practice guideline, does not report the methods/ results of the systematic review in details
#120	Kakadekar 2021	Wrong outcomes: histological findings
#451	Kennedy 2021	Wrong intervention: self administered hormones
#375	Kloer 2021	Wrong outcomes: sexual health and satisfaction outcomes only
#439	Kovar 2019	More than 20% participants did not have gender dysphoria
#297	Kristensen 2021	Wrong outcomes: agression and hostility
#637	Leclere 2015	Wrong design: commentary of a systematic review
#293	Miranda 2021	Published in abstract format only
#624	Morrison 2016	Wrong intervention: facial feminization surgery
#270	Narayan 2021	Wrong design: narrative review
#119	Nolan 2019	Wrong intervention: phonosurgery
#167	Patel 2021	Wrong intervention: facial hair transplantation
#287	Ray 2020	Wrong population: cisgender is the population of interest, transgender included as indirect evidence and not in a systematic manner
#518	Rozga 2020	Published in abstract format only
#265	Sariyaka 2017	Wrong population: More than 20% participants did not have gender dysphoria
#35	Sayegh 2019	Wrong intervention: facial masculinization surgery
#124	Schwarz 2017	Wrong intervention: laryngeal surgery

#97	Siringo 2021	Wrong intervention: facial feminization surgery
#253	Song 2016	Wrong intervention: phonosurgery
#250	Song 2017	Wrong intervention: phonosurgery
#104	Spanos 2020	Wrong outcomes: lean mass, fat mass or insulin resistance
#257	Therattil 2017	Wrong intervention: thyroid chartilage reduction surgery
#328	Tirrell 2022	Wrong intervention: facial feminization surgery
#676	Traish 2010	Wrong design: narrative review
#279	VanDamme 2017	Wrong intervention: voice pitch raising surgery
#171	Vellho 2017	Wrong outcomes: BMI, blood pressure, hematocrit, hemoglobin, lipid profile, and liver enzymes
#112	Wilson 2020	Wrong outcomes: prolactine related outcomes (levels, hyperprolactinemia, prolactinoma)
#245	Worth 2018	Unable to access full text
#122	Ziegler 2018	Wrong outcomes: voice parameters and satisfaction with voice
#499	Zucker 2021	Unable to access full text

ID	Study	Reason
#1458	Al-Tamimi 2019	Wrong patient population
#287	Al-Tamimi 2020	Wrong study design: non comparative
#403	Alcon 2021	Wrong study design: non comparative
#214	Aldridge 2021	Wrong study design: non comparative
#54	Almazan 2021	Wrong patient population
#1387	Boas 2019	Wrong patient population
#1323	Branstrom 2020	Wrong patient population
#1447	Breidenstein 2019	Wrong study design: non comparative
#114	Briles 2022	Insufficient Sample Size <100
#1804	Butler 2019	Wrong patient population
#716	Carmichael 2021	Wrong study design: non comparative
#622	Cocchetti 2021	Wrong outcomes
#1067	Coon 2020	Wrong patient population
#1835	Cristofari 2019	Wrong patient population
#1486	Cuccolo 2019	Wrong patient population
#1276	deBlok 2020	Wrong patient population
#577	deRooij 2021	Wrong patient population
#1625	DeWolf 2019	Wrong patient population
#1759	Djordjevic 2019	Wrong patient population
#244	Falcone 2020	Insufficient Sample Size <100
#258	FosterSkewis 2021	Wrong comparator
#1583	Gallagher 2019	Wrong patient population
#139	Gumussoy 2022	Wrong study design: non comparative
#515	Hisle-Gorman 2021	Wrong study design: non comparative
#350	Hougen 2021	Insufficient Sample Size <100
#1007	Meyer 2020	Wrong study design: non comparative
#499	Miller 2021	Wrong patient population
#621	Mullins 2021	Wrong study design: non comparative
#1653	Naeimi 2019	Insufficient Sample Size <100
#1691	Namba 2019	Insufficient Sample Size <100
#1770	Neuville 2019	Insufficient Sample Size <100
#623	Neuville 2021	Insufficient Sample Size <100
#644	Nieder 2021	Insufficient Sample Size <100
#1624	Nikkels 2019	Wrong patient population
#353	Opsomer 2021	Wrong patient population
#1306	Papadopulos 2020	Wrong comparator
#640	Papadopulos 2021	Insufficient Sample Size <100
#1472	Pigot 2019	Wrong patient population
#899	Pigot 2020	Insufficient Sample Size <100
#1212	Segev-Becker 2020	Insufficient Sample Size <100
#1351	Staples 2020	Wrong outcomes
#645	Staud 2021	Insufficient Sample Size <100
#864	Terrier 2020	Insufficient Sample Size <100
#1083	vanderSluis 2020	Insufficient Sample Size <100

#1204	Veerman 2020	Insufficient Sample Size <100
#1409	Watanabe 2019	Wrong patient population
#512	Waterschoot 2021	Insufficient Sample Size <100

ATTACHMENT D

THE SCIENCE OF GENDER DYSPHORIA AND TRANSSEXUALISM

REPORT SUBMITTED TO THE

FLORIDA AGENCY FOR HEALTHCARE ADMINISTRATION

JAMES M. CANTOR, PHD

17 MAY 2022

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I. Background & Credentials

1. I am a research scientist and clinical psychologist and am currently the Director of the Toronto Sexuality Centre in Canada. For my education and training, I received my Bachelor of Science degree from Rensselaer Polytechnic Institute, where I studied mathematics, physics, and computer science. I received my Master of Arts degree in psychology from Boston University, where I studied neuropsychology. I earned my Doctoral degree in psychology from McGill University, which included successfully defending my doctoral dissertation studying the effects of psychiatric medication and neurochemical changes on sexual behavior, and included a clinical internship assessing and treating people with a wide range of sexual and gender identity issues.

2. Over my academic career, my posts have included Senior Scientist and Psychologist at the Centre for Addiction and Mental Health (CAMH), Head of Research for CAMH's Sexual Behaviour Clinic, Associate Professor of Psychiatry on the University of Toronto Faculty of Medicine, and Editor-in-Chief of the peer reviewed journal, *Sexual Abuse*. That journal is one of the top-impact, peer-reviewed journals in sexual behavior science and is the official journal of the Association for the Treatment of Sexual Abusers. In that appointment, I was charged to be the final arbiter for impartially deciding which contributions from other scientists in my field merited publication. I believe that appointment indicates not only my extensive experience evaluating scientific claims and methods, but also the faith put in me by the other scientists in my field. I have also served on the Editorial Boards of the *Journal of Sex Research*, the *Archives of Sexual Behavior*, and *Journal of Sexual Aggression*. Thus, although I cannot speak for other scientists, I regularly interact with and am routinely exposed to the views and opinions of most of the scientists active in our field today, within the United States and throughout the world.

3. My scientific expertise spans the biological and non-biological development

of human sexuality, the classification of sexual interest patterns, the assessment and treatment of atypical sexualities, and the application of statistics and research methodology in sex research. I am the author of over 50 peer-reviewed articles in my field, spanning the development of sexual orientation, gender identity, hypersexuality, and atypical sexualities collectively referred to as *paraphilias*. I am the author of the past three editions of the gender identity and atypical sexualities chapter of the *Oxford Textbook of Psychopathology*. These works are now routinely cited in the field and are included in numerous other textbooks of sex research.

4. I began providing clinical services to people with gender dysphoria in 1998. I trained under Dr. Ray Blanchard of CAMH and have participated in the assessment and treatment of over one hundred individuals at various stages of considering and enacting both transition and detransition, including its legal, social, and medical (both cross-hormonal and surgical) aspects. My clinical experience includes the assessment and treatment of several thousand individuals experiencing other atypical sexuality issues. I am regularly called upon to provide objective assessment of the science of human sexuality by the courts (prosecution and defense), professional media, and mental health care providers.

5. A substantial proportion of the existing research on gender dysphoria comes from two clinics, one in Canada and one in the Netherlands. The CAMH gender clinic (previously, Clarke Institute of Psychiatry) was in operation for several decades, and its research was directed by Dr. Kenneth Zucker. I was employed by CAMH between 1998 and 2018. Although I was a member of the hospital's adult forensic program, I remained in regular contact with members of the CAMH child psychiatry program (of which Dr. Zucker was a member), and we collaborated on multiple research projects.

II. Summary of Conclusions

- The scientific research consistently demonstrates that there is more than one distinct phenomenon that can lead to gender dysphoria. These types are distinguished by differing epidemiological and demographic patterns, unique psychological and behavioral profiles, and differing responses to the treatment options.
- Studies show that otherwise mentally healthy adults—undergoing thorough assessment (1–2 year Real Life Experience) and supervised by clinics engaged in gate-keeping roles—adjust well to life as the opposite sex.
- Regarding pre-pubescent children with gender dysphoria, there have been 11 outcomes studies. All 11 reported the majority of children to cease to feel dysphoric by puberty. They typically report being gay or lesbian instead.
- Regarding pubescent and adolescent age minors, there have been (also) 11 follow-up studies of puberty blockers and cross-sex hormones. In four, mental health failed to improve at all. In five, mental health improved, but because psychotherapy and medical interventions were both provided, which one caused the improvement could not be identified. The two remaining studies employed methods that did permit psychotherapy effects to be distinguished from medical effects, and neither found medical intervention to be superior to psychotherapy-only.
- The research importantly distinguishes completed suicides—which occur primarily in biological males and involve the intent to die—from suicidal ideation, gestures, and attempts—which occur primarily in biological females and represent psychological distress and cries for help. The evidence is minimally consistent with transphobia being the predominant cause of suicidality. The evidence is very strongly consistent with the hypothesis that other mental health issues, such as Borderline Personality Disorder (BPD), cause suicidality and unstable identities, including gender identity confusion.
- The international consensus of public health care services is that there remains no evidence to support medicalized transition for youth. The responses in the U.S. stand in stark contrast with Sweden, Finland, France, and the United Kingdom, which are issuing increasingly restrictive statements and policies, including bans on all medical transition of minors.

III. Science of Gender Dysphoria and Transsexualism

6. One of the most widespread public misunderstandings about transsexualism and people with gender dysphoria is that all cases of gender dysphoria represent the same phenomenon; however, the clinical science has long and consistently demonstrated that gender dysphoric children (cases of *early-onset* gender dysphoria) do not represent the same phenomenon as adult gender dysphoria

(cases of *late-onset* gender dysphoria),[1] merely attending clinics at younger ages. That is, gender dysphoric children are not simply younger versions of gender dysphoric adults. They differ in every known regard, from sexual interest patterns, to responses to treatments. A third presentation has recently become increasingly observed among people presenting to gender clinics: These cases appear to have an onset in adolescence in the absence of any childhood history of gender dysphoria. Such cases have been called adolescent-onset or "rapid-onset" gender dysphoria (ROGD). Very many public misunderstandings and expert misstatements come from misattributing evidence or personal experience from one of these types to another.

A. Adult-Onset Gender Dysphoria

7. People with adult-onset gender dysphoria typically attend clinics requesting transition services in mid-adulthood, usually in their 30s or 40s. Such individuals are nearly exclusively biological males.[2] They typically report being sexually attracted to women and sometimes to both men and women. Some cases profess asexuality, but very few indicate any sexual interest in or behavior involving men.[3] Cases of adult-onset gender dysphoria are typically associated with a sexual interest pattern (medically, a *paraphilia*) involving themselves in female form.[4]

1. Outcome Studies of Transition in Adult-Onset Gender Dysphoria

8. Clinical research facilities studying gender dysphoria have repeatedly reported low rates of regret (less than 3%) among adult-onset patients who underwent complete transition (*i.e.*, social, plus hormonal, plus surgical transition). This has been widely reported by clinics in Canada,[5] Sweden,[6] and the Netherlands.[7]

9. Importantly, each of the Canadian, Swedish, and Dutch clinics for adults

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1 Blanchard, 1985.
2 Blanchard, 1990, 1991.
3 Blanchard, 1988.
4 Blanchard 1989a, 1989b, 1991.
5 Blanchard, *et al.*, 1989.
6 Dhejneberg, *et al.*, 2014.
7 Wiepjes, *et al.*, 2018.

with gender dysphoria all performed "gate-keeping" procedures, disqualifying from medical services people with mental health or other contraindications. One would not expect the same results to emerge in the absence of such gate-keeping or when gate-keepers apply only minimal standards or cursory assessment.

10. An important caution applies to interpreting these results: The side-effect of removing these people from the samples of transitioners is that if a researcher compared the average mental health of individuals coming into the clinic with the average mental health of individuals going through medical transition, then the post-transition group would appear to show a substantial improvement, even though transition had *no effect at all*: The removal of people with poorer mental health created the statistical illusion of improvement among the remaining people.

2. Mental Health Issues in Adult-Onset Gender Dysphoria

11. The research evidence on mental health issues in gender dysphoria indicates it to be different between adult-onset versus adolescent-onset versus prepubescent-onset types. The co-occurrence of mental illness with gender dysphoria in adults is widely recognized and widely documented.[8] A research team in 2016 published a comprehensive and systematic review of all studies examining rates of mental health issues in transgender adults.[9] There were 38 studies in total. The review indicated that many studies were methodologically weak, but nonetheless demonstrated (1) that rates of mental health issues among people are highly elevated both before *and after* transition, (2) but that rates were less elevated among those who completed transition. Analyses were not conducted in a way so as to compare the elevation in mental health issues observed among people newly attending clinics to improvement after transition. Also, several studies showed more than 40% of patients to become "lost to follow-up." With attrition rates that high, it is unclear to what

[8] *See, e.g.*, Hepp, *et al.*, 2005.
[9] Dhejne, *et al.*, 2016.

extent the information from the remaining participants would accurately reflect the whole population. The very high rate of "lost to follow-up" leaves open the possibility of considerably more negative results overall.

12. The long-standing and consistent finding that gender dysphoric adults continue to show high rates of mental health issues after transition indicates a critical point: To the extent that gender dysphoric children resemble adults, we should not expect mental health to improve as a result of transition—that is, transition does not appear to be what causes mental health improvement. Rather, mental health issues should be resolved before any transition, as has been noted in multiple standards of care documents, as detailed in their own section of this report.

B. Childhood Onset (Pre-Puberty) Gender Dysphoria

1. Follow-up Studies Show Most Children Desist by Puberty

13. Prepubescent children (and their parents) have been approaching mental health professionals for help with their unhappiness with their sex and belief they would be happier living as the other for many decades. The large majority of childhood onset cases of gender dysphoria occur in biological males, with clinics reporting 2–6 biological male children to each female.[10]

14. In total, there have been 11 outcomes studies of these children, listed in Appendix 1. In sum, despite coming from a variety of countries, conducted by a variety of labs, using a variety of methods, all spanning four decades, every study without exception has come to the identical conclusion: Among prepubescent children who feel gender dysphoric, the majority cease to want to be the other gender over the course of puberty—ranging from 61–88% desistance across the large, prospective studies. Such cases are often referred to as "desisters," whereas children who continue to feel gender dysphoric are often called "persisters."

15. Notably, in most cases, these children were receiving professional

[10] Cohen-Kettenis, *et al.*, 2003; Steensma, *et al.*, 2018; Wood, *et al.*, 2013.

psychosocial support across the study period aimed, not at affirming cross-gender identification, but at resolving stressors and issues potentially interfering with desistance. While beneficial to these children and their families, the inclusion of therapy in the study protocol represents a complication for the interpretation of the results: It is not possible to know to what extent the outcomes were influenced by the psychosocial support or would have emerged regardless. In science, this is referred to as a confound.

16. While the absolute number of those who present as prepubescent children with gender dysphoria and "persist" through adolescence is very small in relation to the total population, persistence in some subjects was observed in each of these studies. Thus, a clinician cannot take either outcome for granted.

17. It is because of this long-established and unanimous research finding of desistance being probable but not inevitable, that the "watchful waiting" method became the standard approach for assisting gender dysphoric children. The balance of potential risks to potential benefits is very different for groups likely to desist versus groups unlikely to desist: If a child is very likely to persist, then taking on the risks of medical transition might be more worthwhile than if that child is very likely to desist in transgender feelings.

18. The consistent observation of high rates of desistance among pre-pubertal children who present with gender dysphoria demonstrates a pivotally important—yet often overlooked—feature: because gender dysphoria so often desists on its own, clinical researchers cannot assume that therapeutic intervention cannot facilitate or speed desistance for at least some patients. That is, gender identity is not the same as sexual orientation, and it cannot be assumed that gender identity is as unchangeable as is sexual orientation. Such is an empirical question, and there has not yet been any such study.

19. It is also important to note that research has not yet identified any reliable

procedure for discerning which children who present with gender dysphoria will persist, as against the majority who will desist, absent transition and "affirmation." Such a method would be valuable, as the more accurately that potential persisters can be distinguished from desisters, the better the risks and benefits of options can be weighted. Such "risk prediction" and "test construction" are standard components of applied statistics in the behavioral sciences. Multiple research teams have reported that, on average, groups of persisters are somewhat more gender non-conforming than desisters, but not so different as to usefully predict the course of a particular child.[11]

20. In contrast, one research team (the aforementioned Olson group) claimed the opposite, asserting that they developed a method of distinguishing persisters from desisters, using a single composite score representing a combination of children's "peer preference, toy preference, clothing preference, gender similarity, and gender identity."[12] They reported a statistical association (mathematically equivalent to a correlation) between that composite score and the probability of persistence. As they indicated, "Our model predicted that a child with a gender-nonconformity score of .50 would have roughly a .30 probability . . . of socially transitioning. By contrast, a child with gender-nonconformity score of .75 would have roughly a .48 probability."[13] Although the Olson team declared that "social transitions may be predictable from gender identification and preferences,"[14] their actual results suggest the opposite: The gender-nonconforming group who went on to transition (socially) had a mean composite score of .73 (which is less than .75), and the gender-nonconforming group who did not transition had a mean composite score of .61, also less than .75.[15] Both of those are lower than the value of .75, so both of those would be more likely than not

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11 Singh, *et al.* (2021); Steensma *et al.*, 2013.
12 Rae, *et al.*, 2019, at 671.
13 Rae, *et al.*, 2019, at 673.
14 Rae, *et al.*, 2019, at 669.
15 Rae, *et al.*, 2019, Supplemental Material at 6, Table S1, bottom line.

to desist, rather than to proceed to transition. That is, Olson's model does not distinguish likely from unlikely to transition; rather, it distinguishes unlikely from even less likely to transition.

21. Although it remains possible for some future discovery to yield a method to identify with sufficient accuracy which gender dysphoric children will persist, there does not exist such a method at the present time. Moreover, in the absence of long-term follow-up, it cannot be known what proportions come to regret having transitioned and then *de*transition. Because only a minority of gender dysphoric children persist in feeling gender dysphoric in the first place, "transition-on-demand" increases the probability of unnecessary transition and unnecessary medical risks.

2. "Watchful Waiting" and "The Dutch Protocol"

22. It was this state of the science—that the majority of prepubescent children will desist in their feelings of gender dysphoria and that we lack an accurate method of identifying which children will persist—that led to the development of a clinical approach, The Dutch Protocol,[16] including its "Watchful Waiting" period. Internationally, the Dutch Protocol remains the most empirically supported protocol for the treatment of children with gender dysphoria.

23. The purpose of the protocol was to compromise the conflicting needs among: clients' initial wishes upon assessment, the long-established and repeated observation that those wishes will change in the majority of (but not in all) childhood cases, and that cosmetic aspects of medical transition are perceived to be better when they occur earlier rather than later.

24. The Dutch Protocol was developed over many years by the Netherlands' child gender identity clinic, incorporating the accumulating findings from their own research as well as those reported by other clinics working with gender dysphoric

[16] Delemarre-van de Waal & Cohen-Kettenis (2006).

children. They summarized and explicated the approach in their peer-reviewed report, *Clinical management of gender dysphoria in children and adolescents: The Dutch Approach*.[17] The components of the Dutch Approach are:

- no social transition at all considered before age 12 (watchful waiting period),
- no puberty blockers considered before age 12,
- cross-sex hormones considered only after age 16, and
- resolution of mental health issues before any transition.

25. For youth under age 12, "the general recommendation is watchful waiting and carefully observing how gender dysphoria develops in the first stages of puberty."[18]

26. The age cut-offs of the Dutch Approach were not based on any research demonstrating their superiority over other potential age cut-off's. Rather, they were chosen to correspond to the ages of consent to medical procedures under Dutch law. Nevertheless, whatever the original rationale, the data from this clinic simply contain no information about the safety or efficacy of employing these measures at younger ages.

27. The authors of the Dutch Approach repeatedly and consistently emphasize the need for extensive mental health assessment, including clinical interviews, formal psychological testing with validated psychometric instruments, and multiple sessions with the child and the child's parents.

28. Within the Dutch approach, there is no social transition before age twelve. That is, social affirmation of the new gender may not begin until age 12—as desistance is less likely to occur past that age. "Watchful Waiting" refers to a child's developmental period up to that age. Watchful waiting does not mean do nothing but passively observe the child. Rather, such children and families typically present with substantial distress involving both gender and non-gender issues, and it is during the watchful waiting period that a child (and other family members as appropriate) would

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17 de Vries & Cohen-Kettenis, 2012
18 de Vries & Cohen-Kettenis, 2012, at 301.

undergo therapy, resolving other issues which may be exacerbating psychological stress or dysphoria. As noted by the Dutch clinic, "[T]he adolescents in this study received extensive family or other social support . . . [and they] were all regularly seen by one of the clinic's psychologists or psychiatrists."[19] One is actively treating the person, while carefully "watching" the dysphoria.

3. Follow-Up Studies of Puberty Blockers and Cross-Sex Hormones

29. Very many strong claims have appeared in the media and on social media asserting that transition results in improved mental health or, contradictorily, in decreased mental health. In the highly politicized context of gender and transgender research, many outlets have cited only the findings which appear to support one side, cherry-picking from the complete set of research reports. It total, there have been 11 prospective outcomes studies following up gender dysphoric children undergoing medically induced suppression of puberty or cross-sex hormone treatment. Four studies failed to find evidence of improvement in mental health functioning at all, and some groups deteriorated on some variables.[20] Five studies successfully identified evidence of improvement, but because patients received psychotherapy along with medical services, which of those treatments caused the improvement is unknowable.[21] In the remaining two studies, both psychotherapy and medical interventions were provided, but the studies were designed in such a way as to allow the effects of psychotherapy to be separated from the effects of the puberty-blocking medications.[22] As detailed in the following, neither identified benefits of medication over psychotherapy alone.

a. Four studies found no mental health improvement

30. Carmichael, *et al.* (2021) recently released its findings from the Tavistock

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19 de Vries, *et al.*, 2011, at 2280-2281.
20 Carmichael, *et al.*, 2021; Hisle-Gorman, *et al.*, 2021; Kaltiala, *et al.*, 2020; Kuper, *et al.*, 2020.
21 de Vries, *et al.*, 2011; Tordoff, *et al.*, 2022; van der Miesen, *et al.*, 2020.
22 Achille, *et al.*, 2020; Costa, *et al.*, 2015.

and Portman clinic in the U.K.[23] Study participants were ages 12–15 (Tanner stage 3 for natal males, Tanner stage 2 for natal females) and were repeatedly tested before beginning puberty-blocking medications and then every six months thereafter. Cases exhibiting serious mental illnesses (*e.g.*, psychosis, bipolar disorder, anorexia nervosa, severe body-dysmorphic disorder unrelated to gender dysphoria) were excluded. Relative to the time point before beginning puberty suppression, there were *no* significant changes in any psychological measure, from either the patients' or their parents' perspective.

31. In Kuper, *et al.* (2020), a multidisciplinary team from Dallas published a prospective follow-up study which included 25 youths as they began puberty suppression.[24] (The other 123 study participants were undergoing cross-sex hormone treatment.) Interventions were administered according to practice guidelines from the Endocrine Society.[25] Their analyses found *no statistically significant changes* in the group undergoing puberty suppression on any of the nine measures of wellbeing measured, spanning tests of body satisfaction, depressive symptoms, or anxiety symptoms.[26] Notably, whereas the Dutch Protocol includes age 12 as a minimum for puberty suppression treatment, this team provided such treatment beginning at age 9.8 years (full range: 9.8–14.9 years).[27]

32. Hisle-Gorman, *et al.* (2021) analyzed military families' healthcare data to compare 963 transgender and gender-diverse youth before versus after hormonal treatment, with their non-gender dysphoric siblings as controls. The study participants included youth undergoing puberty-blocking as well as those undergoing cross-sex hormone treatment, but these subgroups did not differ from each other. Study participants had a mean age of 18 years when beginning the study, but their

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[23] Carmichael, *et al.*, 2021.
[24] Kuper, *et al.*, 2020, at 5.
[25] Kuper, *et al.*, 2020, at 3, referring to Hembree, *et al.*, 2017.
[26] Kuper, *et al.*, 2020, at Table 2.
[27] Kuper, *et al.*, 2020, at 4.

initial clinical contacts and diagnoses occurred at a mean age of 10 years. According to the study, "mental health care visits overall did not significantly change following gender-affirming pharmaceutical care,"[28] yet, "psychotropic medication use *increased,*"[29] indicating *deteriorating* mental health.

33. Kaltiala et al. (2020) similarly reported that after cross-sex hormone treatment, "Those who had psychiatric treatment needs or problems in school, peer relationships and managing everyday matters outside of home continued to have problems during real-life."[30] They concluded, "Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development."[31]

b. Five studies confounded psychotherapy and medical treatment

34. The initial enthusiasm for medical blocking of puberty followed largely from early reports from the Dutch clinical research team suggesting at least some mental health improvement.[32] It was when subsequent research studies failed to replicate those successes that it became apparent that the successes were due, not to the medical interventions, but to the psychotherapy that accompanied such interventions in most clinics, including the Dutch clinic.

35. The Dutch clinical research team followed up a cohort of youth at their clinic undergoing puberty suppression[33] and later cross-hormone treatment and surgical sex reassignment.[34] The youth improved on several variables upon follow-up as compared to pre-suppression measurement, including depressive symptoms and

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28 Hisle-Gorman, et al., 2021, at 1448.
29 Hisle-Gorman, et al., 2021, at 1448, emphasis added.
30 Kaltiala et al., 2020, at 213.
31 Kaltiala et al., 2020, at 213.
32 de Vries, *et al.*, 2011; de Vries, *et al.*, 2014
33 de Vries, *et al.*, 2011.
34 de Vries, *et al.*, 2014.

general functioning. No changes were detected in feelings of anxiety or anger or in gender dysphoria as a result of puberty suppression; however, natal females using puberty suppression suffered *increased* body dissatisfaction both with their secondary sex characteristics and with nonsexual characteristics.[35]

36. As the report authors noted, while it is possible that the improvement on some variables was due to the puberty-blockers, it is also possible that the improvement was due to the mental health support, and it is possible that the improvement occurred only on its own with natural maturation. So any conclusion that puberty blockers improved the mental health of the treated children is not justified by the data. Because this study did not include a control group (another group of adolescents matching the first group, but *not* receiving medical or social support), these possibilities cannot be distinguished from each other. The authors of the study were explicit in noting this themselves: "All these factors may have contributed to the psychological well-being of these gender dysphoric adolescents."[36]

37. In a 2020 update, the Dutch clinic reported continuing to find improvement in transgender adolescents' psychological functioning, reaching age-typical levels, "after the start of specialized transgender care involving puberty suppression."[37] Unfortunately, because the transgender care method of that clinic involves both psychosocial support and puberty suppression, it again cannot be known which of those (or their combination) is driving the improvement. Also, the authors indicate that the changing demographic and other features among gender dysphoric youth might have caused the treated group to differ from the control group in unknown ways. As the study authors noted again, "The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-

[35] Biggs, 2020.
[36] de Vries, *et al.* 2011, at 2281.
[37] van der Miesen, *et al.*, 2020, at 699.

term mental health outcomes."[38]

38. Allen, *et al.* (2019) reported on a sample of 47 youth, ages 13–20, undergoing cross-sex hormone treatment. They reported observing increases in measures of well-being and decreases in measures of suicidality; however, as the authors also noted, "whether a patient is actively receiving psychotherapy" may have been a confounding variable.[39]

39. Tordoff, *et al.* (2022) reported on a sample of youth, ages 13–20 years, treated with either puberty blockers or cross-sex hormones. There were improvements in mental health functioning; however, 62.5% of the sample was again receiving mental health therapy.[40]

c. Two studies showed no superiority of medical intervention above psychotherapy

40. Costa, *et al.* (2015) reported on preliminary outcomes from the Tavistock and Portman NHS Foundation Trust clinic in the UK. They compared the psychological functioning of one group of youth receiving psychological support with a second group receiving both psychological support as well as puberty blocking medication. Both groups improved in psychological functioning over the course of the study, but no statistically significant differences between the groups was detected at any point.[41] As those authors concluded, "Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescence. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescence."[42] Because psychological support does not pose the physical health risks that hormonal interventions or surgery does (such as loss of reproductive function) however, one

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38 van der Miesen, *et al.*, 2020, at 703.
39 Allen, *et al.*, 2019.
40 Tordoff, et al., 2022, Table 1.
41 Costa, *et al.*, at 2212 Table 2.
42 Costa, *et al.*, at 2206.

cannot justify taking on the greater risks of social transition, puberty blockers or surgery without evidence of such treatment producing superior results. Such evidence does not exist. Moreover, this clinical team subsequently released the final version of this preliminary report, finding that neither group actually experienced significant improvement,[43] making moot any discussion of the source any improvement.

41. Achille, *et al.* (2020) at Stony Brook Children's Hospital in New York treated a sample of 95 youth with gender dysphoria, providing follow-up data on 50 of them. (The report did not indicate how these 50 were selected from the 95.) As well as receiving puberty blocking medications, "Most subjects were followed by mental health professionals. Those that were not were encouraged to see a mental health professional."[44] The puberty blockers themselves "were introduced in accordance with the Endocrine Society and the WPATH guidelines."[45] Upon follow-up, some incremental improvements were noted; however, after statistically adjusting for psychiatric medication and engagement in counselling, "*most predictors did not reach statistical significance*."[46] That is, puberty blockers did not improve mental health any more than did mental health care on its own.

d. Conclusions

42. The authors of the original Dutch studies were careful not to overstate the implications of their results, "We *cautiously* conclude that puberty suppression *may be* a valuable *element* in clinical management of adolescent gender dysphoria."[47] Nonetheless, many other clinics and clinicians intrepidly proceeded on the basis of only the perceived positives, broadened the range of people beyond those represented in the research findings, and removed the protections applied in the procedures that

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43 Carmichael, et al., 2021.
44 Achille, *et al.*, 2020, at 2.
45 Achille, *et al.*, 2020, at 2.
46 Achille, *et al.*, 2020, at 3 (italics added).
47 de Vries, *et al.* 2011, at 2282, italics added.

led to those outcomes. Many clinics and individual clinicians have reduced the minimum age for transition to 10 instead of 12. While the Dutch Protocol involves interdisciplinary teams of clinicians, many clinics now rely on a single assessor, in some cases one without adequate professional training in childhood and adolescent mental health. Comprehensive, longitudinal assessments (*e.g.*, 1 to 2 *years*[48]) became approvals after one or two assessment sessions. Validated, objective measures of youths' psychological functioning were replaced with clinicians' subjective (and first) opinions, often reflecting only the clients' own self-report. Systematic recordings of outcomes, so as to allow for detection and correction of clinical deficiencies, were eliminated.

43. Notably, Dr. Thomas Steensma, central researcher of the Dutch clinic, has decried other clinics for "blindly adopting our research" despite the indications that those results may not actually apply: "We don't know whether studies we have done in the past are still applicable to today. Many more children are registering, and also a different type."[49] Steensma opined that "every doctor or psychologist who is involved in transgender care should feel the obligation to do a good pre- and post-test." But few if any are doing so.

4. Mental Health Issues in Childhood-Onset Gender Dysphoria

44. As shown by the outcomes studies, there is little evidence that transition improves the mental well-being of children. As shown repeatedly by clinical guidelines from multiple professional associations, mental health issues are expected or required to be resolved *before* undergoing transition. The reasoning behind these conclusions is that children may be expressing gender dysphoria, not because they are experiencing what gender dysphoric adults report, but because they mistake what their experiences indicate or to what they might lead. For example, a child

48 de Vries, *et al.*, 2011.
49 Tetelepta, 2021.

experiencing depression from social isolation might develop the hope—and the unrealistic expectation—that transition will help them fit in, this time as and with the other sex.

45. If a child undergoes transition, discovering only then that their mental health or social situations will not in fact change, the medical risks and side-effects (such as sterilization) will have been borne for no reason. If, however, a child resolves the mental health issues first, with the gender dysphoria resolving with it (which the research literature shows to be the case in the large majority), then the child need not undergo transition at all, but retains the opportunity to do so later.

46. Elevated rates of multiple mental health issues among gender dysphoric children are reported throughout the research literature. A formal analysis of children (ages 4–11) undergoing assessment at the Dutch child gender clinic showed 52% fulfilled criteria for a DSM axis-I disorder.[50] A comparison of the children attending the Canadian versus Dutch child gender dysphoria clinic showed only few differences between them, but a large proportion in both groups were diagnosable with clinically significant mental health issues. Results of standard assessment instruments (Child Behavior Check List, or CBCL) demonstrated that the average score was in the clinical rather than healthy range, among children in both clinics.[51] When expressed as percentages, among 6–11-year-olds, 61.7% of the Canadian and 62.1% of the Dutch sample were in the clinical range.

47. A systematic, comprehensive review of all studies of Autism Spectrum Disorders (ASDs) and Attention-Deficit Hyperactivity Disorder (ADHD) among children diagnosed with gender dysphoria was recently conducted. It was able to identify a total of 22 studies examining the prevalence of ASD or ADHD I youth with gender dysphoria. Studies reviewing medical records of children and adolescents

[50] Wallien, *et al.*, 2007.
[51] Cohen-Kettenis, *et al.*, 2003, at 46.

referred to gender clinics showed 5–26% to have been diagnosed with ASD.[52] Moreover, those authors gave specific caution on the "considerable overlap between symptoms of ASD and symptoms of gender variance, exemplified by the subthreshold group which may display symptoms which could be interpreted as either ASD or gender variance. Overlap between symptoms of ASD and symptoms of GD may well confound results."[53] As noted elsewhere herein, when two or more issues are present at the same time, researchers cannot distinguish when a result is associated with or caused by the issue of interest or one of the side issues.[54] The rate of ADHD among children with GD was 8.3–11%. Conversely, in data from children (ages 6–18) with Autism Spectrum Disorders (ASDs) show they are more than seven times more likely to have parent-reported "gender variance."[55]

C. Adolescent-Onset Gender Dysphoria

1. Features of Adolescent-Onset Gender Dysphoria

48. In the social media age, a third profile has recently begun to present clinically or socially, characteristically distinct from the two previously identified profiles.[56] Unlike adult-onset or childhood-onset gender dysphoria, this group is predominately biologically female. This group typically presents in adolescence, but lacks the history of cross-gender behavior in childhood like the childhood-onset cases have. It is that feature which led to the term Rapid Onset Gender Dysphoria (ROGD).[57] The majority of cases appear to occur within clusters of peers and in association with increased social media use[58] and especially among people with autism or other neurodevelopmental or mental health issues.[59]

49. It cannot be easily determined whether the self-reported gender dysphoria

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52 Thrower, *et al.*, 2020.
53 Thrower, *et al.*, 2020, at 703.
54 Cohen-Kettenis *et al.*, 2003, at 51; Skelly *et al.*, 2012.
55 Janssen, *et al.*, 2016.
56 Kaltiala-Heino, *et al.*, 2015; Littman, 2018.
57 Littman, 2018.
58 Littman, 2018.
59 Kaltiala-Heino, *et al.*, 2015; Littman, 2018; Warrier, *et al.*, 2020.

is a result of other underlying issues or if those mental health issues are the result of the stresses of being a sexual minority, as some writers are quick to assume.[60] (The science of the *Minority Stress Hypothesis* appears in its own section.) Importantly, and unlike other presentations of gender dysphoria, people with rapid-onset gender dysphoria often (47.2%) experienced *declines* rather than improvements in mental health when they publicly acknowledged their gender status.[61] Although long-term outcomes have not yet been reported, these distinctions demonstrate that one cannot apply findings from the other types of gender dysphoria to this type. That is, in the absence of evidence, researchers cannot assume that the pattern found in childhood-onset or adult-onset gender dysphoria also applies to adolescent-onset gender dysphoria. The multiple differences already observed between these groups argue against predicting that features present in one type would generalize to be present in all types of gender dysphoria.

2. Social Transition and Puberty Blockers with Adolescent Onset

50. There do not yet exist prospective outcomes studies either for social transition or for medical interventions for people whose gender dysphoria began in adolescence. That is, instead of taking a sample of individuals and following them forward over time (thus permitting researchers to account for people dropping out of the study, people misremembering the order of events, etc.), all studies have thus far been *retrospective*. It is not possible for such studies to identify what factors caused what outcomes. No study has yet been organized in such a way as to allow for an analysis of the adolescent-onset group, as distinct from childhood-onset or adult-onset cases. Many of the newer clinics (not the original clinics which systematically tracked and reported on their cases' results) fail to distinguish between people who had childhood-onset gender dysphoria and have aged into adolescence versus people

[60] Boivin, *et al.*, 2020.
[61] Biggs, 2020; Littman, 2018.

whose onset was not until adolescence. (Analogously, there are reports failing to distinguish people who had adolescent-onset gender dysphoria and aged into adulthood from adult-onset gender dysphoria.) Studies selecting groups according to their current age instead of their ages of onset produces confounded results, representing unclear mixes according to how many of each type of case wound up in the final sample.

3. Mental Illness in Adolescent-Onset Gender Dysphoria

51. In 2019, a Special Section appeared in the *Archives of Sexual Behavior* titled, "Clinical Approaches to Adolescents with Gender Dysphoria." It included this brief yet thorough summary of rates of mental health issues among adolescents expressing gender dysphoria, by Dr. Aron Janssen of the Department of Child and Adolescent Psychiatry of New York University:[62] The literature varies in the range of percentages of adolescents with co-occurring disorders. The range for depressive symptoms ranges was 6–42%,[63] with suicide attempts ranging 10 to 45%.[64] Self-injurious thoughts and behaviors range 14–39%.[65] Anxiety disorders and disruptive behavior difficulties including Attention Deficit/Hyperactivity Disorder are also prevalent.[66] Gender dysphoria also overlaps with Autism Spectrum Disorder.[67]

52. Of particular concern in the context of adolescent onset gender dysphoria is Borderline Personality Disorder (BPD; diagnostic criteria to follow). It is increasingly hypothesized that very many cases appearing to be adolescent-onset gender dysphoria actually represent cases of BPD.[68] That is, some people may be misinterpreting their experiencing of the broader "identity disturbance" of symptom Criterion 3 to represent a gender identity issue specifically. Like adolescent-onset

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62 Janssen, *et al.*, 2019.
63 Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013; Wallien, *et al.*, 2007.
64 Reisner, *et al.*, 2015.
65 Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013.
66 de Vries, *et al.*, 2011; Mustanski, *et al.*, 2010; Wallien, *et al.*, 2007.
67 de Vries, *et al.*, 2010; Jacobs, *et al.*, 2014; Janssen, *et al.*, 2016; May, *et al.*, 2016; Strang, *et al.*, 2014, 2016.
68 *E.g.*, Anzani, *et al.*, 2020; Zucker, 2019.

gender dysphoria, BPD begins to manifest in adolescence, is three times more common in biological females than males, and occurs in 2–3% of the population, rather than 1-in-5,000 people. (Thus, if even only a portion of people with BPD experienced an identity disturbance that focused on gender identity and were mistaken for transgender, they could easily overwhelm the number of genuine cases of gender dysphoria.)

53. DSM-5-TR Diagnostic Criteria for Borderline Personality Disorder:

> A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:
>
> 1. Frantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.)
> 2. A pattern of unstable and intense interpersonal relationship characterized by alternating between extremes of idealization and devaluation.
> 3. *Identity disturbance: markedly and persistently unstable self-image or sense of self.*
> 4. Impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
> 5. *Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behavior.*
> 6. Affective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
> 7. Chronic feelings of emptiness.
> 8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
> 9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

(Italics added.)

54. Mistaking cases of BPD for cases of Gender Dysphoria may prevent such youth from receiving the correct mental health services for their condition, and a primary cause for concern is symptom Criterion 5: Recurrent suicidality. (The research on suicide and suicidality are detailed in their own section herein.)

Regarding the provision of mental health care, the distinction between these conditions is crucial: A person with BPD going undiagnosed will not receive the appropriate treatments (the currently most effective of which is Dialectical Behavior Therapy). A person with a cross-gender identity would be expected to feel relief from medical transition, but someone with BPD would not: The problem was not about *gender* identity, but about having an *unstable* identity. Moreover, after a failure of medical transition to provide relief, one would predict for these people increased levels of hopelessness and increased risk of suicidality.

55. Regarding research, there have now been several attempts to document rates of suicidality among gender dysphoric adolescents. The scientific concern presented by BPD is that it poses a potential confound: Samples of gender dysphoric adolescents could appear to have elevated rates of suicidality, not because of the gender dysphoria (or transphobia in society), but because of the number of people with BPD in the sample.

IV. Other Scientific Claims Assessed

A. Suicide and Suicidality

56. Social media increasingly circulate demands for transition accompanied by hyperbolic warnings of suicide should there be delay or obstacle. Claims accompany admissions that "I'd rather have a trans daughter than a dead son," and such threats are treated as the justification for referring to affirming gender transitions as 'life-saving' or 'medically necessary'. Such claims convey only grossly misleading misrepresentations of the research literature, however, deploying terms for their shock value rather than accuracy, and exploiting common public misperceptions about suicide. Indeed, suicide prevention research and public health campaigns repeatedly warn against circulating such exaggerations, due to the risk of copy-cat

behavior they encourage.[69]

57. Despite that the media treat them as near synonyms, suicide and suicidality are distinct phenomena. They represent different behaviors with different motivations, with different mental health issues, and with different clinical needs. *Suicide* refers to completed suicides and the sincere intent to die. It is substantially associated with impulsivity, using more lethal means, and being a biological male.[70] *Suicidality* refers to parasuicidal behaviors, including suicidal ideation, threats, and gestures. These typically represent cries for help rather than an intent to die and are more common among biological females. Suicidal threats can indicate any of many problems or represent emotional blackmail, as typified by "If you leave me, I will kill myself." Professing suicidality is also used for attention-seeking or for the support or sympathy it evokes from others, denoting distress much more frequently than an intent to die.

58. Notwithstanding public misconceptions about the frequency of suicide and related behaviors, the highest rates of suicide are among middle-aged and elderly men in high income countries.[71] Biological males are at three times greater risk of death by suicide than are biological females, whereas suicidal ideation, plans, and attempts are three times more common among biological females.[72] In contrast with completed suicides, the frequency of suicidal ideation, plans, and attempts is highest during adolescence and young adulthood, with reported ideation rates spanning 12.1–33%.[73] Relative to other countries, Americans report elevated rates of each of suicidal ideation (15.6%), plans (5.4%), and attempts (5.0%).[74] Suicide attempts occur up to 30

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69 Gould & Lake, 2013.
70 Freeman, *et al.*, 2017.
71 Turecki & Brent, 2016
72 Klonsky et al., 2016; Turecki & Brent, 2016
73 Borges et a., 2010; Nock et al., 2008
74 Klonsky, et al., 2016.

times more frequently than completed suicides.[75] The rate of completed suicides in the U.S. population is 14.5 per 100,000 people.[76] The widely discrepant numbers representing completed suicides versus transient suicidal ideation has left those statistics open to substantial abuse in the media and social media. Despite public media guidelines urging "Avoid dramatic headlines and strong terms such as 'suicide epidemic'," [77] that is exactly what mainstream outlets have done.[78]

59. There is substantial research associating sexual orientation with suicidality, but much less so with completed suicide.[79] More specifically, there is some evidence suggesting gay adult men are more likely to die by suicide than are heterosexual men, but there is less evidence of an analogous pattern among lesbian women. Regarding suicidality, surveys of self-identified LGB Americans repeatedly report rates of suicidal ideation and suicide attempts 2–7 times higher than their heterosexual counterparts. Because of this association of suicidality with sexual orientation, one must apply caution in interpreting findings allegedly about gender identity: Because of the overlap between people who self-identify as non-heterosexual and as non-cis-gendered, correlations detected between suicidality and gender dysphoria may instead reflect (be confounded by) homosexuality. Indeed, other authors have made explicit their surprise that so many studies, purportedly of gender identity, entirely omitted measurement or consideration of sexual orientation, creating the situation where features that seem to be associated with gender identity instead reflect the sexual orientation of the members of the sample.[80]

60. Among post-transition transsexuals, completed suicide rates are elevated,

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75 Bachman, 2018.
76 World Health Organization, 2022.
77 Samaritans, 2020.
78 E.g., MSNBC, 2015, *Trans youth and suicide: An epidemic.*
79 Haas, *et al.*, 2011.
80 McNeil, *et al.* (2017)

but are nonetheless rare.[81] Regarding suicidality, there have been three recent, systematic reviews of the research literature.[82] All three included specific methods to minimize any potential effects of cherry-picking findings from within the research literature. Compiling the results of 108 articles reported from 64 research projects, Adams and Vincent (2019) found an overall average rate of 46.55% for suicidal ideation (ranging 18.18%–95.5%) and an overall average rate of 27.19% for suicidal attempts (ranging 8.57%–52.4%). These findings confirmed those reported by McNeil, *et al.* (2017), whose review of 30 articles revealed a range of 37%–83% for suicidal ideation and 9.8%–43% for suicidal attempts. Thus, on the one hand, these ranges are greater than those reported for the mainstream population—They instead approximate the rates reported among sexual orientation minorities. On the other hand, with measures so lacking in reliability that they produce every result from 'rare' to 'almost everyone', it is unclear which, if any of them, represents a valid conclusion.

61. McNeil *et al.* (2017) observed also the research to reveal rates of suicidal ideation and suicidal attempts to be related—not to transition status—but to the social support received: The studies reviewed showed support to decrease suicidality, but transition not to. Indeed, in some situations, social support was associated with *increased* suicide attempts, suggesting the reported suicidality may represent attempts to evoke more support.[83]

62. Marshall et al. (2016) identified and examined 31 studies, again finding rates of suicidal ideation and suicide attempts to be elevated, particularly among biological females, indicating that suicidality patterns correspond to biological sex rather than self-identified gender.[84]

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81 Wiepjes, *et al.*, 2020.
82 Adams & Vincent, 2019; Marshall, *et al.*, 2016; McNeil, *et al.* (2017).
83 Bauer, *et al.*, 2015; Canetto, et al., 2021.
84 Marshall, et al., 2016.

63. Despite that mental health issues, including suicidality, are repeatedly required by clinical standards of care to be resolved before transition, threats of suicide are instead oftentimes used as the very justification for labelling transition a 'medical necessity'. However plausible it might seem that failing to affirm transition causes suicidality, the epidemiological evidence indicates that hypothesis to be incorrect: Suicide rates remains elevated even after complete transition, as shown by a comprehensive review of 17 studies of suicidality in gender dysphoria.[85]

64. The scientific study of suicide is inextricably linked to that of mental illness, and Borderline Personality Disorder is repeatedly documented to be greatly elevated among sexual minorities[86].

B. Conversion Therapy

65. Activists and social media increasingly, but erroneously, apply the term "conversion therapy" moving farther and farther from what the research has reported. "Conversion therapy" (or "reparative therapy" and other names) was the attempt to change a person's sexual orientation; however, with the public more frequently accustomed to "LGB" being expanded to "LGBTQ+", the claims relevant only to sexual orientation are being misapplied to gender identity. The research has repeatedly demonstrated that once one explicitly acknowledges being gay or lesbian, this is only very rarely are mistaken. That is entirely unlike gender identity, wherein the great majority of children who declare cross-gender identity cease to do so by puberty, as already shown unanimously by all follow-up studies. As the field grows increasingly polarized, any therapy failing to provide affirmation-on-demand is mislabeled "conversion therapy."[87] Indeed, even actions of non-therapists, unrelated

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85 McNeil, *et al.*, 2017.
86 Reuter, *et al.*, 2016; Rodriguez-Seiljas, *et al.*, 2021; Zanarni, *et al.*, 2021.
87 D'Angelo, *et al.*, 2021.

to any therapy, have been labelled conversion therapy, including the prohibition of biological males competing on female teams.[88]

C. Assessing Demands for Social Transition and Affirmation-Only or Affirmation-on-Demand Treatment in Pre-Pubertal Children.

66. Colloquially, affirmation refers broadly to any actions that treat the person as belonging to a new gender. In different contexts, that could apply to social actions (use of a new name and pronouns), legal actions (changes to birth certificates), or medical actions (hormonal and surgical interventions). That is, social transition, legal transition, and medical transition (and subparts thereof) need not, and rarely do, occur at the same time. In practice, there are cases in which a child has socially only partially transitioned, such as presenting as one gender at home and another at school or presenting as one gender with one custodial parent and another gender with the other parent.

67. Referring to "affirmation" as a treatment approach is ambiguous: Although often used in public discourse to take advantage of the positive connotations of the term, it obfuscates what exactly is being affirmed. This often leads to confusion, such as quoting a study of the benefits and risks of social affirmation in a discussion of medical affirmation, where the appearance of the isolated word "affirmation" refers to entirely different actions.

68. It is also an error to divide treatment approaches into affirmative versus non-affirmative. As noted already, the widely adopted Dutch Approach (and the guidelines of the multiple professional associations based on it) cannot be said to be either: It is a staged set of interventions, wherein social transition (and puberty blocking) may not begin until age 12 and cross-sex hormonal and other medical interventions, later.

69. Formal clinical approaches to helping children expressing gender dysphoria

[88] Turban, 2021, March 16.

employ a gate-keeper model, with decision trees to help clinicians decide when and if the potential benefits of affirmation of the new gender would outweigh the potential risks of doing so. Because the gate-keepers and decision-trees generally include the possibility of affirmation in at least some cases, it is misleading to refer to any one approach as "the affirmation approach." The most extreme decision-tree would be accurately called affirmation-*on-demand,* involving little or no opportunity for children to explore at all whether the distress they feel is due to some other, less obvious, factor, whereas more moderate gate-keeping would endorse transition only in select situations, when the likelihood of regretting transition is minimized.

70. Many outcomes studies have been published examining the results of gate-keeper models, but no such studies have been published regarding affirmation-on-demand with children. Although there have been claims that affirmation-on-demand causes mental health or other improvement, these have been the result only of "retrospective" rather than "prospective" studies. That is, such studies did not take a sample of children and follow them up over time, to see how many dropped out altogether, how many transitioned successfully, and how many transitioned and regretted it or detransitioned. Rather, such studies took a sample of successfully transitioned adults and asked them retrospective questions about their past. In such studies, it is not possible to know how many other people dropped out or regretted transition, and it is not possible to infer causality from any of the correlations detected, despite authors implying and inferring causality.

D. Assessing the "Minority Stress Hypothesis"

71. The elevated levels of mental health problems among lesbian, gay, and bisexual populations is a well-documented phenomenon, and the idea that it is caused by living within a socially hostile environment is called the *Minority Stress Hypothesis*.[89] The association is not entirely straight-forward, however. For example,

[89] Meyer, 2003.

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

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although lesbian, gay, and bisexual populations are more vulnerable to suicide ideation overall, the evidence specifically on adult lesbian and bisexual women is unclear. Meyer did not include transgender populations in originating the hypothesis, and it remains a legitimate question to what extent and in what ways it might apply to gender identity.

72. Minority stress is associated, in large part, with being a visible minority. There is little evidence that transgender populations show the patterns suggested by the hypothesis. For example, the minority stress hypothesis would predict differences according to how visibly a person is discernable as a member of the minority, which often changes greatly upon transition. Biological males who are very effeminate stand out throughout childhood, but in some cases can successfully blend in as adult females; whereas the adult-onset transitioners blend in very much as heterosexual cis-gendered males during their youth and begin visibly to stand out in adulthood, only for the first time.

73. Also suggesting minority stress cannot be the full story is that the mental health symptoms associated with minority stress do not entirely correspond with those associated with gender dysphoria. The primary symptoms associated with minority stress are depressive symptoms, substance use, and suicidal ideation.[90] The symptoms associated with gender dysphoria indeed include depressive symptoms and suicidal ideation, but also include anxiety symptoms, Autism Spectrum Disorders, and personality disorders.

74. A primary criterion for readiness for transition used by the clinics demonstrating successful transition is the absence or resolution of other mental health concerns, such as suicidality. In the popular media, however, indications of mental health concerns are instead often dismissed as an expectable result caused by Sexual Minority Stress (SMS). It is generally implied that such symptoms will resolve

[90] Meyer, 2003.

upon transition and integration into an affirming environment.

V. Assessing Statements from Professional Associations

A. Understanding the Value of Statements from Professional Associations

75. The value of position statements from professional associations should be neither over- nor under-estimated. In the ideal, an organization of licensed health care professionals would convene a panel of experts who would systematically collect all the available evidence about an issue, synthesizing it into recommendations or enforceable standards for clinical care, according to the quality of the evidence for each alternative. For politically neutral issues, with relevant expertise contained among association members, this ideal can be readily achievable. For controversial issues with no clear consensus, the optimal statement would summarize each perspective and explicate the strengths and weaknesses of each, providing relatively reserved recommendations and suggestions for future research that might resolve the continuing questions. Several obstacles can hinder that goal, however. Committees within professional organizations are typically volunteer activities, subject to the same internal politics of all human social structures. That is, committee members are not necessarily committees of experts on a topic—they are often committees of generalists handling a wide variety of issues or members of an interest group who feel strongly about political implications of an issue, instead of scientists engaged in the objective study of the topic.

76. Thus, documents from professional associations may represent required standards, the violation of which may merit sanctions, or may represent only recommendations or guidelines. A document may represent the views of an association's full membership or only of the committee's members (or majorities thereof). Documents may be based on systematic, comprehensive reviews of the available research or selected portions of the research. In sum, the weight best placed

on any association's statement is the amount by which that association employed evidence versus other considerations in its process.

B. Misrepresentations of statements of professional associations.

77. In the presently highly politicized context, official statements of professional associations have been widely misrepresented. In preparing the present report, I searched the professional research literature for documentation of statements from these bodies and from my own files, for which I have been collecting such information for many years. I was able to identify statements from six such organizations. Although not strictly a medical association, the World Professional Association for Transgender Health (WPATH) also distributed a set of guidelines in wide use and on which other organizations' guidelines are based.

78. Notably, despite that all these medical associations reiterate the need for mental health issues to be resolved before engaging in medical transition, only the AACAP members have medical training in mental health. The other medical specialties include clinical participation with this population, but their assistance in transition generally assumes the mental health aspects have already been assessed and treated beforehand.

79. With the broad exception of the AAP, their statements repeatedly noted instead that:

- Desistance of gender dysphoria occurs in the majority of prepubescent children.
- Mental health issues need to be assessed as potentially contributing factors and need to be addressed before transition.
- Puberty-blocking medication is an experimental, not a routine, treatment.
- Social transition is not generally recommended until after puberty.

Although some other associations have published broad statements of moral support for sexual minorities and against discrimination, they did not include any specific standards or guidelines regarding medical- or transition-related care.

1. World Professional Association for Transgender Health (WPATH)

80. The WPATH standards as they relate to prepubescent children begin with the acknowledgement of the known rates of desistance among gender dysphoric children:

> [I]n follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).[91]

81. That is, "In most children, gender dysphoria will disappear before, or early in, puberty."[92]

82. Although WPATH does not refer to puberty blocking medications as "experimental," the document indicates the non-routine, or at least inconsistent availability of the treatment:

> Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., [2012]).[93]

83. WPATH neither endorses nor proscribes social transitions before puberty, instead recognizing the diversity among families' decisions:

> Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood.[94]

84. It does caution, however, "Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria."[95]

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91 Coleman, *et al.*, 2012, at 172.
92 Coleman, *et al.*, 2012, at 173.
93 Coleman, *et al.*, 2012, at 173.
94 Coleman, *et al.*, 2012, at 176.
95 Coleman, *et al.*, 2012, at 176 (quoting Drummond, *et al.*, 2008; Wallien & Cohen-Kettenis, 2008).

85. The WPATH standards have been subjected to standardized evaluation, the Appraisal of Guidelines for Research and Evaluation ("AGREE II") method, as part of an appraisal of all published Clinical Practice Guidelines (CPGs) regarding sex and gender minority healthcare.[96] Utilizing community stakeholders to set domain priorities for the evaluation, the assessment concluded that the guidelines regarding HIV and its prevention were of high quality, but that "[t]ransition-related CPGs tended to lack methodological rigour and rely on patchier, lower-quality primary research."[97] The WPATH guidelines were recommended for use. Indeed, the WPATH guidelines received unanimous ratings of "Do not recommend."[98]

86. Finally, it should be noted that WPATH is in stark opposition to international standards: Public healthcare systems throughout the world have instead been ending the practice of medical transition of minors, responding to the increasingly recognized risks associated with hormonal interventions and the now clear lack of evidence that medical transition was benefitting most children, as opposed to the mental health counseling accompanying transition.

2. Endocrine Society (ES)

87. The 150,000-member Endocrine Society appointed a nine-member task force, plus a methodologist and a medical writer, who commissioned two systematic reviews of the research literature and, in 2017, published an update of their 2009 recommendations, based on the best available evidence identified. The guideline was co-sponsored by the American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Paediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society (PES), and the World Professional Association for Transgender Health (WPATH).

88. The document acknowledged the frequency of desistance among gender

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96 Dahlen, *et al.*, 2021.
97 Dahlen, *et al.*, 2021, at 6.
98 Dahlen, *et al.*, 2021, at 7.

dysphoric children:

> Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence. . . . In adolescence, a significant number of these desisters identify as homosexual or bisexual.[99]

89. The statement similarly acknowledges inability to predict desistance or persistence, "With current knowledge, we cannot predict the psychosexual outcome for any specific child."[100]

90. Although outside their area of professional expertise, mental health issues were also addressed by the Endocrine Society, repeating the need to handle such issues before engaging in transition, "In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues."[101] This ordering—to address mental health issues before embarking on transition—avoids relying on the unproven belief that transition will solve such issues.

91. The Endocrine Society did not endorse any affirmation-only approach. The guidelines were neutral with regard to social transitions before puberty, instead advising that such decisions be made only under clinical supervision: "We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional."[102]

92. The Endocrine Society guidelines make explicit that, after gathering information from adolescent clients seeking medical interventions and their parents, the clinician "provides correct information to prevent unrealistically high expectations [and] assesses whether medical interventions may result in unfavorable

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99 Hembree, *et al.*, 2017, at 3876.
100 Hembree, *et al.*, 2017, at 3876.
101 Hembree, *et al.*, 2017, at 3877.
102 Hembree, *et al.*, 2017, at 3872.

psychological and social outcomes."[103]

3. Pediatric Endocrine Society and Endocrine Society (ES/PES)

93. In 2020, the 1500-member Pediatric Endocrine Society partnered with the Endocrine Society to create and endorse a brief, two-page position statement.[104] Although strongly worded, the document provided no specific guidelines, instead deferring to the Endocrine Society guidelines.[105]

94. It is not clear to what extent this endorsement is meaningful, however. According to the PES, the Endocrine Society "recommendations include evidence that treatment of gender dysphoria/gender incongruence is medically necessary and should be covered by insurance."[106] However, the Endocrine Society makes neither statement. Although the two-page PES document mentioned insurance coverage four times, the only mention of health insurance by the Endocrine Society was: "If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action."[107] Despite the PES asserting it as "medically necessary," the Endocrine Society stopped short of that. Its only use of that phrase was instead limiting: "We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being."[108]

4. American Academy of Child & Adolescent Psychiatry (AACAP)

95. The 2012 statement of the American Academy of Child & Adolescent Psychiatry (AACAP) is not an affirmation-only policy. It notes:

Just as family rejection is associated with problems such as depression,

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[103] Hembree, *et al.*, 2017, at 3877.
[104] PES, online; Pediatric Endocrine Society & Endocrine Society, Dec. 2020.
[105] Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1; Hembree, *et al.*, 2017.
[106] Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1.
[107] Hembree, *et al.* 2017, at 3883.
[108] Hembree, *et al.*, 2017 at 3872, 3894.

> suicidality, and substance abuse in gay youth, the proposed benefits of treatment to eliminate gender discordance in youth must be carefully weighed against such possible deleterious effects. . . . In general, it is desirable to help adolescents who may be experiencing gender distress and dysphoria to defer sex reassignment until adulthood, or at least until the wish to change sex is unequivocal, consistent, and made with appropriate consent.[109]

96. The AACAP's language repeats the description of the use of puberty blockers only as an exception: "For situations in which deferral of sex reassignment decisions until adulthood is *not clinically feasible*, one approach that has been described in case series is sex hormone suppression under endocrinological management with psychiatric consultation using gonadotropin-releasing hormone analogues."[110]

97. The AACAP statement acknowledges the long-term outcomes literature for gender dysphoric children: "In follow-up studies of prepubertal boys with gender discordance—including many without any mental health treatment—the cross gender wishes usually fade over time and do not persist into adulthood,"[111] adding that "[c]linicians should be aware of current evidence on the natural course of gender discordance and associated psychopathology in children and adolescents in choosing the treatment goals and modality."[112]

98. The policy similarly includes a provision for resolving mental health issues: "Gender reassignment services are available in conjunction with mental health services focusing on exploration of gender identity, cross-sex treatment wishes, counseling during such treatment if any, and *treatment of associated mental health problems*."[113] The document also includes minority stress issues and the need to deal with mental health aspects of minority status (*e.g.*, bullying).[114]

99. Rather than endorse social transition for prepubertal children, the AACAP

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[109] Adelson & AACAP, 2012, at 969.
[110] Adelson & AACAP, 2012, at 969 (italics added).
[111] Adelson & AACAP, 2012, at 963.
[112] Adelson & AACAP, 2012, at 968.
[113] Adelson & AACAP, 2012, at 970 (italics added).
[114] Adelson & AACAP, 2012, at 969.

indicates: "There is similarly no data at present from controlled studies to guide clinical decisions regarding the risks and benefits of sending gender discordant children to school in their desired gender. Such decisions must be made based on clinical judgment, bearing in mind the potential risks and benefits of doing so."[115]

5. American College of Obstetricians & Gynecologists (ACOG)

100. The American College of Obstetricians & Gynecologists (ACOG) published a "Committee Opinion" expressing recommendations in 2017. The statement indicates it was developed by the ACOG's Committee on Adolescent Health Care, but does not indicate participation based on professional expertise or a systematic method of objectively assessing the existing research. It includes the disclaimer: "This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed."[116]

101. Prepubertal children do not typically have clinical contact with gynecologists, and the ACOG recommendations include that the client additionally have a primary health care provider.[117]

102. The ACOG statement cites the statements made by other medical associations—European Society for Pediatric Endocrinology (ESPE),, PES, and the Endocrine Society—and by WPATH.[118] It does not cite any professional association of *mental* health care providers, however. The ACOG recommendations repeat the previously mentioned eligibility/readiness criteria of having no mental illness that would hamper diagnosis and no medical contraindications to treatment. It notes: "*Before* any treatment is undertaken, the patient must display eligibility and readiness (Table 1), meaning that the adolescent has been evaluated by a mental

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115 Adelson & AACAP, 2012, at 969.
116 ACOG, 2017, at 1.
117 ACOG, 2017, at 1.
118 ACOG, 2017, at 1, 3.

health professional, has no contraindications to therapy, and displays an understanding of the risks involved."[119]

103. The "Eligibility and Readiness Criteria" also include, "Diagnosis established for gender dysphoria, transgender, transsexualism."[120] This standard, requiring a formal diagnosis, forestalls affirmation-on-demand because self-declared self-identification is not sufficient for DSM diagnosis.

104. ACOG's remaining recommendations pertain only to post-transition, medically oriented concerns. Pre-pubertal social transition is not mentioned in the document, and the outcomes studies of gender dysphoric (prepubescent) children are not cited.

6. American College of Physicians (ACP)

105. The American College of Physicians published a position paper broadly expressing support for the treatment of LGBT patients and their families, including nondiscrimination, antiharassment, and defining "family" by emotional rather than biological or legal relationships in visitation policies, and the inclusion of transgender health care services in public and private health benefit plans.[121]

106. ACP did not provide guidelines or standards for child or adult gender transitions. The policy paper opposed attempting "reparative therapy;" however, the paper confabulated sexual orientation with gender identity in doing so. That is, on the one hand, ACP explicitly recognized that "[s]exual orientation and gender identity are inherently different."[122] It based this statement on the fact that "the American Psychological Association conducted a literature review of 83 studies on the efficacy of efforts to change *sexual orientation*."[123] The APA's document, entitled "Report of the American Psychological Task Force on appropriate therapeutic responses to

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[119] ACOG, 2017, at 1, 3 (citing the Endocrine Society guidelines) (italics added).
[120] ACOG, 2017, at 3 Table 1.
[121] Daniel & Butkus, 2015a, 2015b.
[122] Daniel & Butkus, 2015b, at 2.
[123] Daniel & Butkus, 2015b, at 8 (italics added).

sexual orientation" does not include or reference research on gender identity.[124] Despite citing no research about transgenderism, the ACP nonetheless included in its statement: "Available research does not support the use of reparative therapy as an effective method in the treatment of LGB*T* persons."[125] That is, the inclusion of "T" with "LGB" is based on something other than the existing evidence.

107. There is another statement,[126] which was funded by ACP and published in the Annals of Internal Medicine under its "*In the Clinic*" feature, noting that "'In the Clinic' does not necessarily represent official ACP clinical policy."[127] The document discusses medical transition procedures for adults rather than for children, except to note that "[n]o medical intervention is indicated for prepubescent youth,"[128] that a "mental health provider can assist the child and family with identifying an appropriate time for a social transition,"[129] and that the "child should be assessed and managed for coexisting mood disorders during this period because risk for suicide is higher than in their cisgender peers."[130]

7. American Academy of Pediatrics (AAP)

108. The policy of the American Academy of Pediatrics (AAP) is unique among the major medical associations in being the only one to endorse an affirmation-on-demand policy, including social transition before puberty without any watchful waiting period. Although changes in recommendations can obviously be appropriate in response to new research evidence, the AAP provided none. Rather, the research studies AAP cited in support of its policy simply did not say what AAP claimed they did. In fact, the references that AAP cited as the basis of their policy instead outright contradicted that policy, repeatedly endorsing watchful waiting.[131] Moreover, of all

[124] APA, 2009 (italics added).
[125] Daniel & Butkus, 2015b, at 8 (italics added).
[126] Safer & Tangpricha, 2019.
[127] Safer & Tangpricha, 2019, at ITC1.
[128] Safer & Tangpricha, 2019, at ITC9.
[129] Safer & Tangpricha, 2019, at ITC9.
[130] Safer & Tangpricha, 2019, at ITC9.
[131] Cantor, 2020.

the outcomes research published, the AAP policy cited *one*, and that without mentioning the outcome data it contained.[132].

109. Immediately following the publication of the AAP policy, I conducted a point-by-point fact-check of the claims it asserted and the references it cited in support. I submitted that to the *Journal of Sex & Marital Therapy*, a well-known research journal of my field, where it underwent blind peer review and was published. I append that article as part of this report. *See* Appendix 2. A great deal of published attention ensued; however, the AAP has yet to respond to the errors I demonstrated its policy contained. Writing for *The Economist* about the use of puberty blockers, Helen Joyce asked AAP directly, "Has the AAP responded to Dr Cantor? If not, have you any response now?" The AAP Media Relations Manager, Lisa Black, responded: "We do not have anyone available for comment."

8. The ESPE-LWPES GnRH Analogs Consensus Conference Group

110. Included in the interest of completeness, there was also a collaborative report in 2009, between the European Society for Pediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES).[133] Thirty experts were convened, evenly divided between North American and European labs and evenly divided male/female, who comprehensively rated the research literature on gonadotropin-release hormone analogs in children.

111. The effort concluded that "[u]se of gonadotropin-releasing hormone analogs for conditions other than central precocious puberty requires additional investigation and cannot be suggested routinely."[134] However, gender dysphoria was not explicitly mentioned as one of those other conditions.

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[132] Cantor, 2020, at 1.
[133] Carel et al., 2009.
[134] Carel et al. 2009, at 752.

VI. International Health Care Consensus

1. United Kingdom

112. The National Health Service (NHS) of the United Kingdom centralizes gender counselling and transitioning services in a single clinic, the Gender Identity Development Service (GIDS) of the Tavistock and Portman NHS Foundation Trust. Between 2008 and 2018, the number of referrals to the clinic had increased by a factor of 40, leading to a government inquiry into the causes[135]. The GIDS was repeatedly accused of over-diagnosing and permitting transition in cases despite indicators against patient transition, including by 35 members of the GIDS staff, who resigned by 2019[136].

113. The NHS appointed Dr. Hilary Cass, former President of the Royal College of Paediatrics and Child Health, to conduct an independent review[137]. That review included a systematic consolidation of all the research evidence, following established procedures for preventing the "cherry-picking" or selective citation favouring or down-playing any one conclusion[138]. The review's results were unambiguous: "The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low"[139], again using established procedures for assessing clinical research evidence (called GRADE). The review also assessed as "very low" the quality of evidence regarding "body image, psychosocial impact, engagement with health care services, impact on extent of an satisfaction with surgery and stopping treatment"[140]. The report concluded that of the existing research, "The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding….They suggest little change with GnRH analogues [puberty

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135 Marsh, 2020; Rayner, 2018.
136 BBC, 2021; Donnelly, 2019.
137 National Health Service, 2020, Sept. 22.
138 National Institute for Health and Care Excellence, 2020.
139 National Institute for Health and Care Excellence, 2020, p. 4.
140 National Institute for Health and Care Excellence, 2020, p. 5.

blockers] from baseline to follow-up"[141].

2. Finland

114. In Finland, the assessments of mental health and preparedness of minors for transition services are centralized by law into two research clinics, Helsinki University Central Hospital and Tampere University Hospital. The eligibility of minors began in 2011. In 2019, Finnish researchers published an analysis of the outcomes of adolescents diagnosed with transsexualism and receiving cross-sex hormone treatment[142]. That study showed that despite the purpose of medical transition to improve mental health: "Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development"[143]. The patients who were functioning well after transition were those who were already functioning well before transition, and those who were functioning poorly, continued to function poorly after transition.

115. Consistent with the evidence, Finland's health care service (Council for Choices in Health Care in Finland—COHERE) thus ended the surgical transition of minors, ruling in 2020 that "Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors" (COHERE, 2020). The review of the research concluded that "[N]o conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development." COHERE also greatly restricted access to puberty-blocking and other hormonal treatments, indicating they "may be considered if the need for it continues *after* the other psychiatric symptoms have

141 National Institute for Health and Care Excellence, 2020, p. 13.
142 Kaltiala et al., 2020.
143 Kaltiala et al., 2020, p. 213.

ceased and adolescent development is progressing normally"[144]. The council was explicit in noting the lack of research needed for decision-making, "There is also a need for more information on the *disadvantages* of procedures and on people who regret them"[145].

3. Sweden

116. Sweden's national health care policy regarding trans issues has developed quite similarly to that of the UK. Already in place 20 years ago, Swedish health care policy permitted otherwise eligible minors to receive puberty-blockers beginning at age 14 and cross-sex hormones at age 16.) At that time, only small numbers of minors sought medical transition services. An explosion of referrals ensued in 2013–2014. Sweden's Board of Health and Welfare reported that, in 2018, the number of diagnoses of gender dysphoria was 15 times higher than 2008 among girls ages 13–17.

117. Sweden has long been very accepting with regard to sexual and gender diversity. In 2018, a law was proposed to lower the age of eligibility for surgical care from age 18 to 15, remove the requirement for parental consent, and lower legal change of gender to age 12. A series of cases of regret and suicide were reported in the Swedish media, leading to questions of mental health professionals failing to consider. In 2019, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) therefore conducted its own comprehensive review of the research[146]. Like the UK, the Swedish investigation employed methods to ensure the encapsulation of the all the relevant evidence[147].

118. The SBU report came to the same conclusions as the UK commission. From 2022 forward, the Swedish National Board or Health and Welfare therefore

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144 Council for Choices in Health Care in Finland, 2020; italics added.
145 Council for Choices in Health Care in Finland, 2020; italics added.
146 Orange, 2020, Feb 22.
147 Swedish Agency for Health Technology Assessment and Assessment of Social Services, 2019.

"recommends restraint when it comes to hormone treatment…Based on the results that have emerged, the National Board of Health and Welfare's overall conclusion is that the risks of anti-puberty and sex-confirming hormone treatment for those under 18 currently outweigh the possible benefits for the group as a whole"[148]. Neither puberty blockers nor cross-sex hormones would be provided under age 16, and patients ages 16–18 would receive such treatments only within research settings (clinical trials monitored by the appropriate Swedish research ethics board).

4. France

119. In 2022, the Académie Nationale de Médecine of France issued a strongly worded statement, citing the Swedish ban on hormone treatments. "[A] great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause…such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause"[149]. For hormones, the Académie concluded "the greatest reserve is required in their use," and for surgical treatments, "[T]heir irreversible nature must be emphasized." The Académie did not outright ban medical interventions, but warned "the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to "detransition". Rather than medical interventions, it advised health care providers "to extend as much as possible the psychological support phase." The Académie reviewed and emphasized the evidence indicating the very large and very sudden increase in youth requesting medical transition. It attributed the change, not to society now being more accepting of sexual diversity, but to social media, "underlining the addictive character of excessive consultation of social networks which is both

[148] Swedish National Board of Health and Welfare, 2022.
[149] Académie Nationale de Médecine, 2022, Feb. 25.

harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence."

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APPENDICES

Appendix 1

The Outcomes Studies of Childhood-Onset Gender Dysphoria

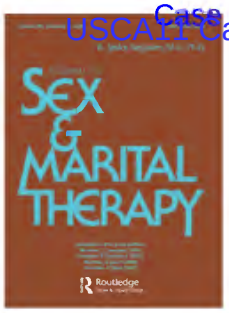
Appendix 2

Peer-reviewed article:

Cantor, J. M. (2020). Transgender and gender diverse children and adolescents: Fact-checking of AAP policy. *Journal of Sex & Marital Therapy, 46,* 307–313. doi: 10.1080/0092623X.2019.1698481

Prospective Outcomes Studies of Gender Dysphoric Children

2/16 4/16 10/16	gay trans-/crossdress straight/uncertain	Lebovitz, P. S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry, 128,* 1283–1289.
2/16 2/16 12/16	trans- uncertain gay	Zuger, B. (1978). Effeminate behavior present in boys from childhood: Ten additional years of follow-up. *Comprehensive Psychiatry, 19, 363–369.*
0/9 9/9	trans- gay	Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. *Journal of Pediatric Psychology, 4,* 29–41.
2/45 10/45 33/45	trans-/crossdress uncertain gay	Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease, 172,* 90–97.
1/10 2/10 3/10 4/10	trans- gay uncertain straight	Davenport, C. W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior, 15,*511–517.
1/44 43/44	trans- cis-	Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
0/8 8/8	trans- cis-	Kosky, R. J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia, 146,* 565–569.
21/54 33/54	trans- cis-	Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry, 47,* 1413–1423.
3/25 6/25 16/25	trans- lesbian/bi- straight	Drummond, K. D., Bradley, S. J., Badali-Peterson, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology, 44*, 34–45.
47/127 80/127	trans- cis-	Steensma, T. D., McGuire, J. K., Kreukels, B. P. C., Beekman, A. J., & Cohen-Kettenis, P. T. (2013). Factors associated with desistence and persistence of childhood gender dysphoria: A quantitative follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52,* 582–590.
17/139 122/139	trans- cis-	Singh, D., Bradley, S. J., and Zucker, K. J. (2021) A follow-up study of boys with gender identity disorder. Frontiers in Psychiatry, 12, 632784. doi: 10.3389/fpsyt.2021.632784



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Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy

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ABSTRACT

The American Academy of Pediatrics (AAP) recently published a policy statement: *Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents*. Although almost all clinics and professional associations in the world use what's called the *watchful waiting* approach to helping gender diverse (GD) children, the AAP statement instead rejected that consensus, endorsing *gender affirmation* as the only acceptable approach. Remarkably, not only did the AAP statement fail to include any of the actual outcomes literature on such cases, but it also misrepresented the contents of its citations, which repeatedly said the very opposite of what AAP attributed to them.

The American Academy of Pediatrics (AAP) recently published a policy statement entitled, *Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents* (Rafferty, AAP Committee on Psychosocial Aspects of Child and Family Health, AAP Committee on Adolescence, AAP Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, 2018). These are children who manifest discontent with the sex they were born as and desire to live as the other sex (or as some alternative gender role). The policy was quite a remarkable document: Although almost all clinics and professional associations in the world use what's called the *watchful waiting* approach to helping transgender and gender diverse (GD) children, the AAP statement rejected that consensus, endorsing only *gender affirmation*. That is, where the consensus is to delay any transitions after the onset of puberty, AAP instead rejected waiting before transition. With AAP taking such a dramatic departure from other professional associations, I was immediately curious about what evidence led them to that conclusion. As I read the works on which they based their policy, however, I was pretty surprised—rather alarmed, actually: These documents simply did not say what AAP claimed they did. In fact, the references that AAP cited as the basis of their policy instead outright contradicted that policy, repeatedly endorsing *watchful waiting*.

The AAP statement was also remarkable in what it left out—namely, the actual outcomes research on GD children. In total, there have been 11 follow-up studies of GD children, of which AAP cited one (Wallien & Cohen-Kettenis, 2008), doing so without actually mentioning the outcome data it contained. The literature on outcomes was neither reviewed, summarized, nor subjected to meta-analysis to be considered in the aggregate—It was merely disappeared. (The list of all existing studies appears in the appendix.) As they make clear, *every* follow-up study of GD children, without exception, found the same thing: Over puberty, the majority of GD children cease to want to transition. AAP is, of course, free to establish whatever policy it likes on

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whatever basis it likes. But any assertion that their policy is based on evidence is demonstrably false, as detailed below.

AAP divided clinical approaches into three types—conversion therapy, watchful waiting, and gender affirmation. It rejected the first two and endorsed *gender affirmation* as the only acceptable alternative. Most readers will likely be familiar already with attempts to use conversion therapy to change sexual orientation. With regard to gender identity, AAP wrote:

> "[C]onversion" or "reparative" treatment models are used to prevent children and adolescents from identifying as transgender or to dissuade them from exhibiting gender-diverse expressions. … Reparative approaches have been proven to be not only unsuccessful[38] but also deleterious and are considered outside the mainstream of traditional medical practice.[29,39–42]

The citations were:

38. Haldeman DC. The practice and ethics of sexual orientation conversion therapy. *J Consult Clin Psychol.* 1994;62(2):221–227.

29. Adelson SL; American Academy of Child and Adolescent Psychiatry (AACAP) Committee on Quality Issues (CQI). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *J Am Acad Child Adolesc Psychiatry.* 2012;51(9):957–974.

39. Byne W. Regulations restrict practice of conversion therapy. *LGBT Health.* 2016;3(2):97–99.

40. Cohen-Kettenis PT, Delemarrevan de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: changing insights. *J Sex Med.* 2008;5(8):1892–1897.

41. Bryant K. Making gender identity disorder of childhood: historical lessons for contemporary debates. *Sex Res Soc Policy.* 2006;3(3):23–39.

42. World Professional Association for Transgender Health. *WPATH De-Psychopathologisation Statement.* Minneapolis, MN: World Professional Association for Transgender Health; 2010.

AAP's claims struck me as odd because *there are no studies of conversion therapy for gender identity.* Studies of conversion therapy have been limited to *sexual orientation,* and, moreover, to the sexual orientation *of adults,* not to gender identity and not of children in any case. The article AAP cited to support their claim (reference number 38) is indeed a classic and well-known review, but it is a review of sexual orientation research *only.* Neither gender identity, nor even children, received a single mention in it. Indeed, the narrower scope of that article should be clear to anyone reading even just its title: "The practice and ethics of *sexual orientation* conversion therapy" [italics added].

AAP continued, saying that conversion approaches for GD children have already been rejected by medical consensus, citing five sources. This claim struck me as just as odd, however—I recalled associations banning conversion therapy for sexual orientation, but not for gender identity, exactly because there is no evidence for generalizing from adult sexual orientation to childhood gender identity. So, I started checking AAP's citations for that, and these sources too pertained only to sexual orientation, not gender identity (specifics below). What AAP's sources *did* repeatedly emphasize was that:

A. Sexual orientation of adults is unaffected by conversion therapy and any other [known] intervention;
B. Gender dysphoria in childhood before puberty desists in the majority of cases, becoming (cis-gendered) homosexuality in adulthood, again regardless of any [known] intervention; and
C. Gender dysphoria in childhood persisting after puberty tends to persist entirely.

That is, in the context of GD children, it simply makes no sense to refer to externally induced "conversion": The majority of children "convert" to cisgender or "desist" from transgender

regardless of any attempt to change them. "Conversion" only makes sense with regard to adult sexual orientation because (unlike childhood gender identity), adult homosexuality never or nearly never spontaneously changes to heterosexuality. Although gender identity and sexual orientation may often be analogous and discussed together with regard to social or political values and to civil rights, they are nonetheless distinct—with distinct origins, needs, and responses to medical and mental health care choices. Although AAP emphasized to the reader that "gender identity is not synonymous with 'sexual orientation'" (Rafferty et al., 2018, p. 3), they went ahead to treat them as such nonetheless.

To return to checking AAP's fidelity to its sources: Reference 29 was a practice guideline from the Committee on Quality Issues of the American Academy of Child and Adolescent Psychiatry (AACAP). Despite AAP applying this source to *gender identity,* AACAP was quite unambiguous regarding their intent to speak to sexual orientation and *only* to sexual orientation: "Principle 6. Clinicians should be aware that there is no evidence that *sexual orientation* can be altered through therapy, and that attempts to do so may be harmful. There is no established evidence that change in a predominant, enduring *homosexual* pattern of development is possible. Although sexual fantasies can, to some degree, be suppressed or repressed by those who are ashamed of or in conflict about them, sexual desire is not a choice. However, behavior, social role, and—to a degree—identity and self-acceptance are. Although operant conditioning modifies sexual fetishes, it does not alter *homosexuality*. Psychiatric efforts to alter *sexual orientation* through 'reparative therapy' *in adults* have found little or no change in *sexual orientation,* while causing significant risk of harm to self-esteem" (AACAP, 2012, p. 967, italics added).

Whereas AAP cites AACAP to support gender affirmation as the only alternative for treating GD children, AACAP's actual view was decidedly neutral, noting the lack of evidence: "Given the lack of empirical evidence from randomized, controlled trials of the efficacy of treatment aimed at eliminating gender discordance, the potential risks of treatment, and longitudinal evidence that gender discordance persists in only a small minority of untreated cases arising in childhood, further research is needed on predictors of persistence and desistence of childhood gender discordance as well as the long-term risks and benefits of intervention before any treatment to eliminate gender discordance can be endorsed" (AACAP, 2012, p. 969). Moreover, whereas AAP rejected watchful waiting, what AACAP recommended was: "In general, it is desirable to help adolescents who may be experiencing gender distress and dysphoria to defer sex reassignment until adulthood" (AACAP, 2012, p. 969). So, not only did AAP attribute to AACAP something AACAP never said, but also AAP withheld from readers AACAP's actual view.

Next, in reference 39, Byne (2016) also addressed only sexual orientation, doing so very clearly: "Reparative therapy is a subset of conversion therapies based on the premise that *same-sex attraction* are reparations for childhood trauma. Thus, practitioners of reparative therapy believe that exploring, isolating, and repairing these childhood emotional wounds will often result in reducing *same-sex attractions*" (Byne, 2016, p. 97). Byne does not say this of gender identity, as the AAP statement misrepresents.

In AAP reference 40, Cohen-Kettenis et al. (2008) did finally pertain to gender identity; however, this article never mentions conversion therapy. (!) Rather, in this study, the authors presented that clinic's lowering of their minimum age for cross-sex hormone treatment from age 18 to 16, which they did on the basis of a series of studies showing the high rates of success with this age group. Although it did strike me as odd that AAP picked as support against conversion therapy an article that did not mention conversion therapy, I could imagine AAP cited the article as an example of what the "mainstream of traditional medical practice" consists of (the logic being that conversion therapy falls outside what an 'ideal' clinic like this one provides). However, what this clinic provides is the very *watchful waiting* approach that AAP rejected. The approach

espoused by Cohen-Kettenis (and the other clinics mentioned in the source—Gent, Boston, Oslo, and now formerly, Toronto) is to make puberty-halting interventions available at age 12 because: "[P]ubertal suppression may give adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis may thus be improved" (Cohen-Kettenis et al., 2008, p. 1894).

Reference 41 presented a very interesting history spanning the 1960s–1990s about how feminine boys and tomboyish girls came to be recognized as mostly pre-homosexual, and how that status came to be entered into the DSM at the same time as homosexuality was being *removed* from the DSM. Conversion therapy is never mentioned. Indeed, to the extent that Bryant mentions treatment at all, it is to say that treatment is entirely irrelevant to his analysis: "An important omission from the *DSM* is a discussion of the kinds of treatment that GIDC children should receive. (This omission is a general orientation of the DSM and not unique to GIDC)" (Bryant, 2006, p. 35). How this article supports AAP's claim is a mystery. Moreover, how AAP could cite a 2006 history discussing events of the 1990s and earlier to support a claim about the *current* consensus in this quickly evolving discussion remains all the more unfathomable.

Cited last in this section was a one-paragraph press release from the World Professional Association for Transgender Health. Written during the early stages of the American Psychiatric Association's (APA's) update of the DSM, the statement asserted simply that "The WPATH Board of Directors strongly urges the de-psychopathologisation of gender variance worldwide." Very reasonable debate can (and should) be had regarding whether gender dysphoria should be removed from the DSM as homosexuality was, and WPATH was well within its purview to assert that it should. Now that the DSM revision process is years completed however, history has seen that APA ultimately retained the diagnostic categories, rejecting WPATH's urging. This makes AAP's logic entirely backwards: That WPATH's request to depathologize gender dysphoria was *rejected* suggests that it is *WPATH's* view—and therefore the AAP policy—which fall "outside the mainstream of traditional medical practice." (!)

AAP based this entire line of reasoning on their belief that conversion therapy is being used "to prevent children and adolescents from identifying as transgender" (Rafferty et al., 2018, p. 4). That claim is left without citation or support. In contrast, what is said by AAP's sources is "delaying affirmation should *not* be construed as conversion therapy or an attempt to change gender identity" in the first place (Byne, 2016, p. 2). Nonetheless, AAP seems to be doing exactly that: simply relabeling any alternative approach as equivalent to conversion therapy.

Although AAP (and anyone else) may reject (what they label to be) conversion therapy purely on the basis of political or personal values, there is no evidence to back the AAP's stated claim about the existing science on gender identity at all, never mind gender identity of children.

AAP also dismissed the watchful waiting approach out of hand, not citing any evidence, but repeatedly calling it "outdated." The criticisms AAP provided, however, again defied the existing evidence, with even its own sources repeatedly calling watchful waiting the current standard. According to AAP:

> [G]ender affirmation is in contrast to the outdated approach in which a child's gender-diverse assertions are held as "possibly true" until an arbitrary age (often after pubertal onset) when they can be considered valid, an approach that authors of the literature have termed "watchful waiting." This outdated approach does not serve the child because critical support is withheld. Watchful waiting is based on binary notions of gender in which gender diversity and fluidity is pathologized; in watchful waiting, it is also assumed that notions of gender identity become fixed at a certain age. The approach is also influenced by a group of early studies with validity concerns, methodologic flaws, and limited follow-up on children who identified as TGD and, by adolescence, did not seek further treatment ("desisters").[45,47]

The citations from AAP's reference list are:

45. Ehrensaft D, Giammattei SV, Storck K, Tishelman AC, Keo-Meier C. Prepubertal social gender transitions: what we know; what we can learn—a view from a gender affirmative lens. *Int J Transgend.* 2018;19(2):251–268

47. Olson KR. Prepubescent transgender children: what we do and do not know. *J Am Acad Child Adolesc Psychiatry.* 2016;55(3):155–156.e3

I was surprised first by the AAP's claim that watchful waiting's delay to puberty was somehow "arbitrary." The literature, including AAP's sources, repeatedly indicated the pivotal importance of puberty, noting that outcomes strongly diverge at that point. According to AAP reference 29, in "*prepubertal* boys with gender discordance—including many without any mental health treatment—the cross gender wishes usually fade over time and do not persist into adulthood, with only 2.2% to 11.9% continuing to experience gender discordance" (Adelson & AACAP, 2012, p. 963, italics added), whereas "when gender variance with the desire to be the other sex is present *in adolescence,* this desire usually does persist through adulthood" (Adelson & AACAP, 2012, p. 964, italics added). Similarly, according to AAP reference 40, "Symptoms of GID *at prepubertal ages* decrease or even disappear in a considerable percentage of children (estimates range from 80–95%). Therefore, any intervention in childhood would seem premature and inappropriate. However, GID persisting *into early puberty* appears to be highly persistent" (Cohen-Kettenis et al., 2008, p. 1895, italics added). That follow-up studies of prepubertal transition differ from postpubertal transition is the very meaning of non-arbitrary. AAP gave readers exactly the reverse of what was contained in its own sources. If AAP were correct in saying that puberty is an arbitrarily selected age, then AAP will be able to offer another point to wait for with as much empirical backing as puberty has.

Next, it was not clear on what basis AAP could say that watchful waiting withholds support—AAP cited no support for its claim. The people in such programs often receive substantial support during this period. Also unclear is on what basis AAP could already know exactly which treatments are "critical" and which are not—Answering that question is the very purpose of this entire endeavor. Indeed, the logic of AAP's claim appears entirely circular: It is only if one were already pre-convinced that gender affirmation is the only acceptable alternative that would make watchful waiting seem to withhold critical support—What it delays is gender affirmation, the method one has already decided to be critical.

Although AAP's next claim did not have a citation appearing at the end of its sentence, binary notions of gender were mentioned both in references 45 and 47. Specifically, both pointed out that existing outcome studies have been about people transitioning from one sex to the other, rather than from one sex to an in-between status or a combination of masculine/feminine features. Neither reference presented this as a reason to reject the results from the existing studies of complete transition however (which is how AAP cast it). Although it is indeed true that the outcome data have been about complete transition, some future study showing that partial transition shows a different outcome would not invalidate what is known about complete transition. Indeed, data showing that partial transition gives better outcomes than complete transition would, once again, support the watchful waiting approach which AAP rejected.

Next was a vague reference alleging concerns and criticisms about early studies. Had AAP indicated what those alleged concerns and flaws were (or which studies they were), then it would be possible to evaluate or address them. Nonetheless, the argument is a red herring: Because all of the later studies showed the same result as did the early studies, any such allegation is necessarily moot.

Reference 47 was a one-and-a-half page commentary in which the author off-handedly mentions criticisms previously made of three of the eleven outcome studies of GD children, but does not provide any analysis or discussion. The only specific claim was that studies (whether early or late) had limited follow-up periods—the logic being that had outcome researchers lengthened the follow-up period, then people who seemed to have desisted might have returned to the clinic as

cases of "persistence-after-interruption." Although one could debate the merits of that prediction, AAP instead simply withheld from the reader the result from the original researchers having tested that very prediction directly: Steensma and Cohen-Kettenis (2015) conducted another analysis of their cohort, by then ages 19–28 (mean age 25.9 years), and found that 3.3% (5 people of the sample of 150) later returned. That is, in long-term follow-up, the childhood sample showed 66.7% desistence instead of 70.0% desistance.

Reference 45 did not support the claim that watchful-waiting is "outdated" either. Indeed, that source said the very opposite, explicitly referring to watchful waiting as the *current* approach: "Put another way, if clinicians are straying from SOC 7 guidelines for social transitions, not abiding by the watchful waiting model *favored by the standards,* we will have adolescents who have been consistently living in their affirmed gender since age 3, 4, or 5" (Ehrensaft et al., 2018, p. 255). Moreover, Ehrensaft et al. said there are cases in which they too would still use watchful waiting: "When a child's gender identity is unclear, the watchful waiting approach can give the child and their family time to develop a clearer understanding and is not necessarily in contrast to the needs of the child" (p. 259). Ehrensaft et al. are indeed critical of the watchful waiting model (which they feel is applied too conservatively), but they do not come close to the position the AAP policy espouses. Where Ehrensaft summaries the potential benefits and potential risks both to transitioning and not transitioning, the AAP presents an ironically binary narrative.

In its policy statement, AAP told neither the truth nor the whole truth, committing sins both of commission and of omission, asserting claims easily falsified by anyone caring to do any fact-checking at all. AAP claimed, "This policy statement is focused specifically on children and youth that identify as TGD rather than the larger LGBTQ population"; however, much of that evidence was about sexual orientation, not gender identity. AAP claimed, "Current available research and expert opinion from clinical and research leaders … will serve as the basis for recommendations" (pp. 1–2); however, they provided recommendations entirely unsupported and even in direct opposition to that research and opinion.

AAP is advocating for something far in excess of mainstream practice and medical consensus. In the presence of compelling evidence, that is just what is called for. The problems with Rafferty, however, do not constitute merely a misquote, a misinterpretation of an ambiguous statement, or a missing reference or two. Rather, AAP's statement is a systematic exclusion and misrepresentation of entire literatures. Not only did AAP fail to provide compelling evidence, it failed to provide the evidence at all. Indeed, AAP's recommendations are *despite* the existing evidence.

Disclosure statement

No potential conflict of interest was reported by the author.

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Rafferty, J., AAP Committee on Psychosocial Aspects of Child and Family Health, AAP Committee on Adolescence, AAP Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness. (2018). Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*, *142*(4), e20182162 doi:10.1542/peds.2018-2162

Steensma, T. D., & Cohen-Kettenis, P. T. (2015). More than two developmental pathways in children with gender dysphoria? *Journal of the American Academy of Child and Adolescent Psychiatry*, *52*, 147–148. doi:10.1016/j.jaac.2014.10.016

Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 1413–1423. doi:10.1097/CHI.0b013e31818956b9

Appendix

Count	Group	Study
2/16 4/16 10/16	gay* trans-/crossdress straight*/uncertain	Lebovitz, P. S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry, 128,* 1283–1289.
2/16 2/16 12/16	trans- uncertain gay	Zuger, B. (1978). Effeminate behavior present in boys from childhood: Ten additional years of follow-up. *Comprehensive Psychiatry, 19,* 363–369.
0/9 9/9	trans- gay	Money, J., & Russo, A. J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. *Journal of Pediatric Psychology, 4,* 29–41.
2/45 10/45 33/45	trans-/crossdress uncertain gay	Zuger, B. (1984). Early effeminate behavior in boys: Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease, 172,* 90–97.
1/10 2/10 3/10 4/10	trans- gay uncertain straight	Davenport, C. W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior, 15,* 511–517.
1/44 43/44	trans- cis-	Green, R. (1987). *The "sissy boy syndrome" and the development of homosexuality*. New Haven, CT: Yale University Press.
0/8 8/8	trans- cis-	Kosky, R. J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia, 146,* 565–569.
21/54 33/54	trans- cis-	Wallien, M. S. C., & Cohen-Kettenis, P. T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry, 47,* 1413–1423.
3/25 6/25 16/25	trans- lesbian/bi- straight	Drummond, K. D., Bradley, S. J., Badali-Peterson, M., & Zucker, K. J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology, 44,* 34–45.
17/139 122/139	trans- cis-	Singh, D. (2012). *A follow-up study of boys with gender identity disorder*. Unpublished doctoral dissertation, University of Toronto.
47/127 80/127	trans- cis-	Steensma, T. D., McGuire, J. K., Kreukels, B. P. C., Beekman, A. J., & Cohen-Kettenis, P. T. (2013). Factors associated with desistence and persistence of childhood gender dysphoria: A quantitative follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52,* 582–590.

*For brevity, the list uses "gay" for "gay and cis-", "straight" for "straight and cis-", etc.

ATTACHMENT E

Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent

Quentin L. Van Meter, M.D.
May 17, 2022

Qualifications

I received my B.A. in Science at the College of William and Mary and my M.D. from the Medical College of Virginia, Virginia Commonwealth University. I am currently a pediatric endocrinologist in private practice in Atlanta, Georgia. I am the President of Van Meter Pediatric Endocrinology, P.C. I am on the clinical faculties of Emory University School of Medicine and Morehouse College of Medicine, in the role of adjunct Associate Professor of Pediatrics. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Georgia since 1991. I have been previously licensed to practice medicine in California, Louisiana, and Maryland.

I did my Pediatric Endocrine fellowship at Johns Hopkins Hospital from 1978-1980. The faculty present at that time had carried on the tradition of excellence established by Lawson Wilkins, M.D. Because of the reputation of the endocrine program as a center for exceptional care for children with disorders of sexual differentiation, I had well-above average exposure to such patients. As a Pediatric Fellow, I was also exposed to adults with Gender Identity Disorder, then called Trans-Sexuality, and received training from John Money, Ph.D., in his Psycho-hormonal Division. Over the past 44 years, I have closely followed the topic of incongruent gender in children adolescents and adults, but I am focusing in this document on working with children and adolescents. To get a more solid understanding of how male and female human beings develop in utero, it is important to start at the point when a sperm meets an egg.

Differentiation in the Fetus

From the moment of conception, a fetus is determined to be either a male (XY), female (XX), or in rare cases, to have a combination of sex-determining chromosomes, many of which are not compatible with life, and some of which are the cause of identifiable clinical syndromes. The presence of a Y chromosome in the developing fetus directs the developing gonadal tissue to develop as a testicle. The absence of a functional Y chromosome allows the gonadal tissue to develop as an ovary. Under the influence of the mother's placental hormones, the testicle will produce testosterone which directs the genital tissue to form a penis and a scrotum. Simultaneously, the testicle produces anti-Müllerian Hormone (AMH) which regresses development of the tissue that would otherwise develop into the uterus, fallopian tubes, and upper third of the vagina. This combination of actions in early fetal development is responsible for what we subsequently see on fetal sonograms, and what we observe at birth as male or female genitalia. It is only when the genital structures are ambiguous in appearance that sex determination is withheld until a thorough expert team evaluation has occurred.

For reasons most often occurring as random events, there are malfunctions of the normal differentiation. These aberrations of normal development are responsible for what we classify as Disorders of Sexual Differentiation (DSD), and they represent a very small fraction of the human population. The incidence of such circumstances occurs in 1:4500 to 1:5500 births.[1] Sex is binary, male or female, and is determined by chromosomal complement and corresponding reproductive role. The exceedingly rare DSDs are all medically identifiable deviations from this sexual binary norm. The 2006 consensus statement of the Intersex Society of North America and the 2015 revision of the Statement do not endorse DSD as a third sex.[2] DSD outcomes range from appearance of female external genitalia in an XY male (complete androgen insensitivity syndrome) to appearance of male external genitalia in an XX female (severe congenital adrenal hyperplasia).

As one would expect, there are variations of the degree of hormonally driven changes that create ambiguous genital development that prevent assigning of a specific classification as either male or female at birth. DSD patients are not "transgender"; they have an objective, physical, medically verifiable, physiologic condition. Transgender people generally do not have intersex conditions or any other verifiable physical anomaly. People who identify as "feeling like the opposite sex" or "somewhere in between" do not comprise a third sex. They remain biological men or biological women.

In some DSDs there exist more than one set of chromosomes. When there is a divergence of the appearance of the external genitalia from the chromosomally determined sex due to the presence of both an ovarian and testicular cell lines in a patient simultaneously, the patient is classified as having ovo-testicular DSD (formerly termed a true hermaphrodite). When there is a disruption in the development of genital structures but there is solely testicular tissue present in the chromosomal male or solely ovarian tissue in the chromosomal female, the term 46 XY DSD or 46 XX DSD is used instead respectively (formerly termed male pseudohermaphrodite or female pseudohermaphrodite).

The decision to assign a sex of rearing is complex and is specific to the diagnosis. Patients with complete androgen insensitivity (CAIS) are XY DSD but are never reared as a male. Because testosterone never influences development, they become happy, functional female adults with infertility. Females with severe congenital adrenal hyperplasia (CAH) are XX DSD but are not reared as males despite the male appearance of the genitalia at birth. Although these girls may show a tendency for male play behaviors as children, they generally assume a female sexual identity. Therapeutic interventions in the DSD individuals from infancy onward are aimed at what function can be expected from their disordered sexual anatomy in terms of function and fertility. Most often, the chromosomal sex aligns with the sex of rearing.

Gender Identity

"Gender" is a term that refers to the psychological and cultural characteristics associated with biological sex. It is a psychological concept and sociological term, not a biological one. The term gender possessed solely a linguistic meaning prior to the 1950s. This changed when sexologists of the 1950s and 1960s co-opted the term to conceptualize cross-dressing and transsexualism in their psychological practice. "Gender identity" is a term coined by my former endocrine faculty member John Money in the 1970s and has come to refer to an individual's mental and emotional sense of being male or female. The norm is for individuals to have a gender identity that aligns with one's biological sex.

Gender discordance (formerly Gender Identity Disorder) is used to describe a psychological condition in which a person experiences marked incongruence between his experienced gender and the gender associated with his biological sex. He will often express the belief that he is the opposite sex. Up until 2010, gender discordance occurred in 0.001% of biological females and in 0.0033% of biological males.[3] Exact numbers are hard to document since reporting is often anecdotal. Gender discordance is not considered a normal developmental variation.

"Gender Dysphoria" is a diagnostic term to describe the emotional distress caused by gender incongruity.[4] John Money played a prominent role in the early development of gender theory and transgenderism. He understood gender to be "the social performance indicative of an internal sexed identity."[5] He joined the Johns Hopkins faculty in 1951 specifically to have access to children diagnosed with DSD, hoping to prove his theory that gender was arbitrary and fluid. Money experimented with DSD infants by assigning them to the opposite biological sex through surgical revision, counseling, and hormonal manipulation during puberty. His mode of operation was to have a theory and then experiment with patients to see how his theory worked.

Ethics in Clinical Research on Human Subjects

It is important to discuss the need for ethics to play a role in the design of clinical studies involving human patients. To have a hypothesis, as did John Money, is not at issue. However, to clearly elucidate the potential for harm and balance that knowledge with the potential benefits is key and essential. After the travesties of open-ended experimentation in the Nazi concentration camps, international guidelines were established to protect human subjects from just such experimentation.[6] John Money ignored these guidelines as he assigned genders to infants and toddlers with ambiguous genitalia. There was no informed consent of the patients, who were infants and toddlers, and their parents were just told to follow the advice of Dr. Money and to trust that he had the correct information. There was no standardized protocol to follow, and no known outcome that could be guaranteed. This kind of endeavor did not anticipate or prevent adverse outcomes and was the antithesis of ethical science. Money never submitted his research proposals for review by an independent external review board. This left the patients unprotected and vulnerable to harm, and, indeed, in the case of the Reimer twins, to death due to drug addiction/overdose in one brother to and suicide in the other.[7]

Near the end of my fellowship training at Johns Hopkins, a male infant was sent to our clinic to assess the cause of his very small penis and testicles. My attending physician and I laid out a diagnostic work-up based on the known science which would help us understand whether the problem was due to a pituitary deficiency or an inability of tissue response to hormones. We purposely left John Money off the care "team," having some serious concerns about his tendency to dismiss science and to experiment. We sent the family home with their son and were quite surprised when the mother returned six weeks later with a baby wearing a pink dress and an eyelet bonnet. Without our knowledge, Dr. Money had intervened and told the family that our protocol was nonsense and the baby needed to be reared as female. On physical exam, there was clear evidence that not only was the baby able to produce testosterone, but his penis responded well, as expected, to the hormone production by his own body. The family was relieved but had not been spared suffering under the experimentation by Dr. Money. They had suffered deeply when they divulged to their extended family that their baby boy was actually a baby girl, and then they suffered even more when they recanted and resumed calling him a boy.

Because of his experience with infants, Money initially garnered support from endocrine colleagues and surgical colleagues, and Johns Hopkins became a renowned center for care of patients with DSD in the 1970s, receiving referrals from around the world. Follow-up studies on these infants later showed, however, that altering their natal sexual identity via social intervention could lead to severe psychological harm. Clinical case reports of children with DSD have revealed that gender identity is indeed not immune to environmental input.[8]

Meanwhile, Money had expanded into the field of adult patients with persistent gender identity disorder. This very small group of patients chose voluntarily, as adults, to enter a very precise protocol which began with living socially as the opposite sex for a year, eventually receiving hormonal therapy to change their physical appearance to some extent. The final step was surgical revision of the body structures that would otherwise be at odds with their desired gender identity. This small group of patients was followed for a number of years past their final surgical procedures and required continuous counseling. These patients expressed some degree of subjective satisfaction but showed no objective improvement in overall wellbeing.[9] The legacy of John Money fell into disrepute and the transsexual treatment program at Johns Hopkin was closed in the 1980s based on the lack of evidence that this protocol produced an effective cure.

Etiology of Gender Disorders

Transgender affirming professionals claim transgender individuals have a "feminized brain" trapped in a male body at birth and vice versa based upon various brain studies. Diffusion-weighted MRI scans have demonstrated that the pubertal testosterone surge in boys increases white matter volume. A study by Rametti and colleagues found that the white matter microstructure of the brains of female-to-male (FtM) transsexual adults, who had not begun testosterone treatment, more closely resembled that of men than that of women.[10] Other

diffusion-weighted MRI studies have concluded that the white matter microstructure in both FtM and male-to-female (MtF) transsexuals falls halfway between that of genetic females and males.[11] These studies, however, are of limited clinical significance due to the small number of subjects and failure to account for neuroplasticity.

Neuroplasticity is the well-established phenomenon in which long-term behavior alters brain microstructure. For example, the MRI scans of experienced cab drivers in London are distinctly different from those of non-cab drivers, and the changes noted are dependent on the years of experience.[12] There is no evidence that people are born with brain microstructures that are forever unalterable, but there is significant evidence that experience changes brain microstructure.[13,14] Therefore, any transgender brain differences would more likely be the result of transgender behavior than its cause.

Furthermore, infants' brains are imprinted prenatally by their own endogenous sex hormones, which are secreted from their gonads beginning at approximately eight weeks' gestation.[15,16,17] There are no published studies documenting MRI-verified differences in the brains of gender-disordered children or adolescents. The DSD guidelines also specifically state that current MRI technology cannot be used to identify those patients who should be raised as males or raised as females.[18] Behavior geneticists have known for decades that while genes and hormones influence behavior, they do not hard-wire a person to think, feel, or behave in a particular way. The science of epigenetics has established that genes are not analogous to rigid "blueprints" for behavior. Rather, humans "develop traits through the dynamic process of gene-environment interaction. ... [genes alone] don't determine who we are." [19]

Regarding transgenderism, twin studies of adults prove definitively that prenatal genetic and hormone influence is minimal. The largest twin study of transgender adults found that only 20 percent of identical twins were both transgender-identified.[20] Since identical twins contain 100 percent of the same DNA from conception and develop in exactly the same prenatal environment exposed to the same prenatal hormones, if genes and/or prenatal hormones contributed to a significant degree to transgenderism, the concordance rates would be close to 100 percent. Instead, 80 percent of identical twin pairs were discordant. This difference would indicate that at least 80 percent of what contributes to transgenderism as an adult in one co-twin consists of one or more non-shared post-natal experiences including but not limited to non-shared family experiences. These findings also mean that persistent GD is due predominately to the impact of nonshared environmental influences. These studies provide compelling evidence that discordant gender is not hard-wired genetically.

Gender Dysphoria vs. Gender Identity Disorder

Up until the recent revision of the DSM-IV criteria, the American Psychological Association (APA) held that Gender Identity Disorder (GID) was the mental disorder described as a discordance between the natal sex and the gender identity of the patient. Dr. Kenneth Zucker, who is a highly respected clinician and researcher from Toronto, carried on evaluation and

treatment of GID patients for forty years. His works, widely published, found that the vast majority of boys and girls with GID identify with their biological sex by the time they emerge from puberty to adulthood, through either watchful waiting or family and individual counseling.[21] His results were mirrored in studies from Europe.[22,23]

When the DSM-V revision of the diagnosis of GID was proposed by the APA committee responsible for revision, Dr. Zucker strongly opposed the change to the term Gender Dysphoria, which purposefully removed gender discordance as a mental disorder apart from the presence of significant emotional distress. With this revision, Gender Dysphoria describes the mental anguish which is experienced by the gender discordant patient. The theory that societal rejection is the root cause of Gender Dysphoria was validly questioned by a study from Sweden which showed that the dysphoria was not eliminated by hormones and sex reassignment surgery even with widespread societal acceptance.[24]

Treatment of Gender Dysphoria

The treatment of children and adolescents with gender discordance and accompanying gender dysphoria should include an in-depth evaluation of the child and family dynamics. This evaluation provides a basis on which to proceed with psychologic therapy. The entire biologic and social family should be involved in psychological therapy designed to assist the patient, if at all possible, to align gender identity with natal sex. Psychological support by competent counselors with an intent of resolving the gender conflict should be provided as long as the patient continues to suffer emotionally. Given the high degree of eventual desistance of gender discordance/dysphoria by the end of puberty, it would be ethical and logical to counsel the patient and family to rear the child in conformity with natal sex.

There should be no interruption of natural puberty. Natural pubertal maturation in accordance with one's natal sex is not a disease. It is designed to carry malleable, immature children forward to be healthy adults capable of conceiving their own progeny by providing either a sperm or an egg. Puberty affects physical changes, some of them painful, unique to the natal sex to reflect the laws of nature. Interruption of puberty has been reserved for children who begin puberty at an age much younger than normal in an effort to preserve final height potential and avoid the social consequences of precocious maturation.[25]

There are a number of physical changes that are a consequence of normally timed puberty that could be classified as disadvantageous: changes in body proportions can alter success with dance and gymnastics; acne can be severe and disfiguring; a boy soprano can suddenly hardly carry a tune. It has not been the ethical standard of care to stop puberty so that these changes can be circumvented. Erikson described the stage of adolescence as "Identity versus Role Confusion" during which the teen works at developing a sense of self by testing roles then integrating them into a single identity.[26] This process is often unpleasant regardless of the presence or absence of gender identity conflicts. The major benefit of enduring puberty in a GD patient is that it provides a strong likelihood of alignment of his gender identity with his

natal sex. There is no doubt that these patients need compassionate care to get them through their innate pubertal changes.

The light at the end of the tunnel is the proven scientific evidence that 80%- 95% of pre-pubertal children with GD will come to identify with their biological sex by late adolescence. Some will require lifelong supportive counseling while others will not.[27] Intervention at a young age with gonadotropin releasing hormone analogs (often referred to as puberty blockers) to either stop puberty early on or prevent it from starting before it naturally occurs is suggested by guidelines developed by WPATH without scientific basis. These guidelines are essentially nothing more than an open-ended experiment in the manner of John Money. They represent the ideas of their authors with clear admission that there is no long-term evidence that harm will exceed benefits as these patients grow to old age. There is evidence that bone mineral density is irreversibly decreased if puberty blockers are used during the years of adolescence.[28] To treat puberty as a pathologic state of health that should be avoided by using puberty blockers (GnRH analogs) is to interrupt a major necessary physiologic transformation at a critical age when such changes can effectively happen. We have definite evidence of the need for estrogen in females to store calcium in their skeleton in their teen years. That physiologic event can't be put off successfully to a later date. It is very difficult to imagine ethical controlled clinical trials that could elucidate the effects of delaying puberty until the age of consent.

The use of cross-sex hormones during this same time frame has no basis of safety and efficacy. The use of such treatment in adults raises scientifically valid concerns that were amply expressed in the 2009 Endocrine Society Guidelines on Transgender treatment. The next step in WPATH-recommended intervention is to use cross-sex hormone therapy during the time when the patient would naturally be experiencing endogenous pubertal changes. This too is not based on scientifically proven theories. The use of cross-sex hormones can cause permanent infertility.[29]

The final recommended step is so-called "sex reassignment surgery," which can include surgical removal of the breasts in natal females, or removal of the penis and scrotum in natal males. Each of these steps has adverse outcomes, some reversible and others not. Mastectomies leave scars, and there is great difficulty in creating a functional vaginal-like orifice, and certainly no success in creating an innervated erectile penis where none existed previously. Sex reassignment surgery is, by nature, permanent.

Recurrent Themes that Are Repeatedly Published

Puberty blockers are stated to be completely reversible in their effects on the adolescent who has entered puberty based on clinical studies in young children with precocious puberty who have been treated with these drugs. This is comparing apples to oranges. Precocious puberty, by definition, is defined as puberty which starts before the 8th birthday for a female child or the before the 9th birthday in a male child. The end of treatment is carefully timed so that resumption of puberty occurs at the average age for females (10.5 years) and males (11.5

years). This allows the necessary functions of puberty to prepare the body for reproduction and affects the bones, gonads, and brain, among other body systems. On the other hand, blocking puberty at the age of normal puberty prevents the needed accretion of calcium into the skeleton and prevents the maturation of the gonads. There is no long-term data that compares bone, gonad, and brain health in pubertal-aged patients who have had puberty interrupted and those who have not, as was noted as a concern in the Endocrine Society Guidelines. There are no such ongoing studies completed that guarantee the full reversibility of blocking puberty in this age group, but there is evidence that normal bone density can't be fully reestablished. Without any verifiable safety data, using the puberty blockers for interrupting normal puberty is not a sanctionable off-label use of these drugs and is therefore to be considered uncontrolled, non-consentable experimentation on children.

Advocates for the social, medical and surgical affirmation of gender incongruent children insist that they are only following established standards of care. There are no standards of care for transgender health. Standards of care established by broad consensus are reached by inclusion of the whole spectrum of opinions, clinical experience and published science in the formation thereof. The guidelines published by WPATH[30], the Endocrine Society,[29,31] the American Academy of Pediatrics[32], and the Pediatric Endocrine Society[33] are solely the opinions of like-minded practitioners who excluded any contrary opinion. The Endocrine Society Guidelines, as mentioned before, clearly stated that they are not to be considered standards of care. Before true consensus-driven standards of care are established for the treatment of transgender patients of all ages, following the current guidelines is risky experimentation in a manner reminiscent of John Money's tactics.

What We Do Know and Do Not Know

We do know that social affirmation of an incongruent gender tears the fabric of the patient's life into pieces- pitting family members against each other, ruining child friendships and it introduces the child to a fantasy world, much of it on the internet. Kenneth Zucker aptly documented the detrimental effects of such affirmation and the immense amount of work it takes to undo these effects when the child does come to realize they can't change their sex and wants to go back to identifying with their sex[34]. We do not know that social affirmation does anything other than push the child away from the proven, 80-90% effective, so-called watch-and wait treatment option. Embarrassingly unscientific short term convenience sample studies purport to show that all gender incongruent children who are socially affirmed have improved mental health and are therefore better off than those children who are not allowed to socially transition.[35]

We do know that blocking puberty during the age when puberty naturally happens lessens accretion of calcium into the skeleton and that this can't be regained by allowing puberty to resume or by using cross sex hormones. We do know that the ovary and testicle cease to mature with treatment. What we do not know is whether allowing puberty to resume will allow the ovary and testicle to fully mature and have full function in terms of fertility. We do

not know if brain development that is halted with puberty blockers can return to full . function once puberty is allowed to resume.

We do know that elevated levels of testosterone in females and of estrogen in males create significant medical morbidity. This knowledge comes from the evaluation and treatment of naturally occurring disease states in children and adults. Treatment of these conditions is aimed at returning hormone levels to normal, thereby avoiding cancers, heart disease, and stroke. We do not know that elevating testosterone in females and estrogen in males to levels ten-fold higher than these known disease states is safe, but common sense would say it can't possibly be safe.

The Myth of Increased Suicide

The affirmation advocates repeatedly refer to the established increased risk of suicide if any of the affirmation strategies are not followed to completion. They point to their own published studies touting dramatic improvement in mental health status of patients who are affirmed in all three ways, but they cite data from convenience sampling, which never should be sued to prove anything other than association, at best. Such studies can never prove causation. There are only two total population studies in the peer-reviewed medical literature.[24,36,37] They show that when every recorded case in the population of Sweden was analyzed, neither medical affirmation nor medical affirmation followed by surgical affirmation improved the mental health of the patients in the long run.

What of the Nearly Logarithmic Increase in Incidence of Gender Incongruence?

Data collection in this regard is subject to estimates based on surveys, which can easily alter the numbers upward or downward, depending on who designed the survey and to whom it was presented. Fear, self-loathing or suicide will necessarily lower the numbers of survey participants whose lives are made miserable by the choice to affirm an incongruent gender. Instant gratification, payback to strict parents, and current celebrity will draw survey participants to express euphoric satisfaction with their decision to affirm their incongruent gender, especially when the surveys are circulated by trans-activist organizations, such as the Trevor Project. What had been in 2010 a nearly invisible fraction of adults who admitted to living with an incongruent gender has exponentially increased in frequency to as many as one out of five students in a suburban Pittsburgh school district in 2021. After I completed my fellowship at Johns Hopkins in 1980, it was not until 1993 that a biologic male presented to my private practice office with a desire to be treated with estrogen to feminize his body so that he could appear to be a female and identify as such. There was nothing in published medical literature that I could find to guide my treatment options. I canvassed my broad contact pediatric endocrinology network across the United States, and nobody had heard of such a clinical case, and none had any suggestions about what I should do. In the ensuing 19 years, the number of transgender treatment centers have burgeoned from zero to several hundred between university-based centers and Planned parenthood. Minority stress theory is frequently used to cover this explosion in numbers, but that is utterly impossible. What does

explain this increase is online recruiting and grooming of vulnerable children and adolescents by a generously funded political movement aimed at dissolving the reality and birthright of biologic sex. This will not end well. By the time a plethora of legal action against those who promoted and engineered the social, medical, and surgical affirmation of incongruent gender knocks down this house of cards, millions of children and adolescents will have been medically, surgically, and mentally maimed as well sterilized.

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ATTACHMENT F

Florida Medicaid Project: Surgical Procedures and Gender Dysphoria

Patrick Lappert, M.D.

May 17, 2022

Florida Medicaid Project: Surgical Procedures and Gender Dysphoria

Patrick Lappert, M.D.

Overview

The "Gender Affirmation" care model for children who suffer from gender identity issues is experimental in nature because it is based in low to very low-quality scientific evidence. There is no body of quality scientific evidence to support the hypothesis that gender dysphoria with its associated problems of self-harm and suicide, is improved long-term by gender affirmation surgical procedures.

The best evidence available today demonstrates that transgender is not a single condition that can be explained by any single factor. There are vast differences in age of presentation, predominant sex, persistence into adulthood, and resolution during adolescent development. Moreover, there are numerous and common co-morbid conditions such as autism-spectrum disorder, major anxiety disorders, and clinical depression that severely affect any sense of certainty about the true cause of the child's dysphoria, as well as their capacity to understand and give assent to irreversible medical and surgical procedures that lead to permanent sterility, sexual impotence, and a lifetime of medical problems associated with affirmation care.

The process of obtaining medical informed consent as part of gender affirming surgery is morally indefensible, and likely legally indefensible as well. Parents of suffering children are led by medical professionals to believe that there is only one valid option of care (affirmation medicine and surgery), utterly concealing the historic reality that greater than 92% of children desist in their cross-sex self-identification when treated using the "watchful waiting" therapeutic strategy. Parents are told that if they do not consent to affirmation care, there is a high likelihood that their child will die from suicide. This is not informed consent, but rather consent under duress.

Gender identity is being presented as a fixed and unchanging, biologically determined, personal characteristic. It is not. The medical literature has consistently shown over many years that the vast majority of children with cross-sex gender identity resolve the issue during adolescence and adopt a gender identity that is congruent with their biological sex.

Because surgeons who perform gender affirmation surgeries have no diagnostic test to predict who among the self-identified transgender minors would have persisted in their cross-sex self-identification into adulthood, and who among those children would have desisted, they have no way to know, in any particular case if the irreversible surgery is being performed on a person who would have continued to self-identify in the cross-sex persona into adulthood. Given the historically well-known desistance rate, it is possible that as many as 90% of children are undergoing surgery based upon an incorrect diagnosis.

"Gender Affirming" breast surgery for self-identifying transgender minors is not medically and ethically equivalent to similar procedures performed for objectively identifiable medical conditions. Transgender breast surgery is always cosmetic (aesthetic) in nature because the indication is a hoped-for improvement in the interior emotional life of the patient. Transgender surgery is not based in any medical diagnosis and does not seek to restore any form or function that may have been lost due to trauma, disease, or developmental accident. It begins with normal structures and changes their appearance in order to achieve a subjective improvement and is therefore cosmetic surgery.

Because gender affirming surgery is cosmetic (aesthetic) in nature, such surgeries must never be offered if they are known to predictably produce an irreversible loss of function. To knowingly sacrifice a human capacity (breast feeding, capacity for sexual intimacy, fertility) in the pursuit of a cosmetic result in a minor who is incapable of giving informed consent, is morally indefensible. The hoped-for subjective improvement that is sought in transgender surgery is a short-lived improvement and is only supported by low to very low-quality scientific evidence. Long term longitudinal cohort studies that are based in level III evidence show that affirmation surgical care is of no benefit in reducing self-harm including suicide.

Problems with Informed Consent

The protection of children in situations requiring informed consent is a crucial problem that the state has a historic and abiding interest in. In the particular situation of self-identified transgender children, it becomes a most significant problem, given that they are being submitted for permanently life-altering interventions. In my opinion as a plastic and reconstructive surgeon, the life-altering nature of hormonal and surgical interventions needs to be addressed from the moment of the child's entry into the gender-transition system, given the fact that the overwhelming majority of children who first begin puberty blockade, go onto the physically altering and permanent changes produced by cross sex hormones, and many ultimately also pursue surgery, as is attested to by multiple papers, the content of which is examined below. Informed consent has several requirement that need to be met if such consent is to be deemed valid. These requirements include a thorough discussion of the details of the proposed procedure including risks, known complications, and some measure of the likelihood of a favorable outcome. The discussion must include alternative treatments, and their risks, known complications and their likelihood of a favorable outcome. In the case of the interventions associated with gender-transition medicine and surgery, the favorable outcomes should be evident over the lifetime of the patient, given that they are permanently sacrificing structures and capacities (breasts and breast-feeding, or genitals and fertility).

Because the commonly cited medical literature used in support of these surgeries is of low to very low quality, it must be recognized that such surgeries must be considered experimental in nature given the unknown long-term effects of treatment, and the vast uncertainty in the patient selection and diagnostic processes. Yet the experts who provide opinion in support of these surgeries speak with absolute certainty of their efficacy, and the absence of any alternative treatment. Considering these factors severally and together it becomes difficult to imagine a

more flawed consent process. It also becomes understandable how parents can be drawn into uninformed participation given the simultaneous presentation of dire consequences if gender dysphoria is left untreated, and the insistence that affirmation care including surgery is the only way to bring lasting happiness to the child.

Chest Masculinization" in Natal Females is Not Ethically Equivalent to Mastectomies for Breast Cancer

When mastectomy is performed for the management of breast cancer, or to mitigate the proven risk of developing breast cancer in women, it is done on the basis of objective diagnoses either by pathological examination of biopsy tissue, or as in the case of prophylactic mastectomy, on the basis of genetic analysis that shows known markers of increased risk of developing breast cancer. These tests (microscopic examination of tissue specimens, detection of cell surface markers with proven association with malignancy, and genetic screening of at-risk patients) have known positive predictive value for the diagnosis of breast cancer, and these tests have known error rates that can be used when obtaining informed consent for mastectomy. The validity of these tests has been proven using scientific methodologies that produce high quality evidence in longitudinal population studies with control populations, and very long follow up. As the result, when a woman gives consent for mastectomy to control or prevent the potentially lethal disease, it is with a clear and proven evaluation of the risks and benefits that consent is obtained. Mastectomy is being performed based upon an objective diagnosis of a potentially lethal condition, and the surgical procedure has proven benefit in management of that condition.

In stark contrast, this is not the case when mastectomy is performed to "masculinize" the chest of girls and women who self-identify as transgender or who self-report symptoms of dysphoria. In the self-identified transgender adolescent, breasts are being removed on the basis of a diagnosis that is made by the patient since there are no tests with known error rates that can be used to predict who will benefit from this disfiguring and irreversible surgery. The claim is made that chest masculinization has proven benefit in reducing dysphoria and the associated risk of suicide. But published studies that make this claim of benefit offer evidence that is low to very low quality, typically small case collections with self-selection bias, very short follow up, and no case controls.

The best data presently available on the long-term effects of medical and surgical transitioning are long-term, longitudinal, population-based studies. For example, Dehjne, et al., examined the putative long-term benefit of full transitioning (including hormonal and surgical treatments) found in the Swedish medical database. (See Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOSOne February 22, 2011 https://doi.org/10.1371/journal.pone.0016885). That database includes all persons in the Swedish medical system, from pre-natal to death. It reports all episodes of care and all demographic information in a uniform vocabulary. Furthermore, Sweden has been on the forefront of "gender affirmation" long before the American medical

system seriously considered its claims. Because of the nature of Sweden's database, it is possible to study a cohort of patients that very closely matches the inquiry group with regards to age, sex, economic status, etc. It is possible to ask with great precision such questions as, "What is the likelihood that a fully transitioned transgender male will be hospitalized for psychiatric illness when compared to the age/sex matched control group?" Even more, one could urgently ask, "What is the relative risk of suicide in transgender persons, when compared to age/sex matched controls?"

Why are such longitudinal, population-based studies superior to the case-collection/case series methodology? Because confounding variables such as age, sex, and self-selection biases are removed. In the flawed case-collection methodology, the reported cases are typically only those who return for follow up. You have no way of knowing if the patient had a good outcome or didn't return for follow up because they were in a psychiatric hospital, were incarcerated, or committed suicide. In the Swedish longitudinal study, the suicide is in the same database, as are the other issues of hospitalization, incarceration, and addiction treatment, among other rates of comorbidity. Thus the longitudinal population study can give us what is called a "hazard ratio" for a particular study population (patients who have completed transgender transition in this case).

What this Swedish study shows us that the risk of completed suicide in all transgender persons is 19.1 times higher than in the control cohort. If you look only at patients who have transitioned — patients after "treatment" — from female to "male presentation," the risk of completed suicide is 40 times higher than in the general population. (Note: this finding is consistent with the historic Branstrom 10-year follow up study, which found no benefits to "transitioning treatments" but did note an increased risk of serious suicide attempts and anxiety disorders AFTER "treatment.") (Correction to Bränström and Pachankis, Am J Psychiatry 177:8, August 2020; see detailed citations in the "Notes" section of this report below).

Another cautionary note was added to the literature by the reputed Cochrane Review, a UK based international association of researchers who examine the quality of scientific evidence used in medical decision making. The Cochrane Review recently published findings concerning the medical evidence used to support the decision to give young women cross sex hormones as part of the transition process. The authors summarize the world literature review thus: "We found insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition. This lack of studies shows a gap between current clinical practice and clinical research." (Does hormone therapy help transgender women undergoing gender reassignment to transition? See, Haupt C, Henke M, Kutschmar A, Hauser B, Baldinger S, Saenz SR, Schreiber G., Cochrane Review, 28 Nov 2020).

Similar issues of very poor, low quality scientific support for chest masculinization surgery can be seen in a recent article by Tolstrup et al. published in the journal Aesthetic Plastic Surgery (See Anders Tolstrup, Dennis Zetner, Jacob Rosenberg, Outcome Measures in Gender-Confirming Chest Surgery: A Systematic Scoping Review, Aesthetic Plast Surg 2020 Feb;44(1):219-228. doi: 10.1007/s00266-019-01523-1. Epub 2019 Oct 29). The article reports a

comprehensive review of the world literature concerning the efficacy of "gender confirming" chest surgery in transgender patients. The authors found 849 articles on the subject, published in peer reviewed medical journals. Of these 849 articles, only 47 could be included in the review. This means that only 5.5% of all the published, peer-reviewed transgender surgery articles demonstrated even rudimentary scientific rigor. Of those 47 articles, the authors report that only 29 of the articles addressed mental health outcomes (3.4% of all the articles). What is startling is that the mental health outcomes were judged only on the basis of uncorroborated, untested, and unassessed patient subjective reporting with descriptors that varied so widely from article to article that results could not even be compared. The authors summarize by saying, "Evaluation of outcomes in gender-confirming chest surgery showed large variations in reporting, and further streamlining of reporting is therefore required to be able to compare surgical outcomes between studies." None of these negligent articles even bothered to examine rates of psychiatric hospitalization, substance abuse, self-harm behaviors, and suicide. This tells us that the main reason for performing these surgeries (psychological distress and suicide risk) isn't even evaluated with regard to efficacy.

An example of an article with very low-quality data, reckless (now banned practices), and methodology, published in a "leading journal," and promoted as evidence for the efficacy of "chest masculinization" surgery makes this fact very clear. The lead author (Olson-Kennedy, a leading national advocate for the transgender treatment enterprise) is a board-certified pediatrician who leads the gender clinic for the Los Angeles Children's Hospital. The article appeared in 2018 (See J. Olson-Kennedy, J. Warus, MD1, et al., Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults; Comparisons of Nonsurgical and Postsurgical Cohorts., JAMA Pediatr. 2018;172(5):431-436. doi:10.1001/jamapediatrics. 2017.5440. In their summary of findings, the authors reported that "chest dysphoria" is common among "trans males" (natal females seeking to present as males) and claimed that dysphoria is "decreased by surgery." They claim that regret for surgery is "rare." The article reports breast removal surgery on at least one girl aged 13 years. (Note that this reckless, experimental practice has now apparently been abandoned as unethical/experimentation on children by England, Sweden, and Finland. The average age of patients in the study was 19. Children were entered into the study through recruitment from among patients visiting the clinic and by telephone over a six-month period. The authors found that, of the patients recruited from among visitors to the clinic (convenience sampling), there was an over-representation of non-operated patients, so the authors were forced to reach out to all the post-surgical patients by phone. Twenty-six percent of the clinic's post-surgical patients could not be reached for various reasons including no working phone, or failure to respond to multiple messages. The 26% drop-out rate is never even questioned by these authors. Were surgical patients lost to follow up because of dissatisfaction, psychiatric hospitalization, or suicide? This problem is called "self-selection bias," and it is evidence of careless study design. Of the remaining 74% of patients, only 72% completed the survey. This is a second example of self-selection bias. Why would some post-surgical patients who had been successfully contacted, not complete the survey? The authors — demonstrating multiple levels of confirmation bias — do not even ask such essential questions. (See detailed citations in the "Notes" section of this report below).

In the study, dysphoria was evaluated using what the author called "a novel measure," which amounted to a series of subjective questions about happiness that was in part designed by the adolescent test subjects themselves. Essentially, the methodology used an entirely unvalidated ("junk science") test instrument, with no known error rates and no proven predictive power. Furthermore, the post-surgical patients were administered the survey at widely varying time intervals post-surgery. The longest interval between surgery and the satisfaction survey was 5 years, but children less than a year post-surgery were included in this obviously flawed sample, and yet the authors claim evidence of "negligible regret." This is a remarkable, misleading, and deceptive claim given that long-term, longitudinal population studies show that there is a dramatic rise in post-surgical problems such as depression, hospitalization, substance abuse, and suicide beginning at around seven years post-surgery (Ibid). Surely the authors are familiar with the world literature on transgender outcomes?

Having deceptively or negligently promised in the introduction to their paper that "chest dysphoria" is reduced by surgery, at the conclusion the authors confessed to the fact that the study design and execution produced very low-quality data that is not useful for patient selection, or prediction of outcomes. They even confessed that the study does not address the efficacy of surgery in improving outcomes regarding the single most compelling reason for performing the operation: mitigation of depression and suicide. The authors write, "An additional limitation of the study was the small sample size. The nonsurgical cohort was a convenience sample, recruited from those with appointments during the data collection period. There could be unknown imbalances between the nonsurgical and postsurgical cohorts that could have confounded the study findings."

Finally, the authors did not even bother to validate their "Chest Dysphoria Scale." Such a "made-up" scale is unlikely to accurately represent distress or correlate with properly validated measures of quality of life, depression, anxiety, or functioning. Their own analysis at the conclusion or the paper directly contradicts the deceptive claim made in their introduction.

This is the kind of "junk science" that is used to support transgender medicine and surgery. The paper is only a few years old. It was written by board certified physicians who practice in one of the nation's largest pediatric gender clinics and was published in a peer-reviewed medical journal. It is essentially useless in making any clinical decisions regarding who should be offered surgery, what is the likelihood they will benefit from it, and what is the likelihood they will regret their decision. Most importantly, it does not even measure the effect of therapy on suicide risk. The very morbidity (the risk of suicide) that they claim is improved by surgery is not even measured in their low-quality study.

Because of the very low-quality scientific support for mastectomy in the management of gender dysphoria, valid consent would demand that these procedures be described as experimental, would need the approval of ethics panels to monitor human experimentation, and would require the use of valid controls found in long-term, longitudinal population-based study models. These are the kinds of patient protections now endorsed in England, Sweden and Finland but still

ignored in the US environment where proper scientific critiques of such studies can get faculty "cancelled."

Even though the transgender treatment industry has been performing these surgeries for over 50 years, gender treatment centers continue to publish the same low quality, methodologically defective studies based upon collected cases that are degraded in value by self-selection bias, confirmation bias, and short-term follow-up, while continuing to deceptively claim that such defective research provides a sufficient scientific basis for performing irreversible, disfiguring, and ultimately sterilizing hormonal treatments and surgeries on children.

"Chest Masculinization" in Natal Females is Not Ethically Equivalent to Gynecomastectomy

Gynecomastectomy is the surgical treatment of gynecomastia, a fairly common condition in which males develop female-type breast gland tissue. Proponents of "masculinization" mastectomy in natal females erroneously equate the ethics of removing healthy breast tissue from gender dysphoric children with the removal of abnormal breast tissue in men (gynecomastia). In the case of gynecomastectomy in male patients, the operation is performed to remove the objectively diagnosed presence of female type glandular breast tissue present in a male patient. Physical examination demonstrates the presence of a dense retro-areolar mass which is tender and sometimes disfiguring. Pathological examination of the removed tissue will demonstrate the presence of female-type fibroglandular tissue in a male patient. This is an objectively abnormal condition. It should further be noted that the absence of such abnormal, female-type fibroglandular tissue in the submitted surgical specimen places the chest recontouring in the category of cosmetic surgery and is therefore not typically paid for by third-party payors.

A comprehensive literature review on the subject of gynecomastectomy and suicidal behavior conducted by Sollie in 2018 (Management of gynecomastia—changes in psychological aspects after surgery—a systematic review: Gland Surg. 2018 Aug; 7(Suppl 1): S70–76.doi: 10.21037/gs.2018.03.09) did not produce a single paper claiming improvement in suicide rate in patients who underwent this surgery. There were many reports concerning improvement in the pain that men with this objective condition suffer with. The remainder of the reported data was in the category of subjective "satisfaction survey". This tells us that the author did not distinguish between medically indicated and aesthetic surgeries. Nonetheless, no claim is made of decreased suicide rates in a suicidal population of male patients. This is because any male patient seeking removal of abnormal, female-type, breast tissue who reported suicidal ideation would be considered incompetent to give consent and would require a psychiatric evaluation and treatment to manage suicidal thinking before being considered for surgery. This kind of decision in favor of psychiatric support does not appear to be at work in the transgender affirmation world. There, and there alone, is suicidal thinking considered a qualification for a surgery.

"Chest Masculinization" in Natal Females is Not Ethically Equivalent to Breast Reduction

It should be obvious that "Chest Masculinization" surgery in natal females is not ethically equivalent to breast reduction surgery in non-transgender females. In the case of breast reduction for females with excessively large breasts (macromastia, or gigantomastia), the operation is performed to relieve a debilitating orthopedic complaint of neck, back, and shoulder pain associated with the postural/mechanical effects of the weight of the breasts. These patients experience significant activity restriction and chronic pain that is not relieved by medical management or physical therapy. Furthermore, there is voluminous actuarial data, based upon many years of longitudinal population-based study by medical insurance agencies that is used to predict who will benefit from surgery, and who will not. These physical, objective tests, based upon the actual measurement of the breasts, and the patient's overall body habitus, have known error rates that can be used to predict the likelihood that a breast reduction will relieve the orthopedic complaints of neck, back, and shoulder pain. When the tissue specimens are submitted to pathology, they are weighed in order to ensure that enough tissue has been removed so that there will be a very high likelihood that the surgery will relieve the orthopedic condition of neck, back, and shoulder pain (Accuracy of Predicted Resection Weights in Breast Reduction Surgery, Theodore A. Kung, MD, Raouf Ahmed, MBBS1 Christine O. Kang, MPH,1 Paul S. Cederna, MD, and Jeffrey H. Kozlow, MD; Plast Reconstr Surg Glob Open. 2018 Jun; 6(6): e1830.

Based upon that, adequate pre-operative consent can be obtained. The supporting data is based in very high-quality methodology. There is no quality research data, no pre-operative test or study, and no known error rates that can be used to predict the likelihood that any child suffering from gender dysphoria will benefit from the experimental procedures of mastectomy and chest "masculinization." As noted above, because of the very low quality data, transgender chest masculinization is at best experimental and at worst, should be viewed as a form of medical child abuse — it is important to note that Finland, Sweden, and the UK apparently now all agree with this analysis, as they have all retreated from such reckless surgical procedures for (See detailed citations in the "Notes" section of this report below).

It is crucial to remember that "chest masculinization-affirmation surgery" of healthy breast tissue results in a complete loss of function, that this loss is two-fold (breast feeding and erotic sensibility), and the cause of the loss is two-fold (gland removal and severing of the intercostal nerve). (See Breast Reduction with Use of the Free Nipple Graft Technique; Stephen R. Colen, MD; Aesthetic Surgery Journal, (Breast Reduction with Use of the Free Nipple Graft Technique; Stephen R. Colen, MD; Aesthetic Surgery Journal, Volume 21, Issue 3, May 2001, Pages 261–271, https://doi.org/10.1067/maj.2001.116439).

If a patient who undergoes "chest masculinization" should regret the surgery, they do have the option of breast reconstruction. However, all that will be produced is a counterfeit of a breast. The patient will have lost the function of breast feeding. Additionally, the most commonly performed "masculinization" surgery involves the removal of the nipples, and subsequent re-

attachment in the form of a nipple graft. Those nipples will have lost their native nerve connections that provoke erotic sensibility. All that can be hoped for is the eventual random ingrowth of local skin sensation, but there will never be erotic sensation because the particular branch of the fourth intercostal nerve which communicates with particular centers in the brain responsible for oxytocin release and erotic provocation will have been permanently severed. This means that breast function has been completely and irreversibly sacrificed for the sake of producing a cosmetic result (a masculine appearing chest). This is the exact opposite of the goals of any reconstructive surgery. It must therefore be understood that "chest masculinization" is a cosmetic procedure that has violated the most essential principle of cosmetic surgery: never sacrifice function for the sake of a cosmetic result.

Erroneous use of the word "Reconstructive" to describe Gender Affirmation Surgeries

The transgender treatment enterprise uses the word "reconstructive" to characterize a group of surgical treatments that seek to alter the sexed appearance of the person. It is important to understand that these procedures, because of the indications for surgery, the motivations for surgery, and the outcomes of surgery, are not reconstructive, but are to be properly understood to be cosmetic in nature.

Reconstructive surgeries are procedures that seek to establish or restore structures and their functioning that have been lost due to trauma, disease, in-utero developmental abnormalities, or surgical treatment for disease. Such reconstructive surgeries must begin with the objective characterization of the defect, including abnormalities of form, and associated loss of function. This process of defining the defect begins with a thorough understanding of normal human form and function and seeks to select, develop, and execute procedures that will restore both. In some cases function may be emphasized more than form, as when the mangled hand of a man is reconstructed. In other cases, reconstruction of form is all that is possible because as yet there are no techniques to restore function. An example of this is seen in the reconstruction of a woman's breast following cancer care. All that can be offered is the appearance of a breast; she will never be able to feed an infant through the reconstructed part.

This is to be contrasted with cosmetic, or aesthetic surgery in which the appearance of a structure is modified in order to produce a subjective (aesthetic) result for the patient. No functional restoration is addressed because no functional or structural loss exists. The object of the surgery is aesthetic. There is no lost form or function that needs to be reconstructed. It is aesthetic surgery because the motivation is aesthetic (subjective feelings about appearance). Further evidence for this is the fact that nearly the entirety of the outcome studies cited in support of these surgeries use subjective questionnaires which the patient fills out. The questions used are typical of those used to evaluate any aesthetic surgery. They are called "satisfaction surveys". Such surveys are prone to suffer from self-selection bias, confirmation bias, and high drop-out rates.

One of the key problems that the transgender treatment enterprise faces on a daily basis is the issue of third-party payment for services. No health insurance provider, including federal and state agencies will pay for cosmetic surgery. For this reason, it is necessary, in order for the business model to succeed, that providers characterize their services as reconstructive. This is doubly difficult given the intense political pressure that has been exerted upon the medical community to "de-pathologize" the condition of transgender. This is seen in the abandoning of the diagnostic nomenclature of "body dysmorphic disorder", and "gender identity disorder" in favor of the more recent DSM manual using the term "gender dysphoria". This leads transgender treatment providers into the difficult situation of claiming that transgender is not a pathology, while at the same time insisting that the services are medically necessary and describing the procedures as reconstructive without characterizing any physical/ functional defect.

As we consider the specific "gender affirming" surgical procedures we will see that comparison to medically indicated surgeries on both men and women actually serves to reinforce the evidence that these surgeries are essentially and fundamentally cosmetic.

Masculinizing and Feminizing Chest Surgeries are Not "Medically Necessary"

Supporters of "transitioning" treatments justify surgical treatment based upon "medical necessity." They claim that gender dysphoria can lead to debilitating anxiety and depression, as well as serious incidents of self-harm, including self-mutilation, suicide attempts, and suicide. Yet with only a single exception, in the studies they cite no measures are made of the effects of surgery on what is claimed to constitute the "medical necessity" for these procedures.
In contrast, the Branstrom study[1] documented no reliable benefits for transgender surgery/hormonal treatments and no reduction in suicide and even an increase in serious suicide attempts requiring hospitalization in patients receiving surgery. These recent, long-term, published, peer reviewed, credible research findings are quite contrary to the claims of supporters of "transitioning treatments" — as are the National Science Reviews in this area from England-NICE, Sweden, and Finland. (See detailed citations in the Notes section in this declaration).

Scientific rigor would demand an examination of objective outcomes such as: rates of substance abuse, psychiatric hospitalization, self-harm, or suicide, and how they were changed by surgery. One paper does ask these crucial questions concerning efficacy is a very comprehensive, long term, longitudinal population cohort study which actually shows the opposite of what experts claim for these patient outcomes. When followed beyond eight years post operatively, this paper shows that patients receiving these treatments have the same alarmingly high rates of hospitalization, substance abuse, self-harm, and completed suicide as persons who have had no medical or surgical intervention.

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[1] *Correction of a key study: No evidence of "gender-affirming" surgeries improving mental health.* Home. (2020, August 30). Retrieved May 17, 2022, from https://segm.org/ajp_correction_2020

In summary, on the issue of the efficacy of these surgeries, the scientific support is very weak, while the scientific evidence rejecting the hypothesis of efficacy is remarkably strong (See Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden; Cecilia Dhejne, Paul Lichtenstein, Marcus Boman, Anna L. V. Johansson, Niklas Långström, Mikael Landén; PLOS One February 22, 2011 https://doi.org/10.1371/journal.pone.0016885).

The surgical removal of the breasts, and the re-contouring of the chest through liposuction is a common procedure for women who seek to present as men. These operations are performed in both men and women, for a variety of reasons. They are generally very safe, and typically performed in the outpatient setting. It is important to understand that the only way of distinguishing cosmetic breast surgery from "medically necessary" surgery is based upon the diagnosis of underlying pathology. For example, breast reduction may be cosmetic, or it may be medically indicated. In both cases, the patient presents with a complaint that her breasts are too big. The distinction between cosmetic breast reduction and medically indicated breast reduction is based upon the presenting symptoms of orthopedic problems when working, such as chronic neck back and shoulder pain caused by the weight of the breasts. But even then, the weight of the removed tissue is factored into the objective verification that the surgery was "medically necessary." There is a vast body of medical and actuarial data that demonstrates the relationship between the weight of the breast tissue removed and the probability that back pain will be cured by performing a breast reduction.

The same issues are at stake in breast enhancement for men seeking to present as women. Cross-sex hormones will have caused varying degrees of gynecomastia (breast enlargement in men). Surgical enhancement procedures are exactly the same in both men and women.

Medically necessary surgery in women is based upon the diagnosis of an objective medical condition, such as Poland's syndrome (congenital absence of a breast), surgical absence of the breast following cancer care. In men, the objective diagnosis of gynecomastia might warrant surgery based upon medical necessity, but it would be the removal of tissue that has objective pathological features (breast gland proliferation in a man). A rare diagnosis of breast cancer in a man might warrant chest wall reconstruction after cancer care. On the other hand, cosmetic surgery of the breast is entirely about the subjective feelings of the patient, and that is all that we find in the case of the self-identified transgender patient.

In the case of transgender chest surgery, the diagnosis is based on the patient's subjective report of dysphoria, but the medical necessity is based on the expectation that surgery will relieve the patient of the risk of, among other things, major depression, self-harm behaviors, and suicide. None among the many papers typically cited by supporters of "transitioning treatments" address themselves to the question of medical necessity for either masculinizing surgery, or feminizing surgery. They only address technical issues, management of complications, and subjective outcomes that employ precisely the same language that is used to assess every

other cosmetic surgery of the breast. Such papers often begin with standard language about the suffering of self-identified transgender adolescents, and their risk of self-harm. They will claim that the reported surgeries somehow reduce the risk of suicide, or the frequency or severity of self-harm, but they never report actual results of improvement in the risk of suicide, or substance abuse, or cutting, or sexual risk taking. The claim of benefit is unsupported in the scientific literature.

In summary, the medical necessity of transgender chest surgery is not supported by scientific evidence and appears to be firmly in the category of cosmetic surgery. What is more, the surgeries when performed on natal females causes a life-long loss of function, placing those surgeries in the category of malpractice. No other cosmetic procedure is expected to produce major functional loss. Such a result would only be the result of a complication, or other surgical misadventure. To actually have a 100% certainty of loss when surgical consent is being obtained constitutes a complete neglect of one of the foundational principles in plastic surgery: Never sacrifice function for the sake of a cosmetic result.

About the Author

Education and Training: I received my Bachelor of Arts in Biological Sciences at the University of California, Santa Barbara, 1979. There I was engaged in research in cell membrane physiology with Dr. Philip C. Laris, studying stoichiometry of the sodium: potassium ATPase pump. I received my M.D., Doctor of Medicine degree at the Uniformed Services University of the Health Sciences, 1983 at Bethesda, Md. I served my General Surgery Residency at the Naval Hospital Oakland/UC Davis East Bay Consortium, 1987-1991 and served as Chief Resident, Department of Surgery, Naval Hospital Oakland, 1990-1991. I also served a Plastic Surgery Residency at the University of Tennessee-Memphis, 1992-1994. My professional background, experience, and publications are described in more detail in my curriculum vitae, which is attached as Exhibit A to this declaration.

Board Certifications in Medicine: I have been Board Certified in Surgery (American Board of Surgery, 1992), in Plastic Surgery (American Board of Plastic Surgery, 1997; American Board of Plastic Surgery, 2008).

Medical Staff Appointments: I served as the Staff General Surgeon at the Naval Hospital Oakland, CA 1991-1992 and as Associate Professor of Surgery, UC Davis-East Bay, 1991-1992. I also served as a Plastic and Reconstructive Surgeon, Naval Medical Center, Portsmouth, Virginia, 1994-2002 and as Chairman, Department of Plastic and Reconstructive Surgery, Naval Hospital Portsmouth, Virginia, 1996-2002. I later served as Clinical Assistant Professor, Department of Surgery, Uniformed Services University of the Health Sciences, 1995-2002 and as Founding Director, Pediatric Cleft Palate and Craniofacial Deformities Clinic, Naval Hospital Portsmouth, Virginia, 1996-2002 also as the Founding Director, Wound Care Center, Naval Hospital Portsmouth, Virginia, 1995-2002. I have also served as a Staff Plastic Surgeon in Nebraska and Alabama.

U.S. Surgeon General Service: I served as a Specialty Leader, Plastic and Reconstructive Surgery, Office of the Surgeon General-USN, 1997-2002.

Faculty Appointments: I served as Teaching Faculty at Eastern Virginia Medical School, Division of Plastic Surgery, 1995-2002. I also served on the teaching faculty of the Via College of Osteopathic Medicine, 2017-2020.

Military Service: I served as an Aviation Officer Candidate, Naval Aviation Schools Command, NAS Pensacola, 1978 and was Commissioned an Ensign, MC, USNR 1979 and Commissioned as a Lieutenant, MC, USN 1983. I served as a Designated Naval Flight Surgeon, Naval Aerospace Medical Institute, 1985, and I was Assigned Marine Fighter/Attack Squadron-451, serving as Flight Surgeon, and serving as Radar Intercept Officer in the Marine F4S Phantom, accumulating 235 flight hours, and trained for qualification as an Air Combat Tactics Instructor. I was deployed to the Western Pacific as UDP forward deployed fighter squadron in Korea, Japan, and the Philippines. I served in the US Navy for 24 years, and I served in the USMC for 3 years. I retired with the rank of Captain, USN in 2002.

Publications - Peer Reviewed Medical Journals: Lappert PW. Peritoneal Fluid in Human Acute Pancreatitis. Surgery. 1987 Sep; 102(3):553-4; Toth B, Lappert P. Modified Skin Incisions for Mastectomy: The Need for Plastic Surgical Input in Preoperative Planning. J Plastic and Reconstructive Surgery. 1991; 87 (6): 1048-53; Lappert P. Patch Esophagoplasty. J Plastic and Reconstructive Surgery. 1993; 91 (5): 967-8; Smoot E C III, Bowen D G, Lappert P, Ruiz J A. Delayed development of an ectopic frontal sinus mucocele after pediatric cranial trauma. J Craniofacial Surg. 1995;6(4):327–331; Lappert PW. Scarless Fetal Skin Repair: "Unborn Patients" and "Fetal Material". J Plastic and Reconstructive Surgery. 1996 Nov; 98(6): 1125; Lappert PW, Lee JW. Treatment of an isolated outer table frontal sinus fracture using endoscopic reduction and fixation. Plastic and Reconstructive Surgery 1998; 102(5): 1642-5.

Publications - Medical Textbooks: Wound Management in the Military. Lappert PW, Weiss DD, Eriksson E. Plastic Surgery: Indications, Operations, and Outcomes, Vol. 1; 53-63. Mosby. St. Louis, MO 2000.

Operations and Clinical Experience: Consultations and Discussions: As a physician and surgeon, I have treated many thousands of patients in 7 states and 4 foreign nations. My practice has included Primary Care, Family Medicine, Aerospace Medicine, General Surgery, Reconstructive Surgery for combat injured, cancer reconstructive surgeries including extensive experience with microvascular surgery, Pediatric Congenital Deformity, and the care of chronic wounds. I have practiced in rural medicine, urban trauma centers, military field hospitals, university teaching hospitals, and as a solo private practitioner. In my private practice I have had occasion to treat many self-identified transgender patients for skin pathologies related to their use of high dose sex steroids, laser therapies for management of facial hair both in transitioners and detransitioners. I have performed breast reversal surgeries for detransitioning patients. My practice is rated as "LGBTQ friendly" on social media. I have consulted with families with children who are experiencing gender discordance. I have given many presentations to professional meetings of educators and counselors on the subject of transgender, and the present state of the science and treatment. I have discussed the scientific issues relevant to the case with many physicians and experts over a number of years and also discussed related issues with parents and others.

ATTACHMENT G

Florida Medicaid Project: Treatment for Transgender Children

Medical Experimentation without Informed Consent:

An Ethicist's View of Transgender Treatment for Children

G. Kevin Donovan, MD, MA
5-12-2022

Florida Medicaid Project: Treatment for Transgender Children

Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children

I. The Issue

Growing controversy attends the diagnosis and treatment of individuals identifying as transgender, particularly those who are still children or adolescents. As was recently pointed out, leading medical, mental health, and public health organizations support understanding gender-diverse youth and providing gender-affirming medical (hormonal) and other(surgical) care as the standard of care, including the American Academy of Pediatrics, American Psychological Association, Centers for Disease Control and Prevention, Society for Adolescent Health and Medicine, and the American Medical Association. Major nursing organizations—the American Nurses Association and the American Academy of Nursing— have made statements that young people's access to inclusive, safe, and competent health care is a human rights issue. (Wolfe, I., & Goepferd, A. "Child Abuse in Texas." *The Hastings Center*. 14 Mar. 2022) However, this widespread support is not going unchallenged, even by those who have been providing medical interventions for these children and adolescents.

Recently, questions have arisen about the appropriateness of both the diagnosis, and the safety and efficacy of these interventions that have been strongly encouraged up until now. Currently, less than half of state Medicaid programs provide gender affirming care. (Mallory, C., & Tentindo,W. "Medicaid coverage of gender-affirming care." Williams Institute, UCLA School of Law. Oct 2019). The Florida Surgeon General has said that minors should not undergo gender transition procedures, puberty blockers and hormone treatments. "Florida Department of Health Releases Guidance on Treatment of Gender Dysphoria for Children and Adolescents." 20220420-Gender-Dysphoria-Press-Release | Florida Department of Health.) In Texas, the state attorney general issued a decision that gender-affirming medical treatments such as puberty-suppressing hormones fall under the definition of child abuse in Texas state law. In fact, 34 states have introduced legislation to limit hormonal and surgical interventions for such transgender patients. This aligns with similar reassessments and limitations in the United Kingdom, Sweden, Finland, and France. A new position statement from the Royal Australian and New Zealand College of Psychiatrists (RANZCP) stresses the importance of a mental health evaluation for people with gender dysphoria — in particular for children and adolescents — before any firm decisions are made on whether to prescribe hormonal treatments to transition or to perform surgeries, often referred to as "gender-affirming care." "There is a paucity of quality evidence on the outcomes of those presenting with gender dysphoria. In particular, there is a need for better evidence in relation to outcomes for children and young people," the guidance states.

Given the legitimate concerns about the diagnosis, treatment, and the paucity of supportive, scientific studies in regard to the interventions being offered to minors who identify as transgender, I will offer a view of these from the perspective of an ethicist and pediatrician. This will be done in the face of strong and sometimes heated opposition to any variance from the currently prevailing recommendations. Each category of currently recommended or potential treatments will be briefly considered within this framework. The evidence base for these will be reviewed, and an overall argument made that such interventions must be considered as medical experimentation, subject to the requirements of research in childhood with informed consent. Finally, I will conclude with an examination of the fundamental flaw of the transgender project in childhood, and how it is leading to inevitable and controversial challenges.

In order to do this, we must review the ethical requirements for medical research in childhood and the elements of **informed consent**. Because of numerous abuses in the past, a strong system of regulations and oversight has been developed for the protection of human subjects in the United States. This began with the Belmont Report: (https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html) The report not only described the ethical principles listed below, but led to guidelines for research protections that are now codified in Federal regulations (Code of Federal Regulations, or 'CFR') and monitored by the U.S. Department of Health and Human Services (DHHS). These led to the establishment of IRBs (Institutional Review Boards) which are responsible for the protection of human subjects in federally funded research—IRBs are the Federally mandated committees that review research activities for the protection of human subjects. The Office for Human Research Protections (OHRP) provides leadership in the protection of the rights, welfare, and wellbeing of subjects involved in research conducted or supported by the DHHS. The OHRP helps ensure this by providing clarification and guidance, developing educational programs and materials, maintaining regulatory oversight, and providing advice on ethical and regulatory issues in biomedical and social-behavioral research. These measures have laid the ground rules for human research, in adults and children including the need for informed consent.

Although adults may be included in research, this should only be done with *fully informed consent*, and the requirements will differ for children and other vulnerable subjects. The bedrock of these protections lies in obtaining the informed consent from the participant. Informed consent to medical treatment and research involvement is fundamental to both ethics and law. The process requires that a *fully autonomous patient* have the ability to *understand relevant medical information* about the proposed interventions, including the *risks, benefits, if any, and alternatives* (including doing nothing/non-participation). and consent *voluntarily* without *coercion*. This is rooted in respect for the **ethical principles** of **autonomy**, **beneficence**, and **justice**.

Autonomy is derived from respect for persons, which requires that we not only respect those who are fully autonomous but protect those individuals that are not fully autonomous. Vulnerable subjects such as children cannot legally or ethically participate in the consent process due to their age and maturity level. The rules for their involvement are set out by the Code of Federal Regulations (46 CFR 401-409). While consent cannot be given for another person, parents or guardians can give "permission" and children can give assent to the extent that they are able. The process of obtaining assent should be appropriate to the age, maturity, and psychological development of the child. The consent process must contain three ethically required components: *information*, *comprehension*, and *voluntariness*. Deficiencies in any of these categories would invalidate the process. The main contention here is that deficiencies in *all* these categories can be found in the current approach to minors who identify as transgender, and current attempts at treatment should not proceed as they are now practiced.

Beneficence is reflected in the complementary expressions of (1) do no harm and (2) maximize possible benefits and minimize possible harms. An assessment of risks and benefits will depend heavily on the delivery of accurate and complete information as described above. An assessment of risk will include both the probability and the severity of envisioned harms, both physical and psychological.

Finally, ***justice*** requires fairness in distribution of risks and benefits. It suggests that not only should like cases be treated alike, but different approaches are appropriate for different circumstances. This is highly relevant in the selection process for those being subjected to the various interventions while still minors.

Thus the process of informed consent must proceed with a correct diagnosis, the nature and purpose of recommended interventions, the known burdens and benefits of all options, including doing nothing or forgoing the intervention. While not able to do an exhaustive review of these elements as they apply to the main treatment approaches recommended for transgender minors, we can briefly examine each category to assess for obvious deficiencies. The issue of deficient information will be significant in each category, and questions of comprehension and voluntariness will be addressed at the end.

II. The Interventions

Surgery

A variety of surgeries have been performed on transgender adults. These range from removal of both breasts (bilateral mastectomy) and associated chest reconstruction, nipple repositioning, dermal implant and tattooing, to gender surgery for trans men which includes construction of a penis (phalloplasty or metoidioplasty), construction of a scrotum (scrotoplasty) and testicular implants, or a penile implant. Removal of the womb (hysterectomy) and the ovaries and fallopian tubes (salpingo-oophorectomy) may also be considered. Surgery for trans women includes removal of the testes (orchidectomy), removal of the penis (penectomy), construction of a vagina (vaginoplasty), construction of a vulva (vulvoplasty), construction of a clitoris (clitoroplasty), as well as breast implants for trans women, facial feminisation surgery and hair transplants. Certainly there are multiple known risks to this long list of surgeries. These used to be described as "sex-change" operations: they are now termed "gender affirming surgeries." The semantic shift is important, as we will see.

Most, but not all, practitioners would delay undertaking these permanent alterations in minor children and adolescents. This may be as much for legal reasons as for medical considerations. However, the lack of sexual maturity in younger patients, especially if previously delayed by puberty blocking agents, makes the sparse tissue more difficult to work with and outcomes less favorable, with problems such as wound rupture more likely. These are not challenges that are routinely described to minors at the beginning of their treatment progression with puberty blocking agents or hormones. This deficit of information would be a major failing.

Hormonal Treatment

Treatment with cross-sex hormones is a mainstay of gender affirming care. These result in the changes in body habitus, facies, voice tone, and hair development that transgender patients seek. They are described as "gender affirming", "life-saving" and "a human right" by their proponents. They have been prescribed by Planned Parenthood clinics and others after a first visit for gender dysphoria (https://www.plannedparenthood.org/planned-parenthood-greater-texas/patient-resources/transgender-healthcare). Surely no one would argue that such a precipitous practice has been accompanied by a full psychological evaluation, or disclosure of medical risks. Chief among these is the fact that the resulting bodily changes will not disappear, even if the initial desire for them changes. And this change is no unlikely development – upwards of 80% of minors who identify as transgender will reverse this identity by the time they reach their mid-20's if left untreated, and revert to their previous identification, albeit possibly with a same-sex attraction. It is more than simply changes in one's body that are at risk; sex hormones have an important and lasting effect on brain development and adolescent psychology. To not fully appreciate this fact, or to not have it delineated in the first place, is an egregious failure of informed consent.

Puberty Blockers

Perhaps the greatest failure of informed consent, and non-disclosure of human experimentation outcomes, is found in the supposedly benign use of puberty blocking agents in minors. They are routinely and widely prescribed with the thought that this will "buy time" for those questioning their gender as minors. Children and their supportive parents are assured that they are a benign intervention whose effects are easily reversible, just in case the child decides not to transition. Some potential effect on the development of bone density may be mentioned. The extent of this danger is just now being appreciated, with severe and disabling osteoporosis described in at least one child in Sweden. This led to new guidelines for gender-affirming care issued in February by the National Board of Health and Welfare. It stated that, based on current knowledge: "the risks of puberty suppressing treatment with GnRH-analogues and gender-affirming hormonal treatment currently outweigh the possible benefits, and that the treatments should be offered only in exceptional cases." However, the effect of puberty blocking agents (started in early adolescent development) on long-term sexual function seems to be largely unstudied. Current guidelines recommend starting puberty blockers at the earliest stage of sexual maturation in children (Tanner two). These will not only prevent the enlargement of penile tissue, it will desensitize the orgasmic potential for tissues later exposed to cross-sex hormones. Simply put, transgender adults treated in early adolescence with puberty blockers may never experience orgasm. When children with gender dysphoria are given these powerful hormones (around age 11) they are too young to appreciate the implications of what will happen.

It is not simply a matter of chronology. As children mature into adolescents and adults, their brains are also being formed and reformed under the influence of sex hormones. There is evidence for structural changes, and these are likely to be demonstrated in cognitive and behavioral changes. In fact, the development of the adolescent brain and the maturation of its rational and executive functions does not typically complete until one's early 20s. Although the deleterious effects on sexual development and function in adulthood from puberty blockers may be predicted, no one is entirely certain of the effects on other critical areas such as brain development and bone density. Carefully constructed and monitored studies have not been done. *Until they are, these off-label treatments with puberty blockers and cross sex hormones can only be considered experimental.* Experimental interventions should be done as carefully as any other research, and fully informed consent is the only ethical way to enter into such studies. Clearly, this is not the current practice.

III. The Fundamental Flaw

There appears to have been a headlong rush in the past decade towards the process of gender affirming care described above. After close scrutiny, it can only be seen as off label experimentation, despite the fact that informed consent practices do not conform to this reality. Given this, we must ask ourselves: how can experienced and ethical physicians so mislead others or be so misled themselves? In 2013, the American Psychiatric Association published their update of the Diagnostic and Statistical Manual of Mental Disorders, the DSM-5. In it the diagnosis of "gender identity disorder" was replaced with "gender dysphoria." This was done to "avoid stigma and ensure clinical care for individuals who see and feel themselves to be a different gender" other than the one to which they were born. The APA stated that "it is important to note the gender nonconformity is not in itself a mental disorder. The critical element of gender dysphoria is the presence of clinically significant distress associated with the condition." Dysphoria is a state of uneasiness, unhappiness, or dissatisfaction. With this change in terminology there was also a shift from seeking or correcting the underlying cause of the dysphoria, and a focus on transitioning to the preferred gender.

This revision has probably done more harm than good by accepting a self-diagnosis characterized by the belief that the patient (or their essence) is "trapped in the wrong body." This concept relies on the Cartesian duality, a body-self dichotomy. It reverts to the fallacious "ghost in the machine" concept. In reality, we cannot be trapped in the wrong body; we **are** our bodies, which are an integral and inseparable part of ourselves. To assert that there is a female self inside a male body (or the reverse), is to fail to achieve a full understanding that we are embodied persons, unified body and mind, if you will. A generation ago, sex and gender were taken to be synonyms for the same phenomena. Even now, a transgender female, no matter how much or how long of a hormonal therapeutic regimen they undergo, is still genetically male. Ignoring this fact has led to a contradiction, where sympathetic practitioners recommend "holistic care" while insisting on a fragmented concept of the self. This approach has been warmly embraced, even insisted upon, by many practitioners while viewed as nonsensical and even ludicrous by many laypersons.

Inevitably this has led to added difficulties. Even young patients are encouraged to begin puberty blockers and then hormones based on a self-diagnosis. Self-diagnosing psychiatric conditions is always fraught with the possibility of error. In this case, there can be no confirmatory lab tests, radiologic exams, or genetic findings. Moreover, the dysphoria can only be diagnosed and opened to treatment if it is causing significant trauma to the individual. The clinically significant distress manifests itself in underlying psychiatric diagnoses such as depression and suicidality. It is argued that embarking on affirmative treatment as early as possible is urgently needed to prevent further psychiatric complications, a contested assertion. Studies have shown that adult transgender persons continue to have evidence of depression and suicidality following treatment. The rate of suicide among post-operative transgender adults in a study from Sweden found an incidence 20 times greater than that of the general population. Such treatment may not be urgently needed to protect adolescents; it may not even be effective protection for their adult counterparts.

The claim of urgency coupled with an impulse toward nonjudgmental empathy for the disturbed patients has led to a frantic insistence on a single approach that may seem almost cult like in its insularity and opposition to outside challenges. Both parents (Trinko, K.(Nov. 19, 2018 "What It's Like to Lose Your Children to the 'Transgender Cult,' From a Mom Who Knows." *The Daily Signal*, 30 Oct. 2019) and teachers (Manning, M. for The Mail on Sunday. "Whistleblower Teacher Makes Shocking Claim That 'Most Are Autistic'." *Daily Mail Online*, Associated Newspapers, 19 Nov. 2018, https://www.dailymail.co.uk/news/article-6401593/Whistleblower-teacher-makes-shocking-claim-autistic.html.) report that their children or students are being wrongly encouraged at school to think of themselves as transgender. Sometimes this is the result of overenthusiastic acceptance or "love bombing". Sometimes it appears to influence the susceptible, as in autistic children. Sometimes transgender counseling is taking place even without the parents' knowledge, and this troubling approach has been supported in the literature with statements that adolescents should be legally empowered to obtain puberty-blocking without parental consent (Priest, M. Transgender Children and the Right to Transition: Medical Ethics When Parents Mean Well but Cause Harm. Am J Bioeth. 2019 Feb;19(2):45-59).

Inevitably, this has resulted in complications and conflicts. The media have been replete with reports of such things as contested accessibility of transgender females to such things as domestic abuse shelters, female prisons, and female sports competitions. Similar issues regarding bathroom accessibility in schools recently came to a boil in Virginia, when it came to light that a sexual assault by a self-described trans- female (with a penis) was repeated in another school after the perpetrator was transferred. (Poff, J. "Loudoun superintendent failed to inform state of school sexual assault." Washington Examiner, 4 May 2022.) These issues are far from any resolution by debate, discussion, or legislation. In fact, both sides of the debate have doubled down with insistence that the opposing viewpoint must not only be rejected but considered unethical and made illegal.

Some disturbing trends have developed resulting not only from this dichotomy of opinion about the proper treatment approach, but ultimately based in the acceptance of the mind-body dichotomy. There has been a change in the diagnosed population. As Abigail Schrier pointed out:

> For the nearly 100-year diagnostic history of gender dysphoria, it overwhelmingly afflicted boys and men, and it began in early childhood (ages two to four). According to the DSM-V, the latest edition of the historical rate of incidence was 0.01 percent of males (roughly one in 10,000).
>
> For decades, psychologists treated it with "watchful waiting" — that is, a method of psychotherapy that seeks to understand the source of a child's gender dysphoria, lessen its intensity, and ultimately help a child grow more comfortable in her own body. Now such an approach is disdained by the term "conversion therapy", and labelled as unethical, and even made illegal.

She continues:

> Since nearly seven in 10 children initially diagnosed with gender dysphoria eventually outgrew it, the conventional wisdom held that, with a little patience, most kids would come to accept their bodies. The underlying assumption was children didn't always know best. But in the last decade, watchful waiting has been supplanted by "affirmative care," which assumes children do know what's best. Affirmative care proponents urge doctors to corroborate their patients' belief that they are trapped in the wrong body. The family is pressured to help the child transition to a new gender identity — sometimes having been told by doctors or activists that, if they don't, their child may eventually commit suicide. From there, pressures build on parents to begin concrete medical steps to help children on their path to transitioning to the "right" body. That includes puberty blockers as a preliminary step. Typically, cross-sex hormones follow and then, if desired, gender surgery. (Shrier, A. "Top Trans Doctors Blow the Whistle on 'Sloppy' Care." Emmaus Road Ministries, 5 Oct. 2021)

These pressures apply not only to parents, but to the children themselves because of the strong emphasis on affirmative support for anyone declaring themselves transgender. As one mother described: "A lot of these kids have concurrent mental health issues, and they find a place to fit in because as soon as you say that you're trans, you get love-bombed," she reflects. "You get love-bombed online, you get love-bombed on at school … As soon as you say you're trans, you turn into a star. And kids are thirsty for that kind of affirmation." (Trinko, 2019)

Two phenomena may be associated with this. Strong affirmation for the diagnosis and hormonal treatment may be altering the natural course of the phenomenon in childhood. It may not only be easier to identify as transgender in today's environment; it may be more difficult to turn ones back on the diagnosis. This may help explain a recent report that found that an average of 5 years after their initial social transition, 7.3% of youth had retransitioned (changed gender identity) at least once. At the end of this period, most youth identified as binary transgender youth (94%), including 1.3% who retransitioned to another identity before returning to their binary transgender identity. 2.5% of youth identified as cisgender and 3.5% as nonbinary. Later cisgender identities were more common amongst youth whose initial social transition occurred before age 6 years; the retransition often occurred before age 10. Unlike previous studies of transgender youth, males were not predominant, but were outnumbered by 2 to 1. Moreover, this is a direct contradiction of previous data showing a high rate of reversion towards a sex/gender coherence in children as they mature. (Olson, Kristina R., Durwood, Lily, Horton, Rachel, Gallagher, Natalie M., & Devor, Aaron; Gender Identity 5 Years

After Social Transition. Pediatrics 2022; 10.1542/peds.2021-056082) We must ask if this represents a shift towards being trapped in a wrong diagnosis, rather than a child being trapped in a wrong body.

In fact, there has been another shift. Unlike in the past, we now see increased numbers of females identifying as transgender, and later in their adolescence. Sometimes this occurs in large cohorts within a single school or peer group, a phenomenon labelled "rapid onset gender dysphoria." Both these phenomena call into question the underlying cause for the concept of gender dysphoria. Rather than approaching it as an accurate self-diagnosis that must be affirmed and treated to change the outward sexual appearance, isn't there a better model? We may be making a fundamental mistake in approaching transgender phenomena, not as a disease or disorder, but at most a dysphoria that is a cause for affirmation. This contrasts with our approach to similar conditions claiming a mind- body divergence, such as anorexia nervosa or body integrity identity disorder. The former is familiar to most Americans. The latter is a rare mental disorder characterized by a desire to have a physical disability, claiming discomfort with being able-bodied and often resulting in a request for amputation of the body part that makes them uncomfortable. People with this condition may refer to themselves as "trans abled."

In all three of these conditions there is a claim for a mismatch between one's mental bodily image and physical body. All tend to find an onset in prepubescence and are frequently associated with other mental disturbances. "Affirmative care" is the only recommended standard for transgender patients. It is horribly disturbing to contemplate amputation of a healthy limb because of a mental disorder (although this has been done). No one would seriously consider surgery to limit caloric intake or weight gain for a patient with anorexia nervosa, in order to support and affirm her distorted body image. Nevertheless, sex change operations have been recast as "gender affirming surgeries". The change in language reflects the change in attitude that distorts the approach to treatment for a psychiatric, not medical/surgical, disorder.

Finally, what are we to make of this situation, as a medical profession, and as a society? This question cannot be answered until both the affected people and profession can overcome our collective hubris. It is not enough to admit we don't know all the answers. We must see that we are not yet certain of all the questions that must be answered. In such a situation, competing interests must not pretend to take the moral high ground when no one can be certain where it will be located. First and foremost, we must back off from our current approaches until questions can be answered with proper studies, done with sufficient patients, and sufficient controls, over a sufficient period of time. Any insistence on a single course of therapy without this information could prove to be the same type of morally unacceptable interventions that caused formal research protections to be created in the first place.

In the meantime, we must adopt a more respectful tone with those whom we disagree. As John Milton said, "Where there is much desire to learn, there of necessity will be much arguing, much writing, many opinions; for opinion in good men is but knowledge in the making." Most important of all, in order to protect the current and future well-being of these affected children, we must rely on the ancient principal of medical ethics "In the first place, do no harm." Until we can demonstrate the efficacy and safety of any proposed treatment or intervention, its usage must properly be considered a medical experimentation and require fully informed consent. Anything less is a betrayal of both our principles and our progeny.

About the author: *Dr. Donovan's observations flow from his professional experience. He has been a Board-certified pediatrician for over 40 years, as an academic physician who rose to Vice-chair of the Department of Pediatrics and ultimately interim Chair at the University of Oklahoma in Tulsa. His professional role and interests expanded in the 1990's after he took a sabbatical in medical ethics at*

Georgetown University under the world-famous Dr. Edmund Pellegrino, a founding father of modern bioethics. He subsequently went on to earn a master's degree in Bioethics and founded the first bioethics center in his home university, where he was responsible for ethics training and education for students and physicians. He also served as clinical ethics consultant for three teaching hospitals. He was chair of the Section on Bioethics for the American Academy of Pediatrics (AAP) for three years and then their first liaison member of the AAP Committee on Bioethics. He has also served as the chair for a hospital Intuitional Review Board for 17 years. Finally, he was asked to become Director for the Center for Clinical Bioethics at Georgetown University School of Medicine, where he served from 2012-2020. His duties included teaching, consultation, publishing papers and speaking on bioethics extensively at the local, national, and international level on four continents. He has been interviewed and quoted on National Broadcasting Company (NBC), National Public Radio (NPR), Eternal Word Television Network (EWTN), and Al Jazeera, as well as the New York Times and the Washington Post, among others. He was awarded the Humanism in Medicine award from the Gold Foundation, which recognizes physicians to have successfully integrated humanism into the delivery of care to their patients and families. He has also offered formal testimony on bioethical issues before state legislatures and the U.S. Congress.

TAB 199

THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, et al., *Plaintiffs*, v. JASON WEIDA, et al., *Defendants*.	CASE NO. 4:22-cv-00325-RH-MAF

PLAINTIFFS' TRIAL BRIEF

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INTRODUCTION

Plaintiffs August Dekker, Brit Rothstein, Susan Doe, and K.F. submit this trial brief pursuant to this Court's Scheduling Order (ECF 67) to apprise the Court of the relevant issues of fact and law involved at trial in the above-captioned case and to explain why Plaintiffs should prevail at trial.

STATEMENT OF FACTS

I. The Parties

A. The Plaintiffs

1. Brit Rothstein

Plaintiff Brit Rothstein is a 20-year-old transgender man who is completing his junior year of college at the University of Central Florida. (ECF 11-7, Decl. of B. Rothstein ¶¶ 3, 5 ("Rothstein").) Mr. Rothstein has been enrolled in Medicaid since he was a child and receives his health insurance coverage through Sunshine Health. (*Id.* ¶ 4; *see* Ex. 1, Defs.' Admission No. 6 (ECF 175-1).)[1]

Mr. Rothstein was incorrectly assigned the sex female at birth, but his gender identity is male, a fact of which he has been aware since the third grade. (*Id.* ¶¶ 6-7.) His gender dysphoria intensified over time, and he sought therapy for his

[1] Plaintiffs will use "Ex." to refer to Plaintiffs' trial exhibits filed at ECF 175-184 and also identify the exhibits by ECF number. Attached to this brief are also deposition transcripts which were not filed as exhibits; those will be referred to as "Br. Ex."

dysphoria in seventh grade. (*Id.* ¶ 8-9.) At age 14, in July 2016, Mr. Rothstein received a formal diagnosis of gender dysphoria. (*Id.*, ¶ 11; *see* Ex. 1, Defs.' Admission No. 5 (ECF 175-1).)

At age 17, Mr. Rothstein began receiving medically necessary hormone therapy at Joe DiMaggio hospital under the care of a pediatric endocrinologist with expertise in the treatment of gender dysphoria. (*Id.* ¶ 12.) Access to hormone therapy, in the form of testosterone, has impacted Mr. Rothstein's life in so many positive ways, including, among other things, the changes to his physical body, his mental and emotional health, and his self-confidence. (*Id.* ¶ 13.)

Because Mr. Rothstein and his twin sister were born premature and have medical conditions that have followed them throughout life, his treating providers have closely monitored his labs and levels to ensure his treatment is safe and medically indicated. *See* Ex. 16, Shumer Rebuttal Rep. ¶ 72 ("Shumer Rebuttal") (ECF 175-16); Ex. 234, Rothstein Medical Records (ECF 180-32).)

In May of 2022, after many years of debilitating dysphoria, particularly significant dysphoria related to his chest, a surgeon recommended that Mr. Rothstein undergo masculinizing chest surgery to align his appearance with his gender identity. (ECF 11-7, Rothstein ¶¶ 15-17.) Access to masculinizing chest surgery, sometimes referred to as "top surgery," was necessitated by his dysphoria and the harm he

experienced as the result of wearing a binder for 10-12 hours every day, causing discomfort, irritations, bruising on his ribcage, and even hospitalization. (*Id.* ¶ 16.)

Finding a surgeon with expertise in gender-affirming top surgery, not to mention a provider that accepted Medicaid, was an arduous task given the dearth of providers in Florida. (*Id.* ¶ 16-17.) Mr. Rothstein was elated when, after waiting months for his consultation with Dr. Danker at the University of Miami, Medicaid issued prior authorization approving his top surgery on August 11, 2022, and the University of Miami providers scheduled his long-awaited surgery for December 22, 2022. (*Id.* ¶ 17-18.) Upon learning that AHCA promulgated a rule categorically banning coverage of medically necessary treatment for gender dysphoria for all transgender Medicaid beneficiaries in Florida, Mr. Rothstein's feelings of devastation came as swiftly as his feelings of elation had mere days prior when he learned that Medicaid approved his surgery. (*Id.* ¶ 18.) Due to Mr. Rothstein's income, and the income of his family – which is what qualifies him for Medicaid – he could not afford to pay out of pocket for the surgery. (*Id.* ¶¶ 19-20.) He also cannot afford to pay out of pocket for his testosterone prescriptions. (*Id.*)

Mr. Rothstein's health insurance coverage through Medicaid had covered all of his gender-affirming care, including puberty blocking medication, testosterone, therapy, blood tests, and office visits, prior to the enactment of the Challenged Exclusion. (*Id.* ¶¶ 4, 12.) The Challenged Exclusion will cause Mr. Rothstein to

continue to suffer harm, including impacts on his mental health, and will subject him to increased risk of discrimination, harassment, and violence. (*Id.* ¶ 21; *see also* Ex. 16, Shumer Rebuttal ¶ 71 (ECF 176-16) ("Mr. Rothstein's mental health would deteriorate if unable to receive gender-affirming care.").)

2. Susan Doe

Plaintiff Susan Doe is 13-year-old transgender adolescent girl; Jane and John Doe are Susan's parents. (*See* ECF 11-8, Decl. of J. Doe ("Doe") ¶¶ 2-3.) They adopted Susan out of medical foster care when she was two years old, which entitles her to Medicaid coverage until age 18. (*Id.* ¶¶ 8-9; *see* Ex. 1, Defs.' Admission No. 6 (ECF 175-1).)

Susan first realized she was a girl at age 3. (*Id.* ¶ 10.) The summer before starting second grade, Susan told her parents clearly: "I need to be a girl." (*Id.* ¶ 13.) Thereafter, Susan saw a therapist, who diagnosed her with gender dysphoria. (*Id.* ¶ 13; *see* Ex. 1, Defs.' Admission No. 5 (ECF 175-1).) The therapist recommended that Susan consult with a pediatric endocrinologist (*id.* ¶ 16), and Susan established care with Dr. Bethel Steindel-Spargo at Joe DiMaggio Children's Hospital. (*Id.* ¶ 17.) In July 2020, after Susan began puberty, Dr. Steindel-Spargo prescribed her the puberty-delaying medication GnRHa (Lupron) as medically necessary treatment for her gender dysphoria. (*Id.* ¶19.) Florida Medicaid covered the medication. (*Id.*) Dr.

Steindel-Spargo has been monitoring Susan to determine when it would be medically appropriate for her to begin hormone therapy. (*Id*. ¶ 21.)

Without Medicaid coverage of the care that Susan needs, her parents will have no choice but to try to pay for the treatment out-of-pocket. (*Id*. ¶ 29.) Based on their research, the retail price for a single Lupron injection is roughly $11,000, a prohibitively high cost for a family of four living on a single income. (*Id.* ¶ 29.) Should Susan have to stop taking Lupron and go through endogenous puberty, she would be devastated. (*See id.* ¶ 26.) She has been living as a girl in every aspect of her life since 2017. (*Id.)* Without Lupron, Susan's mental health would suffer as endogenous puberty would be torture for her. (*Id*; Ex. 16, Shumer Rebuttal ¶ 74 (ECF 175-16) (finding that S.D. "has received appropriate care and would likely have a deterioration in health if this care were discontinued").)

3. August Dekker

Plaintiff August Dekker is a 28-year-old transgender man who lives in Hernando County, Florida. (ECF 11-6, Decl. of A. Dekker ¶ 3 ("Dekker").) Mr. Dekker does not work but receives Supplemental Security income due to rheumatoid arthritis. (*Id*. ¶ 4.) He has been a Medicaid beneficiary since 2014. (*Id*. ¶ 5; *see* Ex. 1, Defs.' Admission No. 6 (ECF 175-1).)

As early as age 5, Mr. Dekker experienced symptoms of gender dysphoria, which continued into and through adolescence. *(Id*. ¶ 8) Despite Mr. Dekker's

awareness of his male gender identity, he was forced to hide who he was because of his family's religious beliefs. (*Id.* ¶ 10.) After graduating high-school and gaining independence, he felt free to live openly and, in 2015, began to socially transition to his male identity. Mr. Dekker also sought out mental health care support and in 2017, he received a formal diagnosis of gender dysphoria. (*Id.* ¶ 12; *see* Ex. 1, Defs.' Admission No. 5 (ECF 175-1).) Mr. Dekker then began hormone therapy at the recommendation of his medical providers, which he continues to receive today. (ECF 11-6, Dekker ¶¶ 13, 15.) Mr. Dekker was advised by his rheumatologist about the risks of receiving hormone therapy along with medications he takes to manage his rheumatoid arthritis, but he works closely with his rheumatologist to avoid those risks, including monitoring of his liver function every 8 weeks. (Br. Ex. 1, Dekker Dep. at 12:13-22; 17: 15-18.) Mr. Dekker has been on testosterone therapy without interruption since 2019 and while he is aware of the risks associated with his medications, when he is receiving testosterone therapy, he is the most stable and happy that he has ever been. (Br. Ex. 1, Dekker Dep. at 29:5-10.)

As additional treatment for gender dysphoria, Mr. Dekker received masculinizing chest surgery in April 2022. (ECF 11-6, Dekker ¶16.) Mr. Dekker described the first birthday he celebrated after receiving top-surgery as an afternoon of joy and laughter, where he was able to be shirtless in public, like other men. (*Id.* ¶ 20.) Mr. Dekker describes that obtaining hormone therapy and top surgery helped

to align his body with his identity and brought him a "great deal of relief and comfort," and allowed him to be the version of himself that he pictured growing up to be. (*Id.* ¶18-19.) All of Mr. Dekker's gender-affirming care to date has been covered by Medicaid as medically necessary. (*Id.* ¶ 17.)

Mr. Dekker continues to need hormone therapy to treat his gender dysphoria. (*Id.* ¶ 26.) The gender-affirming care he has received allows him to live without the symptoms of gender dysphoria in his day-to-day life. (*Id.* ¶¶ 18-19.) Under the Challenged Exclusion, Medicaid will no longer cover this care, and because Mr. Dekker cannot afford to pay out-of-pocket for it, he will lose access to hormone therapy, which would result in myriad negative outcomes for him. (*Id.* ¶¶ 23.) Mr. Dekker has lived without testosterone for a period of time and the mental health effects were significant, including overwhelming social anxiety because he was afraid to go outside or leave his house for fear of not being perceived as male. (Br. Ex. 1, Dekker Dep. at 30:2-15.) Stopping this treatment will cause him to undergo physical changes that will cause him psychological distress and increase his risk of discrimination and violence. (ECF 11-6, Dekker ¶¶ 23, 26-27; *see also* Ex. 16, Shumer Rebuttal ¶ 76 (ECF 175-16) (Mr. Dekker "would be at high risk for negative health outcomes if his care were discontinued.").)

4. K.F.

Plaintiff K.F. is a 13-year-old transgender boy who receives Medicaid coverage due to his family's income. (ECF 11-9, Decl. of J. Ladue ¶ 8 ("Ladue"); Ex. 1, Defs.' Admission No. 6 (ECF 175-1).) From a very young age, K.F. knew that his sex assigned at birth did not match his gender identity. (ECF 11-9, Ladue ¶¶ 9-10.) K.F. has never wavered about his gender identity. (*Id.* ¶ 10.) When K.F. came out at age 7, his parents arranged for him to see a mental health professional, who diagnosed K.F. with gender dysphoria after a thorough evaluation. (*Id.* ¶ 13.) He later established care with the Gender Multispecialty Service (GeMS) Program at Boston Children's Hospital, the first pediatric and adolescent transgender health program in the country. (*Id.* ¶¶ 13, 16; *see also* Ex. 11, Karasic Rebuttal Rep. ¶ 64 ("Karasic Rebuttal") (ECF 175-11).)

K.F.'s initial consult at GeMS was with a psychologist and lasted over two hours. (ECF 11-9, Ladue ¶ 16; Ex. 11, Karasic Rebuttal ¶ 63 (ECF 175-11).) GeMS then started him with a pediatric nurse practitioner, Sarah Pilcher, who monitored K.F.'s hormone levels for the onset of puberty. (ECF 11-9, Ladue ¶ 16.)[2] In June 2020, Pilcher determined that it was medically necessary for K.F. to start on puberty

[2] *See also* Ex. 11, Karasic Rebuttal ¶ 64 (ECF 175-11) (noting that the NP was "providing care as part of a team led by a Harvard pediatric endocrinologist"); Ex. 16, Shumer Rebuttal ¶ 69 (ECF 175-16) (stating that NPs, including the provider who K.F. saw, "are qualified to provide excellent, thoughtful and evidence-based care").

delaying medication; he and his mother discussed the risks and benefits of the medication with Pilcher, and K.F. then received a Supprelin implant, which the Massachusetts Medicaid program covered. (*Id.* ¶ 17; Ex. 11, Karasic Rebuttal ¶ 66 (ECF 175-11).)

Upon moving to Florida in August 2020, K.F. enrolled in Medicaid and established care with Florida-based specialists at the Johns Hopkins Gender Clinic. (ECF 11-9, Ladue ¶¶ 8, 19-20.) There, he saw a provider with a Doctorate in Nursing Practice. (*Id.* ¶ 20; Ex. 11, Karasic Rebuttal ¶ 65 (ECF 175-16).) In April 2022, after again discussing the risks and benefits of Supprelin with a pediatric urologist, K.F. received his second implant. (ECF 11-9, Ladue ¶ 20; Ex. 11, Karasic Rebuttal ¶ 66 (ECF 175-11).) His Florida Medicaid managed care plan, Humana, covered the treatment. (ECF 11-9, Ladue ¶ 20.)

K.F.'s treating specialists have indicated that he will likely need to begin hormone therapy when he is fourteen years old. (*Id.* ¶ 24.) Whatever course K.F.'s treatment takes, his family will be unable to afford it without Medicaid coverage. (*Id.* ¶ 30.)

Gender-affirming care created a "night and day" change in K.F. His persistent anxiety and issues functioning at school significantly improved, and he is now "thriving." (*Id.* ¶ 25.) He is doing well academically, socially, and athletically. (*Id.* ¶ 34.) Without access to this care through Medicaid, K.F.'s mental health will suffer

tremendously. (*Id.* ¶¶ 22, 28; Ex. 16, Shumer Rebuttal ¶ 69 (ECF 175-16) ("K.F.'s mental health would deteriorate precipitously if he were unable to continue to receive [gender-affirming] care").)

B. The Defendants

1. Defendant Jason Weida

Jason Weida is sued in his official capacity as Secretary of AHCA, the "single state agency authorized to manage, operate, and make payments for medical assistance and related services under Title XIX of the Social Security Act [Medicaid]." (ECF 1, Compl., at ¶ 17; ECF 65, Ans. at ¶ 17 (admitted).) *See* Fla. Stat. §§ 409.902, 409.963 (2022); *see also* 42 U.S.C. § 1396a(a)(5); 42 C.F.R. § 431.10. Weida is responsible for the enforcement of the Challenged Exclusion. (ECF 1, Compl., at ¶ 17; ECF 65, Ans. at ¶ 17 (admitted).) Weida is responsible for ensuring that the operation of Florida's Medicaid program complies with the United States Constitution and the Medicaid Act and its implementing regulations. (*Id.*) Defendant Weida's official place of business is located in Tallahassee, Leon County, Florida. (*Id.*)

2. Defendant Agency for Healthcare Administration

AHCA is the single state agency in Florida that is responsible for administering and implementing Florida's Medicaid program consistent with the requirements of federal law. (ECF 1, Compl., at ¶ 18; ECF 65, Ans. at ¶ 18

(admitted).) *See* Fla. Stat. § 409.902; 42 U.S.C.§ 1396a(a)(5); 42 C.F.R. § 431.10. AHCA receives federal funding to support the Florida Medicaid Program. (ECF 1, Compl, at ¶ 18; ECF 65, Ans at ¶ 18 (admitted).) AHCA uses the funds it receives from the federal government in part to cover health care services for persons enrolled in the Florida Medicaid Program. *Id.* Moreover, AHCA oversees the promulgation of all Medicaid rules, fee schedules, and coverage policies into the Florida Administrative Code. *Id*; *see also* Fla. Stat. § 409.919 (2022).

II. The History of Discrimination Against Transgender People

Transgender people have faced a long history of discrimination in this country. For much of the nineteenth and twentieth centuries, expression of a person's gender identity, when it did not align with their assigned sex at birth, was criminalized through cross-dressing laws. *See* Jennifer Levi & Daniel Redman, *The Cross-Dressing Case for Bathroom Equality*, 34 Seattle U. L. Rev. 133, 152-53, 171 (2010).

In more recent decades, Congress explicitly excluded gender diverse and transgender people from no less than four civil right laws, including the Fair Housing Act (excluding "transvestites"), the Americans With Disabilities Act ("ADA") (excluding gender identity disorder, "transsexualism," and "transvestism"), the Rehabilitation Act (including an exclusion identical to the ADA exclusion, thereby stripping transgender people of rights they held for almost two decades), and the

ADA Amendments Act (maintaining the prior transgender exclusions while expanding the definition of "disability" under the ADA and Rehabilitation Act for all other impairments). Kevin M. Barry et al., *A Bare Desire to Harm: Transgender People and the Equal Protection Clause*, 57 B.C. L. Rev. 507, 556 (2016).[3]

This discrimination extends well beyond federal legislation. According to a report issued by the U.S. Commission on Civil Rights ("USCCR"), "90 percent of transgender employees report experiencing some form of harassment or mistreatment" in the workplace. (Ex. 131, U.S. Commission on Civil Rights Briefing Report, *Working for Inclusion: Time for Congress to Enact Federal Legislation to Address Workplace Discrimination Against Lesbian, Gay, Bisexual, and Transgender Americans* (2017) ("USCCR Rep."), at 11 (ECF 178-11).) That same report relies on studies indicating that transgender people were three times as likely to be unemployed and more than twice as likely to live in poverty as compared to the general population in the United States. (*See id.* at 15; *see also id.* at 19 (citing survey noting that, of transgender respondents that were employed in the past year, 77-percent reporting "hid[ing] their gender identity, delay[ing] their transition, or quit[ting] their job, due to fear of negative repercussions").) Overall, transgender

[3] To be sure, many of those exclusions were unconstitutional and some, like those in the ADA, are inoperative because they were based on since-obsolete diagnoses pathologizing identity. *See Williams v. Kincaid*, 45 F.4th 759, 769 (4th Cir. 2022). "[A]s a matter of statutory construction, gender dysphoria is not a gender identity disorder." *Id.*

people in the United States are also more likely to lack health insurance or have a disability, and discrimination and a lack of access to care are major drivers of these inequities. (*See* Ex. 6, Decl. of Baker ¶ 28 ("Baker") (ECF 175-6).)

This discrimination, and the relative political powerlessness of transgender people, continue into the present day. "A wave of discriminatory State laws is targeting transgender youth, terrifying families and hurting kids who are not hurting anyone" and "epidemic of violence against transgender women and girls, in particular women and girls of color, has taken lives far too soon." (Ex. 77, U.S. Presidential Proclamation, Transgender Day of Visibility, 2023 (ECF 176-37).)

In 2016, the USCCR issued a statement condemning a spate of state laws and pending bills targeting the transgender community, among others. (*See* Ex. 69, April 18, 2016 USCCR Statement (ECF 176-29).) One year later, in 2017, the Trump Administration indicated that it would ban transgender people from serving in the military. (*See* Ex. 70, August 18, 2017 USCCR Statement (ECF 176-30); *see also* Presidential Memorandum of August 25, 2017: Military Service by Transgender Individuals, 82 Fed. Reg. 167 (Aug. 30, 2017).)

In the past two years alone, "hundreds of anti-transgender bills in States were proposed across America, most of them targeting transgender kids." (Ex. 76, U.S. Presidential Proclamation, Transgender Day of Visibility, 2022 (ECF 176-36).) Indeed, more than 110 anti-trans bills were proposed in states across the country in

2021,[4] and more than 500 such bills have been introduced and/or passed in the first months of 2023 alone.[5] "These bills … to criminalize supportive medical care for transgender kids, to ban transgender children from playing sports, and to outlaw discussing LGBTQI+ people in schools undermine [transgender people's] humanity and corrode our Nation's values." (*Id.*) They are also "damaging to the mental health and wellbeing of transgender youth, putting children and their families at greater risk of bullying and discrimination." (*Id.*)

Florida is no exception. At present, the Florida legislature is currently considering a slew of additional legislation specifically targeting transgender people. *See, e.g.*, Fla, S.B. 254/H.B. 1421 (2023) (criminalizing doctors for providing gender-affirming care to minors and prohibiting gender marker amendments on Florida birth certificates); Fla. H.B. 1223/S.B. 1320 (2023) (redefining "sex" to exclude the existence of transgender people, mandating the use of pronouns corresponding to sex assigned at birth, and banning classroom instruction relating to sexual orientation and gender identity in schools through the 8th grade); Fla. S.B.

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[4] *See* Sam Levin, "In an extraordinary attack on trans rights, conservative state lawmakers proposed more than 110 anti-trans bills this year," Guardian (June 14, 2021), *available at* https://www.theguardian.com/society/2021/jun/14/anti-translaws-us-map.

[5] American Civil Liberties Union, *Over 120 Bills Restricting LGBTQ Rights Introduced Nationwide in 2023 So Far* (Jan. 19, 2023), available at https://www.aclu.org/press-releases/over-120-bills-restricting-lgbtq-rights-introduced-nationwide-2023-so-far.

1674/H.B. 1521 (2023) (prohibiting gender-inclusive restrooms and changing facilities in schools, private businesses, public shelters, and healthcare facilities); Fla. S.B. 954/H.B.1265 (officially titled the "Reverse Woke Act," it would punish companies for providing affirming health insurance policies by holding employers liable in perpetuity for any future "detransition" treatment an employee may ever seek if they provide health insurance coverage for gender-affirming healthcare).

Within the last year, Florida officials have adopted several additional measures targeting LGBTQ people and more specifically, transgender people for disparate treatment. For example, on June 2, 2022, the same day the GAPMS Report was issued, the State Surgeon General urged the Florida Boards of Medicine to adopt a rule prohibiting physicians from providing this well-established medically necessary care to treat minors with gender dysphoria.[6] In response, the Florida Boards of Medicine promulgated a set of rules banning physicians from providing gender-affirming care to transgender minors. *See* Fla. Admin. Code R. 64B8-9.019 (effective March 16, 2023); Fla. Admin. Code R. 64B15-14.014 (effective March 28, 2023).

Around the same time, Florida enacted its infamous "Don't Say Gay" law, Florida Statute § 1001.42(8)(c) (2022), which prohibits "[c]lassroom instruction … on sexual orientation or gender identity" and has since been expanded by the Florida

[6] https://s3.documentcloud.org/documents/22050967/board-letter.pdf

Board of Education through the rulemaking process to apply to students in Kindergarten through 12th grade. Fla. Admin. Code. R. 6A-10.081 (2022). Enforcement of the "Don't Say Gay" law included sending letters from the Senior Chancellor of the Florida Department of Education to school districts whose LGBTQ+ Critical Support Guides, which outline best practices for creating a safe and affirming environment for LGBTQ+ students, were out of compliance with the law.[7] The impacts of these cruel measures are pushing parents of LGBTQ+ youth to move out of Florida to protect their children.[8]

Florida's Governor even removed a state attorney from office for, in part, saying that "transgender people are 'some of the most vulnerable Americans' and that attacks on them 'will deeply harm public safety.'" *Warren v. DeSantis*, No. 4:22CV302-RH-MAF, 2023 WL 345802, at *13 (N.D. Fla. Jan. 20, 2023).[9] And the Florida Department of Business and Professional Regulation lodged a public nuisance complaint against a bar catering to transgender persons when that bar had a drag queen reading event.[10]

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[7] December 14, 2022 - Meeting Agenda (fldoe.org) at https://www.fldoe.org/policy/state-board-of-edu/meetings/2022/2022-12-14/

[8] https://williamsinstitute.law.ucla.edu/wp-content/uploads/Dont-Say-Gay-Impact-Jan-2023.pdf

[9] *See also* https://www.flgov.com/wp-content/uploads/2022/08/Executive-Order-22-176.pdf.

[10] https://images.newrepublic.com/ce24ef552cdf7d41f1371580f1fb4163900f063c.pdf; https://www.myfloridalicense.com/viewcomplaint.asp?SID=&licid=5619209.

Indeed, Florida officials and their spokespersons have made a litany of public statements by denigrating transgender persons.[11] On April 24, 2023, Representative Randy Fine, sponsor of the bill that would impose felony penalties upon physicians who provide evidence-based medical care to transgender minors, began issuing subpoenas to "Florida-based organizations that recommend, endorse, or otherwise promote the [WPATH] standard of care[.]"[12]

Despite this historical and presently ongoing discrimination, being transgender, or receiving a diagnosis of gender dysphoria, has no bearing on an individual's ability to contribute to their community or society at large, especially when transgender people receive effective treatment to manage their symptoms of gender dysphoria (*See* Ex. 7, Karasic ¶¶ 26, 35 (ECF 175-7) ("People who are transgender have no impairment in their ability to be productive, contributing members of society simply because of their transgender status.") (ECF 175-7); *see*

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[11] https://twitter.com/JeremyRedfernFL/status/1558932733153402881?s=20&t=-RT4y02Czo48_y2JU3I6PA; https://twitter.com/GovRonDeSantis/status/1559646179595407362?s=20&t=55DYjYGjIIotEUZx-AY7Og; https://twitter.com/ChristinaPushaw/status/1560750173814689794?s=20&t=ReChkHaAQNRRoiwNfPSCkw.

[12] Florida House of Representatives, Memorandum "Authorization to commence Investigation"; *see also* https://twitter.com/VoteRandyFine/status/1650589678414733314?cxt=HHwWhICxvaekiegtAAAA ("I just signed subpoenas to the Florida Psychiatric Society, a branch of the @APApsychiatric and the Florida Chapter of the @AmerAcadPeds demanding production of all materials justifying their recommendation that castrating and mutilating children is "gender affirming care.")

also, *e.g.*, ECF 11-7 Rothstein ¶¶ 3, 5 (Mr. Rothstein describing how he attends the University of Central Florida on a full scholarship, and is pursuing degree in digital media full-time and participating in a federal work study program); ECF 11-9 ¶¶ 10, 34 (plaintiff K.F. is an intelligent, well-grounded young man who is immersed in his community, participates in golf and baseball, and loves his friends, family, and teammates).)

"Transgender Americans shape our Nation's soul—proudly serving in the military, curing deadly diseases, holding elected office, running thriving businesses, fighting for justice, raising families, and much more." (Ex. 77, U.S. Presidential Proclamation, Transgender Day of Visibility, 2023 (ECF 176-37); *see also* Ex. 76, U.S. Presidential Proclamation, Transgender Day of Visibility, 2022 (ECF 176-36).) Indeed, like other people with medical conditions managed by individualized treatment, many transgender people are highly accomplished and contribute to society in myriad ways. (*See* Brief of Elliot Page, Major Griffin-Gracy, Gwendolyn Herzig, Jazz Jennings, and Fifty-Four Others as Amicus Curiae In Support of Plaintiffs-Appellees in Brandt v. Rutledge 4:21-cv-00450-JM), *available at* https://www.aclu.org/cases/brandt-et-al-v-rutledge-et-al?document=Amicus-Brief-of-Trans-Adult-Voices#legal-documents).

III. Gender Identity & Gender Dysphoria

A. Gender Identity

Gender identity is a person's internal sense of being male or female. (Ex. 7, Decl. of Karasic ¶ 23 ("Karasic") (ECF 175-7); Ex. 8, Decl. of Olson-Kennedy at 8 ¶ 1 ("Olson-Kennedy")[13] (ECF 175-8); Ex. 9, Decl. of Shumer ¶ 26 ("Shumer") (ECF 175-9); Ex. 17, Janssen Rebuttal Rep. ¶ 36 ("Janssen Rebuttal") (ECF 175-17).) Gender identity is a well-understood and accepted concept in medicine and science that has a strong biological basis, is not a product of external influence, and cannot be changed. (Ex. 8, Olson-Kennedy at 8 ¶¶ 1-2 (ECF 175-8); Ex. 9, Shumer ¶ 29-33 (ECF 175-9); Ex. 7, Karasic ¶ 23 (ECF 175-7).) Indeed, "[e]fforts to change or suppress a person's … gender identity are grounded in the belief that being [transgender] is abnormal" and "are dangerous, discredited, and ineffective practices." (Ex. 74, SAMHSA, *Ending Conversion Therapy* (Oct. 2015) (ECF 176-33), at 8; *see also* Ex.7, Karasic ¶ 37 (ECF 175-7); Ex. 8, Olson-Kennedy, at ¶¶ 14-16 (ECF 175-8); Ex. 9, Shumer ¶ 28; Ex. 17, Janssen Rebuttal ¶ 41 (ECF 175-17).)

Everyone has a gender identity, and it does not always align with a person's "sex assigned at birth." (Ex. 7, Karasic ¶ 23 (ECF 175-7); Ex. 8, Olson-Kennedy at 8 ¶ 1 (ECF 175-8); Ex. 17, Janssen Rebuttal ¶¶ 35, 39 (ECF 175-17).)

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[13] Olson-Kennedy's Expert Declaration has two sets of paragraphs 1-19 due to a numbering error. Where necessary, her Declaration will be referred to by both a page number and paragraph number for clarity.

Sex assigned at birth refers to the sex designation given to a person when they are born, typically based on the appearance of external genital characteristics. (Ex. 7, Karasic ¶ 22 (ECF 175-7); Ex. 8, Olson-Kennedy at 9 ¶ 4 (ECF 175-8).) "Sex" as a concept in science and medicine is complicated and multifactorial – there are multiple sex characteristics, including genitalia, gonads, chromosomal makeup, endogenous hormones, gender identity, and variations in brain structure and function. (Ex. 7, Karasic ¶ 22 (ECF 175-7); Ex. 8, Olson-Kennedy at 9 ¶ 5 (ECF 175-8); Ex. 9, Shumer ¶ 25 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶ 41 (ECF 175-17).)

The term "transgender" refers to a person whose gender identity does not align with their sex assigned at birth. (Ex. 8, Olson-Kennedy at 8 ¶ 3 (ECF 175-8); Ex. 17, Janssen Rebuttal ¶ 35 (ECF 175-17).)

B. Gender Dysphoria

Gender dysphoria is a serious medical condition experienced by many transgender people characterized by the distress due to the incongruence between their sex assigned at birth and their gender identity. (Ex. 8, Olson-Kennedy at 10 ¶ 7 (ECF 175-8); Ex. 10, Decl. of Schechter ¶ 20 ("Schechter") (ECF 175-10); Ex. 7, Karasic ¶ 24 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶¶ 48-49 (ECF 175-17).) The diagnosis is contained in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* ("DSM-5"). (Ex. 7, Karasic ¶

25 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶ 49 (ECF 175-17); Ex. 8, Olson-Kennedy at 10-11 ¶¶ 7-8 (ECF 175-8); Ex. 10, Schechter ¶ 20 (ECF 175-10); *see also* Ex. 33, DSM 5 Gender Dysphoria (ECF 175-33).) The *International Classification of Diseases* (World Health Org., 11th rev.) also recognizes the diagnosis of "gender incongruence." (Ex. 8, Olson-Kennedy at 11 ¶ 8 (ECF 175-8); Ex. 10, Schechter ¶ 20 (ECF 175-10).)Gender dysphoria is characterized by clinically significant distress or impairment in social, occupational, or other important areas of functioning and often manifests as intense and persistent discomfort with the primary or secondary characteristics of a person's sex assigned at birth. (Ex. 7, Karasic ¶ 25 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶ 49 (ECF 175-17); Ex. 8, Olson-Kennedy at 11 ¶ 9 (ECF 175-8); Ex. 9, Shumer ¶ 36 (ECF 175-9); Ex. 10, Schechter ¶ 21 (ECF 175-10).)

Without appropriate treatment, gender dysphoria may cause debilitating anxiety, severe depression, self-harm, and even suicidality. (Ex. 7, Karasic ¶¶ 26, 36, 68 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 57, 122 (ECF 175-8); Ex. 17, Janssen Rebuttal ¶¶ 54, 83 (ECF 175-17); Ex. 9, Shumer ¶ 41 (ECF 175-9); Ex. 10, Schechter ¶ 21 (ECF 175-10); Ex. 15, Edmiston Rebuttal Rep. ¶¶ 34-35 ("Edmiston Rebuttal") (ECF 175-15).)

C. Treatment for Gender Dysphoria

Gender dysphoria is treatable, and interventions are supported by well-established guidelines and decades of research and clinical practice evidence. (*See*

Ex. 9, Shumer ¶ 41 (ECF 175-9); Ex. 5, Decl. of Antommaria ¶ 17 ("Antommaria") (ECF 175-5); Ex. 8, Olson-Kennedy at 12-13 ¶¶ 10-12 (ECF 175-8); Ex. 10, Schechter ¶¶ 24-26 (ECF 175-10); Ex. 7, Karasic ¶¶ 27-28, 33, 56-59 (ECF 175-7); Ex. 142, Nat'l Academies of Sciences, Engineering, and Medicine, *Understanding the Well-Being of LGBTQI+ Populations* ("Nat'l Academies Rep.") (ECF 178-22).)

Treatment seeks to eliminate the distress of gender dysphoria by aligning an individual patient's body and presentation with their internal sense of self. (Ex. 7, Karasic ¶ 36 (ECF 175-7); Ex. 10, Schechter ¶ 22 (ECF 175-10).) Treatment is generally referred to as "gender-affirming care" and may include counseling, puberty-delaying medication, hormone therapy, surgery, or other medically necessary treatments. (*See* Ex. 7, Karasic ¶ 40 (ECF 175-7); Ex. 8, Olson-Kennedy at 12 ¶ 10 (ECF 175-8); Ex. 10, Schechter ¶ 22 (ECF 175-10).)

Gender-affirming medical care is recognized to be medically necessary, safe, and effective treatment that improves the short and long-term health and quality of life outcomes for transgender people. (Ex. 17, Janssen Rebuttal ¶¶ 23-27, 133 (ECF 175-17); Ex. 7, Karasic ¶¶ 53-60, 100 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 24-48, 76, 121 (ECF 175-8); Ex. 12, Olson-Kennedy Rebuttal ¶¶ 73-74 (ECF 175-12); Ex. 10, Schechter ¶¶ 23, 34, 36-43, 81 (ECF 175-10); Ex. 9, Shumer ¶¶ 82, 86, 88, 89 (ECF 175-9).) The medical community does not consider these treatments to be experimental or investigational. (Ex. 5, Antommaria, ¶¶ 32-33 (ECF 175-5); Ex. 14,

Antommaria Rebuttal ¶¶ 21-36 (ECF 175-14); Ex. 17, Janssen Rebuttal ¶ 23 (ECF 175-17); Ex. 8, Olson-Kennedy ¶ 73 (Ex. 175-8); Ex. 10, Schechter ¶¶ 44-46 (ECF 175-10); Ex. 9, Shumer ¶ 89 (ECF 175-9).) Moreover, there is no established safe and effective alternative to gender-affirming care for gender dysphoria. (*See* Ex. 10, Schechter ¶ 58 (ECF 175-10); Ex. 7, Karasic ¶ 37 (ECF 175-7); Ex. 11, Karasic Rebuttal ¶¶ 23-24, 47 (ECF 175-11).)

1. Puberty-Delaying Medications

For adolescents with gender dysphoria who experience severe distress with the onset of puberty, puberty-delaying medications, also known as gonadotropin-releasing hormone agonists ("GnRHa") or "puberty blockers," may be indicated. (Ex. 7, Karasic, ¶ 42 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 22-23 (ECF 175-8); Ex. 9, Shumer ¶ 46 (ECF 17-9); Ex. 17, Janssen Rebuttal Rep. ¶ 89 ("Janssen Rebuttal") (ECF 175-17).) Puberty-delaying medications work by pausing endogenous puberty when the treatment begins, thus limiting the influence of a person's endogenous hormones on their body. (Ex. 8, Olson-Kennedy ¶¶ 23-24 (ECF 175-8); Ex. 7, Karasic ¶ 42 (ECF 175-7); Ex. 9, Shumer ¶ 63 (ECF 175-9).) Such interventions afford the adolescent time to better understand their gender identity while delaying the development of secondary sex characteristics, which can cause severe distress when incompatible with an adolescent's gender identity. (Ex. 8, Olson-Kennedy ¶¶ 23-24 (ECF 175-8); Ex. 12, Olson-Kennedy Rebuttal Rep. ¶ 81 ("Olson-Kennedy

Rebuttal") (ECF 175-12); Ex. 9, Shumer ¶ 66 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶ 92 (ECF 175-17).)

Puberty-delaying medications may be indicated when an adolescent with gender dysphoria enters puberty, at what is called Tanner Stage 2. (Ex. 9, Shumer ¶ 62 (ECF 175-9); Ex. 8, Olson-Kennedy ¶ 24 (ECF 175-8).) Tanner Stage 2 refers to the stage in puberty when the physical effects of testosterone or estrogen are apparent upon physical exam and usually occurs between age 9-14 for individuals assigned male at birth and between age 8-12 for individuals assigned female at birth. (Ex. 9, Shumer ¶ 62 (ECF 175-9).) The treatment is reversible, meaning that if an adolescent discontinues the treatment, puberty will resume. (Ex. 7, Karasic, ¶ 42 (ECF 175-7); Ex. 8, Olson-Kennedy ¶ 24 (ECF 175-8); Ex. 9, Shumer ¶ 65 (ECF 175-9).)

When used to treat gender dysphoria, puberty-delaying medication does not delay puberty beyond the typical age range for puberty, as the protocols use to treat transgender adolescents would cease the provision of puberty-delaying medication without the provision of gender-affirming hormones at about the latter third of typical puberty. (Ex.12, Olson-Kennedy Rebuttal ¶ 23 (ECF 175-12).)

2. Hormone Therapy

For some adolescents and adults with gender dysphoria, hormone therapy (utilizing testosterone for transgender males and testosterone suppression and estrogen for transgender females) may be medically necessary. (Ex. 17, Janssen

Rebuttal ¶ 96 (ECF 175-17); Ex. 8, Olson-Kennedy ¶ 32 (ECF 175-8); Ex. 7, Karasic ¶ 43 (ECF 175-7), Ex. 9, Shumer ¶¶ 46, 72 (ECF 175-9).) Hormones are administered to attain the appropriate masculinization or feminization to align with the patient's gender identity. (Ex. 7, Karasic ¶ 43 (ECF 175-7).) Gender-affirming hormone therapy is a partially reversible treatment in that some of the effects produced by the hormones are reversible, while others are not. (Ex. 7, Karasic ¶ 43 ECF 175-7); Ex. 8, Olson-Kennedy ¶ 32 (ECF 175-8).) Hormone therapy allows for a physical appearance more closely aligning with gender identity and helps to alleviate gender dysphoria. (Ex. 9, Shumer ¶¶ 60, 71 (ECF 175-9).) Laboratory testing ensures proper dosing and hormone levels. (Ex. 9, Shumer ¶¶ 74, 84 (ECF 175-9).)

3. Gender Confirming Surgeries

Gender confirming surgery may be medically indicated for some transgender adults and older adolescents to align their primary and secondary sex characteristics with their gender identity. (Ex. 8, Olson-Kennedy ¶ 42 (ECF 175-8); Ex. 10, Schechter ¶ 22 (ECF 175-10).) Surgical care can include, but is not limited to, mastectomy, breast augmentation, hysterectomy, oophorectomy, orchiectomy, vaginoplasty, and phalloplasty. (Ex. 7, Karasic ¶ 44 (ECF 175-7); Ex. 8, Olson-Kennedy ¶ 42 (ECF 175-8); Ex. 10, Schechter ¶ 28 (ECF 175-10).) Surgeons regularly perform these procedures to treat conditions other than gender dysphoria.

(Ex. 10, Schechter ¶ 38 (ECF 175-10).)

IV. Gender-Affirming Care is the Standard of Care to Treat Gender Dysphoria

A. History of Gender-Affirming Medical Care

Gender-affirming medical care dates back almost a century. (Ex. 5, Antommaria ¶ 32 (ECF 175-5), Ex. 10, Schechter ¶ 46 (ECF 175-10).) The first gender confirming surgeries were performed in the 1920s at Magnus Hirschfeld's Institute for Sexual Science. (Ex. 143, Institute of Medicine, The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding 48-49 (The National Academies Press 2011) ("Inst. of Medicine Rep.") (ECF 178-23).) Many of the surgical techniques currently used in phalloplasties and vaginoplasties were developed over 30 years ago. (Ex. 10, Schecter ¶ 46 (ECF 175-10).) Hormone treatment for gender dysphoria began after estrogen and testosterone became commercially available in the 1930s. (Ex. 5, Antommaria, ¶ 32 (ECF 175-5); Ex. 11, Karasic Rebuttal ¶ 32 (ECF 175-11); Ex. 12, Olson-Kennedy Rebuttal ¶ 27 (ECF 175-12); *see also* Ex. 143, Inst. of Medicine Rep., at 49 (ECF 178-23) ("During the 1930's, endocrinologist Harry Benjamin became one of the first physicians in the United States to routinely administer hormone therapy to individuals desiring to change their sex.").) The first United States clinics providing gender affirming medical care to transgender patients were opened in the 1960s and 1970s. (Ex. 8, Olson-Kennedy ¶ 71 (ECF 175-8); Ex. 11,

Karasic Rebuttal ¶ 32 (ECF 175-11); Ex. 142, Nat'l Academies Rep. at 360 (ECF 178-22).) And puberty delaying medications have been used since at least the late 1990s to prevent the development of irreversible secondary sex traits that may exacerbate adolescents' gender dysphoria. (Ex. 5, Antommaria ¶ 32 (175-5); Ex. 8, Olson-Kennedy ¶ 24 (ECF 175-8); Ex. 142, Nat'l Academies Rep., at 364 (ECF 178-22).)

As research and clinical experience evolved, the medical paradigm related to gender nonconformity began to shift, and, instead of encouraging transgender individuals to conform to gender expectations, clinical management instead began to focus on "ameliorating the negative effects of stigma" and "assisting transgender individuals in finding a gender expression that is comfortable and consistent with their gender identity." (*See* Ex. 143, Inst. of Medicine Rep., at 51-52 (ECF 178-23).) In 1979, an interdisciplinary group of physicians, therapists, and researchers created the Harry Benjamin International Gender Dysphoria Association, now known as the World Professional Association for Transgender Health ("WPATH"). (*Id.* at 50.)

In 2013, the American Psychiatric Association replaced the former diagnosis of "gender identity disorder" contained in prior iterations of the DSM with the new and distinct diagnosis of "gender dysphoria" in the DSM-5. (Ex. 8, Olson-Kennedy at 10 ¶ 7 (ECF 175-8); Ex.7, Karasic ¶ 35 (ECF 175-7); Ex. 11, Karasic Rebuttal ¶ 26 (ECF 175-11); Ex. 9, Shumer ¶¶ 36-37 (ECF 175-9); Ex. 142, Nat'l Academies

Report, at 362 (ECF 178-22).) The DSM-5 defined gender dysphoria to "emphasize[] the clinically significant distress and impairment that can accompany incongruence between assigned sex and gender identity" rather than to pathologize a person's gender incongruence as disordered. (Ex. 17, Janssen Rebuttal ¶ 53 (ECF 175-17); Ex. 7, Karasic ¶ 35 (ECF 175-7); Ex. 11, Karasic Rebuttal ¶ 26 (ECF 175-11); Ex. 8, Olson-Kennedy at 10 ¶ 7 (ECF 175-8); Ex. 12, Olson-Kennedy Rebuttal ¶ 15 (ECF 175-12); Ex. 9, Shumer ¶¶ 36-37 (ECF 175-9); Ex. 10, Schechter ¶ 20 (ECF 175-10); Ex. 142, Nat'l Academies Rep., at 362 (ECF 178-22).) That is because "being transgender is widely accepted as a variation in human development and is not considered a mental illness." (Ex. 7, Karasic ¶ 35 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶ 53 (ECF 175-17); *see also* Ex. 74, SAMHSA, *Moving Beyond Change Efforts* (2023) at 9 (ECF 176-34).)

The World Health Organization has similarly replaced transsexualism and gender identity disorder with the diagnosis of gender incongruence and moved it to a new chapter on sexual health from the chapter on mental and behavioral disorders. (Ex. 8, Olson-Kennedy at 11 ¶ 8 (ECF 175-8); Ex. 10, Schechter ¶ 20 (ECF 175-10); Ex 7, Karasic ¶ 35 (ECF 175-7); Ex. 142, National Academies Report, at 362 (ECF 178-22).)

For more than four decades, medical organizations have studied the treatment of gender dysphoria and created evidence-based standards for the medical treatment

of transgender patients. For example, WPATH first published its standards of care for the treatment of gender dysphoria in 1979, which have been continuously maintained and are now in their eighth version (*See* Ex. 7, Karasic ¶ 27 (ECF 175-7); Ex. 8, Olson-Kennedy at 12 ¶ 10 (ECF 175-8); Ex. 9, Shumer ¶ 48 (ECF 175-9); Ex. 10, Schechter ¶ 24 (ECF 175-10); Ex. 17, Janssen Rebuttal ¶ 55 (ECF 175-17); Ex. 142, Nat'l Academies Rep., at 361 (ECF 178-22); *see also* Ex. 34, E. Coleman et al., *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8,* 23 Internat'l J. of Transgender Health S1 (2022) ("WPATH Standards of Care 8") (ECF 175-34).)

B. Current Guidelines for the Provision of Gender-Affirming Care

The WPATH Standards of Care 8 are based on the best available evidence and professional consensus. (Ex. 5, Antommaria ¶ 29 (ECF 175-5); Ex. 7, Karasic ¶ 28 (ECF 175-7); Ex. 8, Olson-Kennedy at 12 ¶ 10 (ECF 175-8); Ex. 9, Shumer ¶ 48 (ECF 175-9); Ex. 10, Schechter ¶¶ 8, 24 (ECF 175-10); Ex. 17, Janssen Rebuttal ¶ 56 (ECF 175-17); Ex. 142, Nat'l Academies Rep., at 361 (ECF 178-22); *see also* Ex. 34, WPATH Standards of Care 8, at S8, S247-S251 ("Methodology") (ECF 175-34).) Major medical organizations like the American Medical Association ("AMA"), the Endocrine Society American Academy of Pediatrics ("AAP"), American Psychiatric Association, American Psychological Association, Pediatric Endocrine Society, the American College of Physicians, the American Academy of Family

Physicians ("AAFP"), and the American Academy of Child and Adolescent Psychiatry ("AACAP") have joined WPATH in recognizing that gender-affirming care is medically necessary for transgender people and endorse the WPATH Standards of Care 8. (Ex. 5, Antommaria ¶ 30 (ECF 175-5); Ex. 7, Karasic ¶ 34 (ECF 175-7); Ex. 8, Olson-Kennedy at 12 ¶¶ 10-11 (ECF 175-8), 31 ¶ 48; Ex. 9, Shumer ¶¶ 54-55 (ECF 175-9); Ex. 10, Schechter ¶ 27 (ECF 175-10); Ex. 17, Janssen Rebuttal ¶ 60 (ECF 175-17); Ex. 142, Nat'l Academies Rep., at 361 (ECF 178-22).)[14]

The Endocrine Society's clinical practice guidelines, first published in 2009 and later revised in 2017, are largely consistent with the WPATH Standards of Care 8 and were developed using rigorous scientific methods. (*See* Ex 5, Antommaria ¶¶ 17-18 (ECF 175-5); Ex. 7, Karasic ¶¶ 31-33 (ECF 175-7); Ex. 8, Olson-Kennedy 13 ¶ 12 (ECF 175-8); Ex. 9, Shumer ¶ 53 (ECF 175-9); Ex. 10, Schechter ¶ 26 (ECF

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[14] *See, e.g,* Ex. 36, AACAP, *Statement Responding to Efforts to Ban Care* (ECF 175-36); Ex. 37, AAFP, *Care for Transgender Patients* (ECF 175-37); Ex. 38, Am. Acad. of Peds., *Ensuring Comprehensive Care and Support for Transgender and Gender Diverse Children and Adolescents* (ECF 175-38); Ex. 41, Am. Coll. of Physicians, *LGBT Health Disparities Policy* (ECF 176-1);Ex. 45, Am. Psychol. Ass'n., *Guidelines for Psyhoclogical Practice with Transgender and Gender Non-confirming People* (ECF 176-5); Ex. 47, Am. Psychia. Ass'n, *Position Statement on Treatment of Transgender and Gender Diverse Youth* (ECF 176-7); Ex. 48, Am. Psychia. Ass'n, *Position Statement on Access to Care* (ECF 176-8); Ex. 49, Endocrine Soc., *Transgender Health Position Statement* (ECF 176-9); Ex. 50, Ped. Endocrine Soc., *Opposition to Bills that Harm Transgender Youth* (ECF 176-10); Ex. 42, AMA, *Letter to Nat'l Gov. Ass'n* (ECF 176-2); Ex. 43, AMA, *Issue Brief: Health Insurance Coverage for Gender-Affirming Care* (ECF 176-3); Ex. 44, AMA, *Resolution H-185.950* (ECF 176-4).

175-10); Ex. 17, Janssen Rebuttal ¶¶ 57-58 (ECF 175-17); Ex. 142, Nat'l Academies Rep., at 361 (ECF 178-22); *see also* Ex. 123, Wylie Hembree et al., *Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An EndocrineSociety Clinical Practice Guideline*, 102 J. Clin Endocrinol Metab. 3869 (2017) ("Endocrine Soc. Guidelines") (ECF 178-3).)

The WPATH Standards of Care 8 and the Endocrine Society Guidelines provide for medical interventions that are individualized based on patient needs and may include pubertal suppression, hormone therapy, or surgeries. (*See* Ex. 8, Olson-Kennedy at 12 ¶ 10 (ECF 175-8); Ex. 7, Karasic ¶ 40 (ECF 175-7); Ex. 9, Shumer ¶ 57 (ECF 175-9); Ex. 10, Schechter ¶ 25 (ECF 175-10); *see generally* Ex. 34, WPATH Standards of Care 8 (ECF 175-34); Ex. 123. Endocrine Soc. Guidelines (ECF 178-3).) Treatment protocols and recommendations differ depending on whether the patient is an adolescent (minors who have started puberty) or an adult. (Ex. 17, Janssen Rebuttal ¶ 59 (ECF 175-17); *see also* Ex. 34, WPATH Standards of Care 8, at S32, S48, S111, S129 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (ECF 178-3).)

Neither WPATH nor the Endocrine Society Guidelines recommend any medical, pharmaceutical, or surgical interventions prior to the onset of puberty. (Ex. 8, Olson-Kennedy at 17 ¶ 18 (ECF 175-8); Ex. 7, Karasic ¶ 41 (ECF 175-7); Ex. 9, Shumer ¶ 44 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶¶ 25, 59 (ECF 175-17); see

also Ex. 34, WPATH Standards of Care 8, at S69, Endocrine Society Guidelines, at 3870, Recommendation 1.3 (ECF 175-34).) Medical interventions are only indicated once a person experiencing gender dysphoria has begun puberty. (Ex. 9, Shumer ¶ 44, 58 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶ 62 (ECF 175-17).)

1. Assessment and Diagnosis of Gender Dysphoria

The diagnosis of gender dysphoria in adults can generally be made by a health care provider with relevant expertise and training in identifying gender dysphoria as well as co-existing mental health and psychosocial concerns, including a psychiatrist, psychologist, social worker, or therapist. (*See* Ex. 7, Karasic ¶ 49 (ECF 175-7); *see also* Ex. 34, WPATH Standards of Care 8, at S32 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3870 (ECF 178-3).) The diagnostic criteria for gender dysphoria in the DSM 5 require that "the marked incongruence between one's experienced/expressed gender and assigned gender" last least six months duration, (Ex. 7, Karasic ¶ 25 (ECF 175-7); Ex. 8, Olson-Kennedy at 11 ¶ 9 (ECF 175-8); Ex. 9, Shumer ¶ 36 (ECF 175-9); *see also* Ex. 33, DSM 5 (ECF 175-33).)

For minors, WPATH Standards of Care 8 recommend that health care professionals working with transgender and non-binary adolescents be licensed, hold a postgraduate degree in relevant clinical field, have received training and developed expertise in working with children and adolescents, including those with autism spectrum disorder, and have received training and developed expertise in

gender identity and diversity in youth, and in the ability of youth to assent/consent to care (Ex. 7, Karasic ¶ 47 (ECF 175-7); *see also* Ex. 34, WPATH Standards of Care 8, at S48 (ECF 175-34).) The Endocrine Society Clinical Practice Guideline states that for the assessment and diagnosis of gender dysphoria in children and adolescents that only "[mental health professionals] who ha[ve] training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis," which usually includes "a complete psychodiagnostic assessment." (Ex. 7, Karasic ¶ 52 (ECF 175-7); *see also* Ex. 123, Endocrine Society Guidelines, at 3870 (ECF 178-3).) Because gender dysphoria may be accompanied with psychological or psychiatric conditions, clinicians involved in diagnosis and psychological assessment must meet specific competency requirements and undertake or refer patients for appropriate psychological or psychiatric treatment as necessary. (Ex. 7, Karasic ¶ 52 (ECF 175-7).) Children and adolescents diagnosed with gender dysphoria are recommended to engage with a multidisciplinary team of mental health and medical professionals to formulate a treatment plan, in coordination with the parent(s) or guardian(s), with a goal of reduction of gender dysphoria. (Ex. 9, Shumer ¶ 38 (ECF 175-9).)

2. Criteria for Gender-Affirming Medical Interventions

Adults

Gender-affirming medical interventions may be considered for transgender

adults whose gender dysphoria is "marked and sustained" when other possible causes of gender incongruence are excluded, mental or physical health conditions that could negatively impact the outcome of treatment are assessed, and the adult has the capacity to understand the risks and benefits of treatment and provide consent. (Ex. 7, Karasic ¶ 49 (ECF 175-7); Ex. 9, Shumer ¶ 73 (ECF 175-9); Ex. 10, Schecter ¶ 29 (ECF 175-10); *see also* Ex. 34, WPATH Standards of Care 8, at S35-S39, Statement 5.3 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878. Table 4 (ECF 178-3) (requiring "persistent, well-documented gender dysphoria/gender incongruence").) A qualified provider must recommend initiation of the treatment. (Ex. 10, Shechter ¶ 29 (ECF 175-10); *see also* Ex. 34, WPATH Standards of Care 8, at S33-S35, Statement 5.1 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (ECF 178-3).) Before any gender-affirming care is provided, impacts on fertility and fertility preservation options be discussed thoroughly with the patient. (Ex. 7, Karasic ¶ 50 (ECF 175-7); Ex. 9, Shumer ¶ 39 (ECF 175-9); *see also* Ex. 34, WPATH Standards of Care 8, at S39, Statement 5.3g (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (ECF 178-3)). And, prior to any genital reconstruction surgery, the patient must have received a minimum of six months of hormone therapy "as appropriate to their gender goals." (Ex. 10, Schechter ¶ 29 (ECF 175-10); *see also* Ex. 34, WPATH Standards of Care 8, at S132, Statements 13.5-13.6 (ECF 175-34).)

Adolescents

Similarly, the treatment guidelines require that an adolescent's gender dysphoria be "marked and sustained over time" for medical interventions to be considered. (Ex. 9, Shumer ¶ 72 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶ 99 (ECF 175-17); *see also* Ex. 34, WPATH Standards of Care 8, at S60-S61, Statement 6.12b (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (requiring "the persistence of gender dysphoria") (ECF 178-3).)

Prior to offering medical interventions, which are only indicated for individuals who have begun puberty, it is recommended that providers determine that the adolescent has the emotional and cognitive capacity to provide assent for treatment, and that other mental health concerns "that may interfere with diagnostic clarity and capacity to consent have been addressed." (Ex. 9, Shumer ¶ 72 (ECF 175-9); Ex. 17, Janssen Rebuttal ¶ 99 (ECF 175-17); *see also* Ex. 34, WPATH Standards of Care 8, at S62-S63, Statement 6.12(d) (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (ECF 178-3).) The WPATH Standards of Care recommend that parent(s)/guardian(s) be involved in the assessment and treatment process for minors. (Ex. 9, Shumer ¶ 72 (ECF 175-9); *see also* Ex. 34, WPATH Standards of Care 8, at S57-S58, Statement 6.11 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3878, Table 5 (ECF 178-3).)

Some surgical procedures, primarily chest masculinization and breast

augmentation, "can be considered in minors when clinically and developmentally appropriate as determined by a multidisciplinary team experienced in adolescent and gender development." (Ex. 10, Schechter ¶ 30 (ECF 175-10); Ex. 8, Olson-Kennedy ¶ 46 (ECF 175-8); *see also* Ex. 34, WPATH Standards of Care 8, at S133, Statement 13.7 (ECF 175-34).)

Prior to initiating any medically necessary medical or surgical intervention" for gender dysphoria an adolescent will have had a comprehensive biopsychosocial assessment that will include gender identity development, social development and support, diagnostic assessment of co-occurring mental health or developmental concerns, and capacity for decision making. (Ex. 7, Karasic ¶ 48 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶ 77 (ECF 175-17); *see also* Ex. 34, WPATH Standards of Care 8 at S50-S51, Statement 6.3 (ECF 175-34); Ex. 123, Endocrine Society Guidelines, at 3877 (ECF 178-3)). The goals of this assessment are to develop a deep understanding of the young person's experience with gender identity, to consider whether the child or adolescent meets criteria for a diagnosis of gender dysphoria, and to understand what options may be desired and helpful for the adolescent (Ex. 9, Shumer ¶ 43 (ECF 175-9); *see also* Ex. 34, WPATH Standards of Care 8, at S50-S51, Statement 6.3 (ECF 175-34).)

Affirming care for transgender youth means supporting them through their period of exploration of gender expression and increasing self-awareness of their

identity, not steering them in any particular direction. (Ex. 7, Karasic ¶ 51 (ECF 175-7); *see also* Ex. 34, WPATH Standards of Care 8, at S50, Statement 6.2 (ECF 175-34). It is recommended that health professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular outcome is favored and that for some youth, obtaining gender-affirming medical care is important while for others it is not necessary. (*Id.*)

C. Gender-Affirming Care Is Safe and Effective

Gender-affirming medical care is recognized to be medically necessary, safe, and effective treatment that improves the short and long-term health and quality of life outcomes for transgender people. (Ex. 17, Janssen Rebuttal ¶¶ 23-27, 133 (ECF 175-17); Ex. 7, Karasic ¶¶ 53-60, 100 (ECF 175-7); Ex. 8, Olson-Kennedy, ¶¶ 24-48, 76, 121 (ECF 175-8); Ex. 12, Olson-Kennedy Rebuttal ¶¶ 73-74 (ECF 175-12); Ex. 10, Schechter, ¶¶ 23, 34, 36-43, 81 (ECF 175-10); Ex. 9, Shumer ¶¶ 82, 86, 88, 89 (ECF 175-9).) The medical community does not consider these treatments to be experimental or investigational. (Ex. 5, Antommaria ¶¶ 32-33 (ECF 175-5); Ex. 14, Antommaria Rebuttal ¶¶ 21-36 (ECF 175-14); Ex. 17, Janssen Rebuttal ¶ 23 (ECF 175-17); Ex. 8, Olson-Kennedy ¶ 73 (ECF 175-8); Ex. 10, Schechter ¶¶ 44-46 (Ex 175-10); Ex. 9, Shumer, ¶ 89 (ECF 175-9).). Moreover, there is no established safe and effective alternative to gender affirming care for gender dysphoria. (*See* Ex. 10,

Schechter ¶ 58 (ECF 175-10); Ex. 7, Karasic ¶ 37 (ECF 175-7); Ex. 11, Karasic Rebuttal ¶¶ 23-24, 47 (ECF 175-11).)

1. Puberty-delaying medications

Puberty-delaying medications have been used exclusively in pediatrics for several decades to treat precocious puberty. (Ex. 8, Olson-Kennedy ¶ 24 (ECF 175-8); Ex. 16, Shumer Rebuttal ¶ 64 (ECF 175-16).) For both indications, the side effects of these medications are comparable and easily managed, and the risks are greatly outweighed by the benefits of treatment. (Ex. 9, Shumer ¶ 68 (ECF 175-9); Ex. 8, Olson-Kennedy ¶¶ 103-105 (ECF 175-8).) These medications are not experimental merely because they are not FDA-approved for the specific application of treating gender dysphoria. (Ex. 5, Antommaria ¶ 34 (ECF 175-5); Ex. 17, Janssen Rebuttal ¶ 107 (ECF 175-17); Ex. 7, Karasic ¶ 66 (ECF 175-7).) There are other conditions for which puberty-delaying medications may be prescribed that are off label, yet not considered experimental. (Ex. 9, Shumer ¶ 69 (ECF 175-9).) Off-label prescribing is both legal and common and does not impact the safety or efficacy of these medications. (Ex. 5, Antommaria ¶¶ 34-37 (ECF 175-5); Ex. 7, Karasic ¶ 66 (ECF 175-7), Ex. 8, Olson-Kennedy ¶¶ 92-93 (ECF 175-8); Ex. 9, Shumer ¶ 69 (ECF 175-9).)

The clinical guidelines require that potential risks and benefits of treatment with puberty-delaying medications are discussed with adolescent patients and their

families. (Ex. 5, Antommaria ¶ 50 (ECF 175-5); Ex. 9, Shumer ¶ 66 (ECF 175-9); Ex. 16, Shumer Rebuttal ¶¶ 41, 48, 51 (ECF 175-16); Ex. 17, Janssen Rebuttal ¶ 93 (ECF 175-17).) The treatment is reversible, meaning that if an adolescent discontinues the treatment, puberty will resume. (Ex. 7, Karasic, ¶ 42 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 24 (ECF 175-8); Ex. 9, Shumer ¶ 65 (ECF 175-9).) These medications do not have any long-term implications on fertility or sexual function, and there is no evidence that they impact brain development, emotional regulation, or cognition. (Ex. 15, Edmiston Rebuttal Rep. ¶¶ 21-33 ("Edmiston Rebuttal") (ECF 175-15); Ex. 12, Olson-Kennedy Rebuttal ¶¶ 17-23 (ECF 175-12); Ex. 9, Shumer ¶ 73 (ECF 175-9).) And the medical and scientific literature has established that puberty-delaying medication is safe and effective to treat gender dysphoria in adolescents. *See* Ex. 5, Antommaria ¶ 32 (ECF 175-5); Ex. 9, Shumer ¶¶ 63, 78-82 (ECF 175-9); Ex. 8, Olson-Kennedy ¶¶ 25-29, 99-101 (ECF 175-8); Ex. 16, Shumer Rebuttal ¶¶ 51-54 (ECF 175-16); Ex.12; Olson-Kennedy Rebuttal ¶¶ 73-74 (ECF 175-12).)

Many studies have demonstrated that this medication is effective. (*See, e.g.,* Ex. 165, P.T. Cohen-Kettenis & S.H. van Goozen, *Pubertal Delay as an Aid in Diagnosis and Treatment of a Transsexual Adolescent*, 7 Eur Child Adolesc Psychiatry 246, 248 (1998) (ECF 179-5) ("pubertal delay [i]s an additional tool in the diagnosis and treatment of young adolescents with . . . a life-long consistent and

extreme GID [for whom] it may be a physical and psychological beneficial way to intervene"); Ex. 141, Annelou L.C. de Vries et al., *Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study*, 8 J. Sex. Med. 2276, 2278 (2011) (ECF 178-21) (while not resolving gender dysphoria, puberty-delaying medication "relieves the acute distress accompanying gender dysphoria"); Ex. 168, Annelou L.C. de Vries et al., *Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment*, 134 Pediatrics 696, 703 (2014) (ECF 179-8) ("[A] treatment protocol including puberty suppression leads to improved psychological functioning of transgender adolescents."); Ex. 167, Rosalia Costa et al., *Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria*, 12 J. Sex. Med. 2206, 2213 (2015) (ECF 179-7) ("This study confirms the effectiveness of puberty suppression for [gender dysphoric] adolescents.").)

The literature has also established that treatment with puberty-delaying medication is safe. (*See, e.g.,* Ex. 163, Polly Carmichael et al., *Short-term Outcomes of Pubertal Suppression in a Selected Cohort of 12 to 15 Year Old Young People with Persistent Gender Dysphoria in the UK*, 16 PLoS ONE e0243894, at *21, *17 (2021) (ECF 179-3) (concluding that "[t]reatment of young people with persistent and severe [gender dysphoria] aged 12–15 years with [puberty-delaying medication] was efficacious in suppressing pubertal progression. . . . and there were no

unexpected adverse events," and noting that "[a]ll adverse events were minor and anticipated .... [and] less common after 12 months of treatment").)

Puberty-delaying medications have been used in pediatrics for several decades to treat precocious puberty. (Ex. 8, Olson-Kennedy ¶ 24 (ECF 175-8); Ex. 16, Shumer Rebuttal ¶ 64 (ECF 175-16).) For both indications, the side effects of these medications are comparable and easily managed, and the risks are greatly outweighed by the benefits of treatment. (Ex. 9, Shumer ¶ 68 (ECF 175-9); Ex. 8, Olson-Kennedy ¶ 103-105 (ECF 175-8); *see also, e.g.,* Ex. 172, Erica A. Eugster, *Treatment of Central Precocious Puberty*, 3 J. Endocrine Soct'y 965, 965, 967 (2019) (ECF 179-12) (puberty-delaying medications are the "gold-standard treatment of central precocious puberty . . . and have an enviable track record of safety and efficacy").)

For example, while there is a risk of lower bone mineral density with prolonged use of puberty-delaying medications, it can be mitigated by screening for, and treating, vitamin D deficiency when present, and by limiting the number of years of treatment based on a patient's clinical course. (Ex. 204, Stephen M. Rosenthal, *Approach to the Patient: Transgender Youth: Endocrine Considerations*, 99 J. Clin. Endocrine Metab. 4379 (2014) (ECF 180-4).) In addition, studies show that with removal of the puberty-delaying medication or addition of gender-affirming hormone therapy, bone mineral density begins to improve. (Ex. 219, M. C. Vlot,

Effect of Pubertal Suppression and Cross-Sex Hormone Therapy on Bone Turnover Markers and Bone Mineral Apparent Density (BMAD) in Transgender Adolescents, 95 Bone 11 (2020) (ECF 180-19); Ex. 184, Daniel Klink et al., *Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents with Gender Dysphoria*, 100 J. Clin. Endocrine Metab. E270 (2015) (ECF 179-24); *cf.* Ex. 172, Eugster, *supra*, at 967 (ECF 179-12) (reviewing use of puberty-delaying medications for treatment of central precocious puberty and noting that "follow-up of patients several years after cessation of therapy reveals bone mineral accrual to be within the normal range compared with population norms").)

Puberty-delaying treatment does not have long-term implications on fertility. (Ex. 137, Federica Guaraldi et al., *Long-term Outcomes of the Treatment of Central Precocious Puberty*, 14 Eur. Soct'y Endocrinology R79, R83 (2016) (ECF 178-17); Ex. 138, Laetitia Marinerie et al., *Fertility of Women Treated during Childhood with Triptorelin (Depot Formulation) for Central Precocious Puberty*, 93 Horm. Res. Paediatrics 529 (2021) (ECF 178-18).) Adult patients who have had previous treatment with GnRHa followed by hormone therapy could withdraw the hormones and allow pubertal progression if fertility is desired. (*See* Ex. 191, Caitlin E. Martin et al., *Successful Oocyte Cryopreservation Using Letrozole as an Adjunct to Stimulation in a Transgender Adolescent after GnRH Agonist Suppression*, 116

Fertility & Sterility 522 (2021) (ECF 179-31); Ex. 205, Stephanie S. Rothenberg et al., *Oocyte Cryopreservation in a Transgender Male Adolescent*, 380 N. Eng. J. Med. 886 (2019) (ECF 180-5).) Assistive reproduction could be employed if needed. (Ex. 212, Guy T'Sjoen, et al., *Endocrinology of Transgender Medicine*, 40 Endocrine Rev. 97, 105 (2018) (180-12).) Still, standards of care recommend discussing a potential loss of fertility and fertility preservation prior to initiation of puberty-delaying medications. (Ex. 5, Antommaria ¶ 50 (ECF 175-5); Ex. 9, Shumer Rebuttal ¶ 48 (ECF 175-9).)

There is no evidence that the provision of puberty-delaying medications has negative effects on brain development in adolescents. (Ex. 15, Edmiston Rebuttal ¶¶ 26-29, 38 (ECF 175-15); Ex. 16, Shumer Rebuttal ¶¶ 53, 54 (ECF 175-16).) To the contrary, the studies that do exist looking into brain structure and function of transgender adolescents receiving GnRHa treatment have not found any significant effects of treatment on the brain. (Ex. 15, Edmiston Rebuttal ¶ 29 (ECF 175-15).)

2. Hormone Therapy

Hormone medications are approved for the treatment of other conditions and have been used for nearly a century to treat gender dysphoria, supporting their safety and efficacy. (Ex. 7, Karasic ¶ 66 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 106-110 (ECF 175-8); Ex. 9, Shumer ¶ 84 (ECF 175-9).) Hormone therapy is provided only when medically indicated and, after thorough mental health evaluation, in

coordination with the individual's mental health provider. (Ex. 8, Olson-Kennedy ¶ 32 (ECF 175-8); Ex. 9, Shumer ¶¶ 38, 57 (ECF 175-9).) Like with puberty-delaying medications, the fact that hormone treatments may be prescribed off-label does not mean they are untested or unsafe. (Ex. 5, Antommaria ¶¶ 34-37 (ECF 175-5); Ex. 7, Karasic ¶ 66 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 92-93 (ECF 175-8); Ex. 17, Janssen Rebuttal ¶ 107 (ECF 175-17).)

Risks and benefits of hormone treatment are discussed with patients, and their families if the patient is a minor. (Ex. 5, Antommaria ¶¶ 46-50 (ECF 175-5); Ex. 8, Olson-Kennedy ¶ 32 (ECF 175-8); Ex. 9, Shumer, ¶ 74 (ECF 175-9); Ex. 12, Olson-Kennedy Rebuttal ¶ 39 (ECF 175-12); Ex. 17, Janssen Rebuttal ¶¶ 98, 110 (ECF 175-17).) Side effects of hormone therapy are rare and usually related to overtreatment, which can be minimized with monitoring. (Ex. 9, Shumer ¶ 84 (ECF 175-9).) Laboratory testing ensures proper dosing and hormone levels. (Ex. 9, Shumer ¶¶ 74, 84 (ECF 175-9).)

The scientific literature has established that hormone treatment is safe and effective to treat gender dysphoria in adolescents and adults. (*See* Ex. 9, Shumer ¶¶ 86-88 (ECF 175-9); Ex. 8, Olson-Kennedy ¶¶ 34-40 (ECF 175-8); Ex. 17, Janssen Rebuttal ¶¶ 101-102 (ECF 175-17).) The literature demonstrating that hormone treatment is effective to treat gender dysphoria is robust and well-established. (Ex. 8, Olson-Kennedy ¶ 40 (ECF 175-8).) Numerous longitudinal studies document

improvement in gender dysphoria and associated distress. (*See, e.g.,* Ex. 166, Marco Colizzi et al., *Hormonal Treatment Reduces Psychobiological Distress in Gender Identity Disorder, Independently of the Attachment Style*, 10 J. Sex. Med. 3049 (2013) (ECF 179-6); Ex. 173, Alessandra D. Fisher et al., *Cross-Sex Hormone Treatment and Psychobiological Changes in Transsexual Persons: Two-Year Follow-Up Data*, 101 J. Clin. Endo. & Metabolism 4260, 4267 (2016) (ECF 179-13); Ex. 180, Gunter Heylens, et al., *Effects of Different Steps in Gender Reassignment Therapy on Psychopathology*, 11 J. Sex. Med. 119, 124 (2014) (ECF 179-20); *see also, e.g.,* Ex. 221, Katrien Wierckx et al., *Cross-Sex Hormone Therapy in Trans Persons Is Safe and Effective at Short-Time Follow-Up*, 11 J. Sex. Med. 1999 (2014) (ECF 180-21).)

Further, hormone treatment has been shown to have other positive health outcomes when used to treat gender dysphoria. (*See, e.g,* Ex. 156, Kellan E. Baker et al., *Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review*, 5 J. Endo. Soct'y 1, 13 (2021) (ECF 178-36) ("[G]ender-affirming hormone therapy is likely associated with improvements in QOL, depression, and anxiety. No studies showed that hormone therapy harms mental health or quality of life among transgender people."); Ex. 197, Anna Nobili et al., *Quality of Life of Treatment-Seeking Transgender Adults*, 19 Rev. Endo. & Metabolic Disorders 199, 218 (2018) (ECF 179-37) (finding that quality of life

generally improved after the initiation of hormone treatment for gender dysphoria); Ex. 164, Diane Chen et al., *Psychosocial Functioning in Transgender Youth after 2 Years of Hormones*, 388 New England J. Med. 240 (2023) (ECF 179-4) (hormone treatment for adolescents correlates to reductions in depression and anxiety); Ex. 176, Amy E. Green, *Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth*, 70 J. Adol. Health 643 (2022) (ECF 179-16) ("Findings support a relationship between access to [gender-affirming hormone treatment] and lower rates of depression and suicidality.").)

The literature further demonstrates that satisfaction with hormone treatment is high. (*See, e.g.,* Ex. 195, T.O. Nieder et al., *Individual Treatment Progress Predicts Satisfaction with Transition-Related Care for Youth with Gender Dysphoria*, 18 J. Sex. Med. 632 (2021) (ECF 179-35) (among a group of 75 adolescents with gender dysphoria, satisfaction improved the further along the treatment course had progressed); Ex. 164, Chen et al., *supra*¸ at 240 (ECF 179-4) (in study following 315 adolescents for two years after initiation of hormone therapy, life satisfaction increased); Ex. 212, T'Sjoen et al., *supra* at 101 (ECF 180-12) (summarizing various studies and concluding "[o]verall satisfaction after gender-affirming [hormone] treatment is high").)

The literature similarly shows that hormone treatment is safe and has a low

risk of side effects or adverse events. (Ex. 221, Wierckx et al., *supra,* at 1999 (ECF 180-21) (hormone therapy to treat gender dysphoria "carried a low risk for side effects and adverse events at short-time follow-up); Ex. 212, T'Sjoen et al., *supra* at 98 (ECF 180-12)("Long-term estrogen and androgen-lowering medications may be associated with increased risk of thromboembolism, which can be mitigated by changing the formulation and route of estrogen therapy [and t]estosterone treatment in transgender men is seen as safe regarding cardiovascular and oncological disease in the short-term and mid-term.").) Side effects of hormone therapy are rare and usually related to overtreatment, which can be minimized with monitoring. (Ex. 9, Shumer ¶ 84 (ECF 175-9).)

In addition, the literature suggests that long-term hormone treatment does not necessarily impair fertility. (*See, e.g.,* Ex. 225, I. Yaish et al., *Functional Ovarian Reserve in Transgender Men Receiving Testosterone Therapy*, 36 Hum. Reproduction 2753 (2021) (ECF 180-25); Ex. 162, Mirte R. Caanen et al., *Effects of Long-Term Exogenous Testosterone Administration on Ovarian Morphology, Determined by Transvaginal (3D) Ultrasound in Female-to-Male Transsexuals*, 32 Hum. Reproduction 1457 (2017) (ECF 179-2).) Furthermore, the literature shows that withdrawal of hormone therapy is successful in achieving fertility when it is desired. (Ex. 188, Alexis D. Light, et al., *Transgender Men Who Experienced Pregnancy After Female-to-Male Gender Transitioning*, 124 Obstet. Gynecol. 1120

(2014) (ECF 179-28); Ex. 185, Gail Knudson & Petra De Sutter, *Fertility Options in Transgender and Gender Diverse Adolescents*, 97 Acta Obstetricia et Gynecologica Scandinavica 1269 (2017) (ECF 179-25).)

3. Surgery

Gender confirming surgeries use accepted techniques that are well established and used in other surgeries. (Ex. 10, Schechter, ¶ 45 (ECF 175-10).) The use of these techniques does not become experimental merely when used to treat gender dysphoria. (Ex. 10, Schecter, ¶ 45 (ECF 175-10).) The risks of gender confirming surgical procedures are well-known and well-documented in the literature and are no different when used to treat gender dysphoria rather than other health conditions. (Ex. 10, Schecter ¶¶ 37-38, 60 (ECF 175-10); Ex. 13, Schechter Rebuttal Report ¶ 26 ("Schechter Rebuttal") (ECF 175-13).) Though not all transgender people require gender-affirming surgical care, such care is necessary when medically indicated. (Ex. 10, Schechter ¶¶ 23, 25, 31-32 (ECF 175-10); Ex. 13, Schechter Rebuttal ¶ 27 (ECF 175-13).)

The literature shows that surgery is an effective treatment for gender dysphoria. (*See* Ex. 10, Schechter ¶¶ 40-42, 46 (ECF 175-10); Ex. 8, Olson-Kennedy ¶¶ 44-45 (ECF 175-8); Ex. 5, Antommaria ¶ 32 (ECF 175-5).) For example, in a 1998 meta-analysis, Pfafflin and Junge reviewed data from 80 studies, from 12 countries, spanning 30 years. (Ex. 202, Friedemann Pfäfflin & Astrid Junge, *Sex*

Reassignment. Thirty Years of International Follow-up Studies After Sex Reassignment Surgery: A Comprehensive Review, 1961-1991 (1998) (ECF 180-2).) They concluded that "reassignment procedures were effective in relieving gender dysphoria. There were few negative consequences and all aspects of the reassignment process contributed to overwhelmingly positive outcomes." (*Id.*) Subsequent studies confirm this conclusion. Researchers reporting on a large-scale prospective study of 325 individuals in the Netherlands concluded that after surgery there was "a virtual absence of gender dysphoria" in the cohort and "results substantiate previous conclusions that sex reassignment is effective." (Ex. 208, Yolonda L. Smith, et al., *Sex Reassignment: Outcomes and Predictors of Treatment for Adolescent and Adult Transsexuals*, 35 Psych. Med. 89, 94, 89 (2005) (ECF 180-8).) The authors of that study concluded that the surgery "appeared therapeutic and beneficial" across a wide spectrum of factors and "[t]he main symptom for which the patients had requested treatment, gender dysphoria, had decreased to such a degree that it had disappeared." (*Id.* at 96.) Another study of transgender women found that surgical interventions were highly correlated with alleviating gender dysphoria. (Ex. 178, Jochen Hess et al., *Satisfaction with Male-to-Female Gender Reassignment Surgery*, 111 Deutsches Arzteblatt Int'l 795, 795 (2014) (ECF 179-18).) A recent study of 30 transmasculine youth whose gender dysphoria was treated with chest surgery found that "[a]ll post-[surgery] youth reported near or total

resolution of chest dysphoria." (Ex. 192, Jamie E. Mehringer et al, *Experience of Chest Dysphoria and Masculinizing Chest Surgery in Transmasculine Youth*, 147 Pediatrics e2020013300, *6 (2021) (ECF 179-32); *see also* Ex. 198, Johanna Olson-Kennedy et al., *Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts*, 172 JAMA Pediatrics 431 (2018) (ECF 179-38) (finding that transmasculine youth whose dysphoria was treated surgically reported less dysphoria compared to youth who were not treated surgically).) Similarly, a 2019 study found that 100% of transgender women who underwent breast augmentation reported improvement in their gender dysphoria and "would undergo the operation again." (Ex. 193, Travis J. Miller et al, *Breast Augmentation in Male-to-Female Transgender Patients: Technical Considerations and Outcomes*, 21 JPRAS Open, 63, 64 (2019) (ECF 179-33).)

Decades of research demonstrate that gender confirmation surgery leads to positive outcomes for patients. (Ex. 8, Olson-Kennedy ¶¶ 44-46 (ECF 175-8); Ex. 12, Olson-Kennedy Rebuttal, ¶¶ 46-47 (ECF 175-12); Ex. 10, Schechter, ¶¶ 37-43 (ECF 175-10).) The scientific literature clearly demonstrates that people whose gender dysphoria is surgically treated experience other positive health outcomes, including improvements to mental health, sexual function, and psychosocial wellbeing and quality of life. *(See, e.g.,* Ex. 154, Anthony N. Almazan et al.,

Association Between Gender-Affirming Surgeries and Mental Health Outcomes, 156 JAMA Surgery 611, 611 (2021) (ECF 178-34) (finding that "undergoing 1 or more types of gender-affirming surgery was associated with lower past-month psychological distress . . ., past-year smoking . . ., and past-year suicidal ideation"); Ex. 192, Mehringer et al., *supra*, at *6 (ECF 179-32) ("Youth [treated with surgery] reported improvements in mood, confidence, self-esteem, and interpersonal relationships[and] decreased anxiety."); Ex. 177, Miriam Hadj-Moussa et al., *Feminizing Genital Gender-Confirmation Surgery*, 63 Sex. Med. Rev. 457 (2018) (ECF 179-17) (recent literature review concluded that in appropriately selected individuals, gender confirmation surgery is effective at improving sexual functioning, quality of life, and overall happiness in in transgender women who are diagnosed with gender dysphoria); Ex. 220, Romain Weigert et al., *Patient Satisfaction with Breasts and Psychosocial, Sexual, and Physical Well-Being after Breast Augmentation in Male-to-Female Transsexuals*, 132 Plastic & Recon. Surgery 1421 (2013) (ECF 180-20) (finding among transgender women treated with chest surgery that sexual and psychosocial well-being improved significantly at 4 months postoperatively and later); Ex. 181, Sophie E.R. Horbach et al., *Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques*, 12 J. Sex. Med. 1499 (2015) (ECF 179-21) (peer-reviewed study of transgender women who had vaginoplasty found that study participants' mean

improvement in quality of life after surgery was 7.9 on a scale from one to ten); Ex. 201, Nikolaos A. Papadopulos et al., *Male-to-Female Sex Reassignment Surgery Using the Combined Technique Leads to Increased Quality of Life in a Prospective Study*, 140 Plastic & Recon. Surgery 286 (2017) (ECF 180-1) (recent post-operative and six-month follow-up survey of transgender female patients found improvements in quality of life in a significant majority of patients); Ex. 155, Mona Ascha et al., *Top Surgery and Chest Dysphoria Among Transmasculine and Nonbinary Adolescents and Young Adults*, 176 JAMA Pediatrics 1115 (2022) (ECF 178-35) (transmasculine and nonbinary adolescents and young adults who were treated with chest surgery experienced improved body image satisfaction).)

The scientific literature also establishes that surgery to treat gender dysphoria is safe. (*See* Ex. 10, Schechter ¶¶ 23, 36-38 (ECF 175-10).) The risks of gender confirming surgical procedures are well-known and well-documented in the literature and are no different when the same procedures are used to treat other health conditions. (Ex. 10, Schecter ¶¶ 37-38, 60 (ECF 175-10); Ex. 13, Schechter Rebuttal ¶ 26 (ECF 175-13).) For example, one study found that transgender men who received chest reconstruction experienced few clinical complications. (Ex. 174, Michael J. Frederick et al., *Chest Surgery in Female to Male Transgender Individuals*, 78 Ann. Plastic Surg. 249, 253 (2017) (ECF 179-14).) These findings were confirmed by a 2022 study finding that in transgender and nonbinary

adolescents and young adults, top surgery is associated with low complication rates. (Ex. 155, Ascha et al., *supra*, at 1115 (ECF 178-35).) A study of over 1000 gender-affirming surgeries in the United States found that "[c]omplications of all gender-affirming procedures was 5.8%." (Ex. 148, Megan Lane et al., *Trends in Gender-affirming Surgery in Insured Patients in the United States*, 6 Plast. Surg. Global Open e1738 (2018) (ECF 178-28).) Further, the evidence that shows that surgical interventions are safe to treat gender dysphoria is the same evidence that supports these interventions as safe to treat other conditions, such as congenital conditions, cancer, or traumatic injury since they use the same techniques. (*See* Ex. 5, Antommaria ¶¶ 52-53 (ECF 175-5); Ex. 10, Schechter ¶¶ 36-38 (ECF 175-10).)

In addition, the literature establishes that patient satisfaction with gender-affirming surgery is very high. For example, multiple studies have found that transmasculine people who receive chest reconstruction are overwhelmingly satisfied with their surgical outcomes. (Ex. 174, Frederick et al., *supra*, at 253 (ECF 179-14); Ex. 160, Valeria P. Bustos, et al., *Transgender and Gender-Nonbinary Patient Satisfaction after Transmasculine Chest Surgery*, 9 Plastic & Recon. Surgery e3479 (2021) (ECF 178-40).) Similarly, a study of genital surgeries for transgender women found that patients were overwhelmingly satisfied with their surgical outcomes. (Ex. 181, Horbach et al., *supra,* at 8 (ECF 179-21); *see also* Ex. 178, Jochen Hess, *supra,* at 800 (ECF 179-18) (same).)

In contrast, regret rates for gender-affirming surgeries are quite low.[15] (Ex. 10, Schechter ¶¶ 63-67 (ECF 175-10).) A study of 209 gender-affirming mastectomies in transmasculine adolescents aged 12-17, performed at Kaiser Permanente Northern California from 2013 to 2020, showed a regret rate of 1%. (Ex. 210, Annie Tang et al., *Gender-Affirming Mastectomy Trends and Surgical Outcomes in Adolescents*, 88 Ann. Plastic Surg. S325 (2022) (ECF 180-10).) A pooled review across multiple studies of 7,928 adult patients receiving gender-affirming surgery also showed a regret rate of 1%. (Ex. 161, Valeria P. Bustos, et al., *Regret after Gender-affirmation Surgery: A Systematic Review and Metaanalysis of Prevalence*, 9 Plastic & Recon. Surgery e3477 (2021) (ECF 179-1).) Over 50 years of gender-affirming surgery in Sweden, the regret rate, as measured by legal gender change reversal, was 2%. (Ex. 169, Cecilia Dhejne et al., *An Analysis of All Applications for Sex Reassignment Surgery in Sweden, 1960-2010: Prevalence, Incidence, and Regrets*, 42 Arch. Sex. Behav. 1535 (2014) (ECF 179-9).) These are very low regret rates for surgery. For example, 47% of women expressed at least some regret after reconstructive breast

[15] Defendants are also imprecise in defining what they mean by "regret." One recent study found that not only is regret after gender-affirming surgery very low overall, but that "true gender-related regret" defined as a situation where "a person having undergone a transition in gender . . . then desires to return to their assigned sex at birth or a different gender identity," represented less than half of all cases of regret. (*See* Ex. 194, Sasha Karan Narayan et al, *Guiding the Conversation—Types of Regret after Gender-Affirming Surgery and Their Associated Etiologies*, 9 Ann. Translational Med. 605, *7 (2021) (ECF 179-34).)

surgery following mastectomy for breast cancer. (Ex. 208, Joanne Sheehan et al., *Regret Associated with the Decision for Breast Reconstruction*, 23 Psychology & Health 207, 213 (2008) (ECF 180-1).)

4. Levels of Evidence

The quality of the evidence supporting medical and surgical interventions as treatment for gender dysphoria is comparable to that from studies supporting other, well-established treatments and procedures. (*See, e.g.,* Ex 8, Olson-Kennedy ¶¶ 70-90 (ECF 175-8); Ex 5, Antommaria ¶¶ 18-28 (ECF 175-5); Ex 7, Karasic ¶ 55, 83 (ECF 175-7); Ex 10, Schechter ¶ 52-54 (ECF 175-10); Ex 17, Janssen Rebuttal ¶ 106 (ECF 175-17).) Scientific ratings of evidence generally employ extremely high standards that are not satisfied for many commonly prescribed treatments and procedures. The fact that there are not randomized-control trials of surgical procedures, for example, "is to be expected since a randomised controlled study for this scenario would be impossible to carry out." (Ex. 206, Royal College of Psychiatrists, *Good Practice Guidelines for the Assessment and Treatment of Adults with Gender Dysphoria* 50 (2014) (ECF 180-6).) Indeed, one recent article concluded that "only a minority of outcomes for health care interventions are supported by high-quality evidence." (Ex. 182, Jeremy Howick et al., *The Quality of Evidence for Medical Interventions Does Not Improve or Worsen: A*

Metaepidemiological Study of Cochrane Reviews, 126 J. Clin. 154, 154 (2020) (ECF 179-22).)

The fact that a treatment is not supported by high-quality evidence does not mean that the treatment is unsupported in the literature and clinical practice, or that it is not medically necessary; on the contrary, the literature shows that the provision of appropriate gender affirming medical care dramatically improves the health, mental health, and well-being of transgender persons. (Ex. 6, Baker ¶ 31 (ECF 175-6); Ex. 7, Karasic ¶¶ 71-76 (ECF 175-7); Ex. 8, Olson-Kennedy ¶¶ 25-41, 98-101, 107 (ECF 175-8); Ex. 9, Shumer, ¶ 35, 42, 82-83 (ECF 175-9); Ex. 10, Schechter ¶¶ 36-43, 81 (ECF 175-10); Ex. 17, Janssen, ¶ 105 (ECF 175-17).)

D. Psychotherapy alone is not an effective treatment for gender dysphoria.

The literature demonstrates that the consequences of untreated gender dysphoria are dire, including higher levels of stigmatization, discrimination, and victimization, contributing to negative self-image and the inability to function effectively in daily life. (*See* Ex. 6, Baker ¶ 30 (ECF 175-6); Ex. 7, Karasic ¶ 68 (ECF 175-7); Ex. 8, Olson-Kennedy at ¶¶ 48, 122 (ECF 175-8); Ex. 9, Shumer ¶ 41, 90 (ECF 175-9); Ex. 10, Schechter ¶ 82 (ECF 175-10); Ex. 17, Janssen Rebuttal ¶¶ 54, 123-124, 126-132 (ECF 175-17).) There is no established safe and effective alternative to gender-affirming medical care for treating gender dysphoria. (Ex.10, Schechter ¶ 58 (ECF 175-10); Ex.7, Karasic ¶ 37 (ECF 175-7); Ex.11, Karasic

Rebuttal ¶¶ 23-24, 47 (ECF 175-11).)

Alternative approaches to treatment for gender dysphoria suggested by persons opposed to gender affirming care such as "reparative" or "corrective" therapy, which attempts to change sexual orientation or gender identity, and "wait and see" or "watchful waiting" which is inapplicable to adolescents and adults,[16] have been determined to be harmful and put children at risk for symptomatic behaviors. (Ex. 8, Olson-Kennedy, ¶ 14-17 (ECF 175-8).)

The evidence is quite clear that withholding proven gender-affirming medical services from transgender people not only results in the prolonging of their gender dysphoria, but causes additional distress and poses other health risks, such as depression, posttraumatic stress disorder, and suicidality. (*See* Ex. 7, Karasic ¶¶ 37, 101 (ECF 175-7); Ex. 17, Janssen Rebuttal Report ¶¶ 27-29, 123-27 (ECF 175-17); Ex. 10, Schecter Report ¶ 82 (ECF 175-10); *see also, e.g.,* Ex. 200, Ashli Owen-Smith, et al., *Association Between Gender Confirmation Treatments and Perceived Gender Congruence, Body Image Satisfaction, and Mental Health in a Cohort of Transgender Individuals*, 15 J. Sex. Med. 591, 591 (2018) (ECF 179-40)

[16] As described in the literature, "watchful waiting" recommends that caregiver prohibit prepubertal social transition but may allow cross-gender play and clothing within the home, followed by medical care if gender dysphoria persists into adolescence. (Ex. 8, Olson-Kennedy ¶ 17 (ECF 175-8); *see also* Ex. 170, Ehrensaft, *Gender Nonconforming Youth: Current Perspectives*, 2017 (ECF 179-10).)

("Withholding or delaying [gender-affirming care] until depression or anxiety have been treated may not be the optimal treatment course given the benefits of reduced levels of distress after undergoing these interventions"); Ex. 215, Jack Turban et al., *Access to Gender-Affirming Hormones during Adolescence and Mental Health Outcomes Among Transgender Adults*, 17 PLos ONE e0261039, *2 (2022) (ECF 180-15) (those who had access to gender-affirming hormone therapy in adolescence had better mental health outcomes in adulthood, compared to individuals who desired but could not access hormonal interventions); Ex. 152, Zoë Aldridge et al., *Long-Term Effect of Gender-Affirming Hormone Treatment on Depression and Anxiety Symptoms in Transgender People*, 9 Andrology 1808, 1813 (2020) (ECF 178-32) ("These findings do confirm, once again, the high levels of possible anxiety and depressive disorders before [gender-affirming hormone treatment] and the benefit that this treatment brings. It highlights the need to facilitate the expedited use of [gender-affirming hormone treatment] to aid the reduction of poor mental health symptoms in the transgender population, when possible and appropriate."); Ex. 211, Diana M. Tordoff et al., *Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care*, 2 JAMA Network Open e220978 (2022) (ECF 180-11) (provision of puberty-delaying medications and gender-affirming hormones for transgender youth decreases depression); Ex. 176, Green, et al., *supra*, at 647 (provision of puberty-delaying medications and gender-affirming hormones

for transgender youth decreased depression and suicidality) (ECF 179-16).)

ACHA mischaracterizes "watchful waiting" as withholding all medical treatment for an indefinite period. (Ex. 18, GAPMS Report, at 12, 20-22 (ECF 175-18).) The authoritative medical and scientific literature does not support this approach, which, as discussed above, results in depriving people of needed care and the potential for serious harms to health. (Ex. 16, Shumer Rebuttal, ¶ 37 (ECF 175-16).) Rather, under the "watchful waiting" model of treatment for gender diverse youth, as supported by the scientific and clinical literature:

> If a child's cross-gender identifications and affirmations are persistent over time, interventions are made available for a child to consolidate a transgender identity, once it is assessed, through therapeutic intervention and psychometric assessment, as in the best interests of the child. These interventions include social transitions (the shift from one gender to another, including possible name change, gender marker change, and gender pronoun changes), puberty blockers, and later hormones and possible gender-affirming surgeries.

(Ex. 170, Diane Ehrensaft, *Gender Nonconforming Youth: Current Perspectives*, 8 Adol. Health, Med. & Ther. 57 (2017) (ECF 179-10).) While it is true that under this model, "a young child's demonstration of gender nonconformity, be it in identity, expressions, or both, is not to be manipulated in any way, but observed over time" once the child reaches puberty, medical interventions are made available. (*Id.*) This is because "young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood." (Ex. 141, de Vries (2011), *supra*, at 2281 (ECF 178-21).) Notably, however, the Challenged Exclusion

does not allow for any medical interventions for gender dysphoria for anyone and thus is not consistent with the "watchful waiting" approach. *See* Fla. Admin. Code R. 59G-1.050(7) (2022).

The other option Defendants present is psychotherapy alone as an alternative but have offered no evidence to support that claim. While behavioral health interventions are an important component of gender-affirming care for many, the literature has established for decades that mental health interventions alone are insufficient to treat gender dysphoria. (Ex.7, Karasic ¶ 37 (ECF 175-7); Ex.11, Karasic Rebuttal ¶ 48 (ECF 175-11); Ex.17, Janssen Rebuttal ¶ 91 (ECF 175-17); Ex.8, Olson-Kennedy ¶112 (ECF 175-8); Ex. 10, Schechter ¶ 58 (ECF 175-10); *see also* Ex. 158, Harry Benjamin, *The Transsexual Phenomenon* (1966), at 13 (ECF 178-38).) Indeed, the literature has established for decades that mental health interventions alone are insufficient to treat gender dysphoria. As far back as 1966, Harry Benjamin noted in that:

> The desire to change sex has been known to psychologists for a long time. . . . Beyond some attempts with psychotherapy in a (futile) effort to cure them of their strange desires, nothing was or could be done for them medically. . . . Only because of the recent great advances in endocrinology and surgical techniques has the picture changed.

(Ex. 158, Harry Benjamin, *supra*, at 13 (ECF 178-38).)

Moreover, a study just last year compared mental health outcomes for people who accessed gender-affirming hormone therapy as adolescents to those who

accessed treatment as adults, and concluded that "participants who accessed [gender-affirming hormone therapy] earlier had better mental health outcomes, . . . [which] argue[s] against waiting until adulthood to offer [gender-affirming hormone therapy] to transgender adolescents and suggest that doing so may put patients at greater mental health risk." (Ex. 215, Turban (2022), *supra*, at *11 (ECF 180-15).) In other words, lack of access to gender-affirming care directly contributes to poorer mental health outcomes for transgender people.

Nor is "conversion therapy," also known as "reparative therapy" or "gender identity change efforts," an alternative to treatment. As noted above, gender identity cannot be changed. (Ex. 8, Olson-Kennedy at 8 ¶¶ 1-2 (ECF 175-8); Ex. 9, Shumer ¶ 29-33 (ECF 175-9); Ex. 7, Karasic ¶ 23 (ECF 175-7).) But, just last month (March 2023), a report by the U.S. detailed how "[e]fforts to change or suppress a person's sexual orientation or gender identity are grounded in the belief that being LGBTQI+ is abnormal" and therefore "are dangerous, discredited, and ineffective practices." (Ex. 74, SAMHSA, *Moving Beyond Change Efforts* (2023), at 8 (ECF 176-34); *see also* Ex. 73, SAMHSA, Ending Conversion Therapy (Oct. 2015), at 46 (ECF 176-33).) As such, major medical groups have condemned conversion therapy as an intervention to treat gender dysphoria. (*See* Ex. 190, Mallory et al., *supra*, at 2, 4 (ECF 179-30); Ex 8, Olson-Kennedy at 13 ¶ 14 (ECF 175-8); Ex 7, Karasic ¶ 37 (ECF 175-7).)

The scientific literature shows such efforts to be not only ineffective but to also increase the risk for mental health symptoms, including suicide. (*See, e.g.,* Ex. 158, Benjamin (1966), *supra*, at 76, 130 (ECF 178-38) ("Psychotherapy with the aim of curing transsexualism, so that the patient will accept himself as a man, it must be repeated here, is a useless undertaking," and "[p]sychotherapy with the purpose of having the patient accept herself as a woman is as useless in female transsexualism as it is in male"); Ex. 214, Jack L. Turban et al., *Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults*, 77 JAMA Psychiatry 68 (2020) (ECF 180-14); Ex. 190, Christy Mallory et al., *Conversion Therapy and LGBT Youth* 2 (2019 ed.) (collecting studies) (ECF 179-30).)

V. The Medicaid Program

A. Federal Requirements

The Medicaid Act, Title XIX of the Social Security Act of 1965 creates a joint federal-state program that provides health care services to specified categories of low-income individuals. 42 U.S.C. §§ 1396-1396w-6. Medicaid is designed to "enabl[e] each State, as far as practicable...to furnish (1) medical assistance on behalf of families with dependent children and of aged, blind, or disabled individuals, whose income and resources are insufficient to meet the costs of necessary medical services, and (2) rehabilitation and other services to help such families and

individuals attain or retain capability for independence and self-care....” 42 U.S.C. § 1396-1. States are not required to participate in the Medicaid program—but all states do. States that choose to participate must comply with the Medicaid Act and its implementing regulations. *Frew ex rel. Frew v. Hawkins*, 540 U.S. 431, 433 (2004) (“[O]nce a State elects to join the program, it must administer a state plan that meets federal requirements.”). In return, the federal government reimburses each participating state for a substantial portion of the cost of providing medical assistance. *See* 42 U.S.C. §§ 1396b(a), 1396d(b), 1396(c).

The Medicaid Act requires each participating state to designate a single state agency charged with administering or supervising the state’s Medicaid program. *Id.* § 1396a(a)(5). Under the Medicaid Act, a participating state must provide medical assistance to certain eligibility groups, *id.* § 1396a(a)(10)(A)(i), including children and adolescents under age 18 whose household income is below 133% of the federal poverty level, *id.* §§ 1396a(a)(10)(A)(i)(VI)-(VII), 1396a(l). Another mandatory eligibility category is individuals with a disability who receive Supplemental Security Income or meet separate disability and financial eligibility standards established by the state. *Id.* §§ 1396a(a)(10)(A)(i)(II), 1396a(f). States have the option to cover additional eligibility groups. *Id.* §§ 1396a(a)(10)(A)(ii). The Medicaid Act also requires each participating state to cover certain health care services, *id.* §§ 1396a(a)(10)(A), 1396d(a)(4), including Early and Periodic

Screening, Diagnostic, and Treatment (EPSDT) services for beneficiaries under age 21, *id.* §§ 1396a(a)(10)(A), 1396d(a)(4)(B), 1396d(r), 1396a(a)(43). States may cover additional services. *See id.* §§ 1396a(a)(10)(A), 1396d(a)(4). In addition, States must ensure that "the medical assistance made available to any individual . . . shall not be less in amount, duration, or scope than the medical assistance made available to any other such individual." 42 U.S.C. §1396a(a)(10)(B)(i). States must administer Medicaid in "the best interests of recipients." *Id.* § 1396a(a)(19).

B. Florida's Medicaid Program and the GAPMS Process

The State of Florida participates in the federal Medicaid program. Fla. Stat. §§ 409.901-409.9205. Florida regulations require AHCA to cover health care services that are medically necessary. *See* Fla. Admin. Code R. 59G-1.035(6), 59G-1.010 (2022). To qualify as medically necessary, a service must meet several conditions. *See* Fla. Admin. Code R. 59G-1.010 (2022), incorporating by reference AHCA Definitions Policy at 2.83 (2017) (defining medically necessary care). For one, the service must be consistent with generally accepted professional medical standards and not experimental or investigational. *Id.*; Fla. Admin. Code R. 59G-1.035 (2022).

"Generally accepted professional medical standards" ("GAPMS") are defined by regulations as "standards based on reliable scientific evidence published in peer-reviewed scientific literature generally recognized by the relevant medical

community or practitioner specialty associations' recommendations." Fla. Admin. Code R. 59G-1.035(1)(a) (2022). To determine whether a particular service is consistent with generally accepted professional medical standards, AHCA must consider: (a) evidence-based clinical practice guidelines; (b) published reports and articles in the authoritative medical and scientific literature related to the health service (published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations); (c) effectiveness of the health service in improving the individual's prognosis or health outcomes; (d) utilization trends; (e) coverage policies by other creditable insurance payor sources; (f) recommendations or assessments by clinical or technical experts on the subject or field." *Id*. § 59G-1.035(4). After considering those factors, AHCA must submit a report with recommendations to the Deputy Secretary for Medicaid for review, and the Deputy Secretary makes a final determination as to whether the health service is consistent with generally accepted professional medical standards and not experimental or investigational. *Id*. § 59G-1.035(5).

The GAPMS process is used to determine whether to cover a new service, not whether to exclude an existing service. (ECF 120-6, Brackett Feb. 8 Dep. at 93:13-21; Ex. 302, English email to Cogle (ECF 183-4) (stating "[t]he GAPMS process exists to determine whether the service/device requested for coverage is

experimental/investigational" or "medically necessary"); Br. Ex. 2, English Dep. at 41:6-14.)

VI. Defendants' Categorical Exclusion of Medical Services to Treat Gender Dysphoria

A. Florida Medicaid Coverage of Gender-Affirming Medical Care

Until the Challenged Exclusion, Defendants provided Medicaid coverage for the gender-affirming medical care at issue, that is, puberty-delaying medications, hormone therapy, and gender-affirming surgeries, for adolescents and adults for whom it was medically necessary to treat gender dysphoria since at least 2017. (ECF 120-6, Brackett Feb. 8 Dep. at 66:25-68:17, 74:18-75:9, 84:2-18, 243:4-15; Ex. 257, GnRHa Pharmacy Policy (ECF 181-24); Ex. 317, AHCA FY17-21 Gender Affirming Care Coverage Data Charts ("Coverage Data Charts") (ECF 183-20).) For example, AHCA covered over 6,000 prescriptions for hormone therapy on behalf of Medicaid beneficiaries between 2017 and 2021. (Ex. 317, Coverage Data Charts (ECF 183-20); ECF 120-6, Brackett Feb. 8 Dep. at 66:25-68:17, 243:10-12.) AHCA authorized surgeries to treat gender dysphoria, covering at least 67 surgeries to treat gender dysphoria on behalf of Medicaid beneficiaries between 2017 and 2021. (Ex. 317, Coverage Data Charts (ECF 183-20); Br. Ex. 2, Bracket 2/8/23 Dep. at 84:2-18, 243:13-15.) AHCA also covered puberty-delaying medication, or GnRHa, for Medicaid beneficiaries who met AHCA's internal criteria starting in September 2016; between 2017 and 2021, it covered 405 such prescriptions. (Ex. 317, Coverage

Data Charts (ECF 183-20); Ex. 257, GnRHa Pharmacy Policy (181-24); ECF 120-6, Brackett Feb. 8 Dep. at 74:18-75:9, 243:7-9.)

In fact, as a result of a GAPMS process in 2016, AHCA adopted an explicit policy to cover puberty-delaying medications in 2016 resulted from a GAPMS process which determined that puberty suppression to treat gender dysphoria was consistent with generally accepted professional medical standards. (Ex. 254, Elliot 8/29/2016 email (ECF 181-21); Ex. 240, 2016 GAPMS for Puberty Suppression Therapy (ECF 181-4).) The 2016 GAPMS Report explicitly relied on the clinical practice guidelines of the Endocrine Society and the AAP consensus statement in its review of evidence-based clinical practice guidelines. (Ex. 240, 2016 GAPMS for Puberty Suppression Therapy, at 6 (ECF 181-4).) After this determination was made, AHCA again considered the Endocrine Society Guidelines as it implemented a pharmacy policy setting forth the criteria for coverage of GnRHa medication to treat gender dysphoria. (Ex. 257, GnRHa Pharmacy Policy (ECF 181-24); Ex. 255, Borgert email (181-22); ECF 120-6, Brackett Feb. 8 Dep. at 74:18-75:9.)

In practice, and except for the above, AHCA did not have a policy expressly providing for coverage for gender-affirming medical services (i.e., the services at issue in this case), but instead considered whether the service was medically necessary for a particular Medicaid beneficiary on a case-by-case basis. (*See* Ex. 240, 2016 GAPMS for Puberty Suppression Therapy, at 9 (ECF 181-4)

(recommending that any individualized request for [puberty suppression therapy] be reviewed as a part of the "Agency's" special services process"); Ex. 264, Bouquio 6/12/2018 email (ECF 181-31) ("Florida Medicaid does not expressly cover or deny coverage for gender confirmation surgery but does reimburse for procedures typically performed during gender confirmation surgeries"); Ex. 318, List of Appeals for Denial of Hormone Therapy (ECF 183-21) (overturning denials of hormones and GnRHa medications as medically necessary).

Each Plaintiff has been receiving coverage for their medically necessary gender affirming-medical care for many years. (Br. Ex. 2, Brackett 2/8/23 Dep. at 243:16-245:10, 246:15-247:6, 247:9-20; ECF 11-6, Dekker ¶ 17; ECF 11-7, Rothstein ¶ 12; ECF 11-8, Doe ¶ 19; ECF 11-9, Ladue ¶ 20.) And there is no dispute that Defendants cover each of the relevant medical treatments when necessary to treat at least one condition other than Gender Dysphoria. (Ex. 1, Defs' Admissions Nos. 8-12 (ECF 175-1); Ex. 4, Pltfs' Reqs for Admissions, at Definitions ¶ 13 (ECF 175-4).)

Thus, until August 21, 2022, Florida Medicaid covered and deemed medically necessary the full range of gender-affirming treatments, including puberty delaying medication, hormone therapy, and surgical care.

B. Defendants' Promulgation of the Challenged Exclusion

1. The Lead Up to the Challenged Exclusion

On March 2, 2022, the U.S. Department of Health and Human Services' (HHS) Office of Civil Rights issued guidance on gender-affirming care, stating that HHS "stands with…the significant majority of expert medical associations" in "unequivocally stating that gender affirming care for minors, when medically appropriate and necessary, improves their physical and mental health." (ECF 120-2, HHS Notice and Guidance on Gender Affirming Care.) Later that month, HHS issued additional guidance on gender-affirming care, finding that it "yield[s] lower rates of adverse mental health outcomes, build[s] self-esteem, and improve[s] overall quality of life for transgender and gender diverse youth." (ECF No. 120-3, HHS Fact Sheet: Gender Affirming Care and Young People.)

Sensing political opportunity, Governor DeSantis's administration decided it wanted to rebut these guidance documents, notwithstanding that Florida Medicaid already covered such medical care. Thus, immediately thereafter, the Florida state administration took steps to rebut the federal government's position. Following the HHS Guidance and HHS Factsheet, a meeting was convened involving the governor's office, the Florida Department of Health, and select AHCA staff including now-Secretary Jason Weida in early April to assess how to respond. there was at least one meeting between the governor's office, the Florida Department of

Health, and Secretary Jason Weida in early April. (ECF 120-6, Brackett Feb. 8 Dep. at 88:12-89:19.)

During this time, AHCA's in-house counsel Andrew Sheeran and then-Assistant Deputy Director Jason Weida began actively seeking out and hiring these activists to bolster the Agency's unscientific position. (*See* Ex. 273, April 11, 2022, email from Sheeran to Weida regarding a call with James Cantor (ECF 182-4); Ex. 274, April 14, 2022 email from Andrew Sheeran scheduling a call with Miriam Grossman (ECF 182-5); Ex. 275, April 18, 2022, email between Sheeran and Brignardello-Petersen about her role in the "GAPMS process" (ECF 182-6); Ex. 279, April 21, 2022 email between Sheeran and Michelle Cretella (ECF 182-11).)[17]

Seven consultants were retained all together: Miriam Grossman, Andre Van Mol, Quentin Van Meter, G. Kevin Donovan, James Cantor, Patrick Lappert and Romina Brignardello-Peterson—all notable critics of gender-affirming care.[18] (ECF

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[17] Notably, AHCA's corporate representative, Matthew Brackett, who was also the purported author of the June 2022 GAPMS Report, testified that no work on this process began prior to April 20, 2022. (ECF 120-6, Brackett Feb. 8 Dep. at 95:19-96:7.) The extensive communications between Weida, Sheeran, and the consultants prior to April 20, 2022, make clear that is not true.

[18] James Cantor, *Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy* (2020); Andre Van Mol, *Testimony Please Oppose SB 923 Gender-Affirming Care*; Andre Van Mol, *Testimony: Please Support HB 2649, Missouri Save Adolescents from Experimentation (SAFE) ACT*; Jennifer Bilek, *The Billionaires Behind the LGBT Movement*, firththings.com, Jan. 21, 2020; Jennifer Bilek, *LGBTQ+: A Front for the Techno-Medical Complex* (January 26); Jennifer Bilek, *Who Are the Rich, White Men Institutionalizing Transgender Ideology?*, the federalist.com, Feb. 20, 2018; Jennifer Bilek, *Stryker Corporation and the Global*

120, at 10-11.) Several of the consultants sent articles to Weida and Brackett that took the same hostile position towards gender affirming care, some written by the consultants themselves. (Ex. 273, Email from Ashley Lukis dated April 18, 2022 (ECF 182-4); Ex. 284, Email from Andre Van Mol dated May 6, 2022 (ECF 182-21); Pls' Ex. 285, Email from Andre Van Mol dated May 7, 2022 (ECF 182-22).) AHCA had never hired outside consultants to advise on a particular GAPMS process before. (ECF 120-6, Brackett Feb. 8 Dep. at 137:10-12, 139:17-140:3; Br. Ex. 2 English Dep., at 51:15-19; 138:22-139:4). But ACHA hired these consultants because "it was a unique experience for this case." (ECF 120-6, Brackett Feb. 8 Dep. at 180:23-24). AHCA hired only consultants who were known critics of gender-affirming care and had spoken out against such care in public forums and prior court proceedings.[19] Not a single consultant supporting the provision of gender affirming

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Drive for Medical identities (January 26). Jennifer Bilek, *The ACLU Gets Fat on Pharma and Tech Funding, Part 2* (Mach 4); James Kirkup, *The document that reveals the remarkable tactics of trans lobbyists*, Spectator (December 2, 2019).

[19] Some of these consultants' opinions had been rejected by courts around the country. A Texas court had previously barred Van Meter from providing expert testimony regarding medical treatment for gender dysphoria. *See* Stephen Caruso, *A Texas Judge Ruled That This Doctor Was Not an Expert*, PENNSYLVANIA CAPITAL-STAR (Sept. 15, 2020) (reporting on the now-sealed case) (Pls' Ex. 104). Cantor's opinion regarding gender-affirming care was also given little weight by a federal judge due to his lack of experience in this field. *Eknes-Tucker v. Marshall*, Case No. 2:22-CV-184, 2022 WL 1521889, at *5 (M.D. Ala. May 13, 2022). A federal judge later disqualified Lappert from testifying regarding aspects of gender-affirming care, citing the lack of scientific support for his opinions and "evidence that calls Dr. Lappert's bias and reliability into serious question." *Kadel*

care was hired to advise AHCA; none were even considered. (ECF 120-6, Brackett Feb. 8 Dep. at 135:10-15).

Following this, the FDOH issued a set of guidelines on April 20, 2022, titled "Treatment of Gender Dysphoria for Children and Adults" ("FDOH Guidelines"). (ECF No. 120-7.) The FDOH recommended against prescribing puberty-delaying medication and hormone treatments to children and adolescents. (*Id.*) It also recommended against surgery as a treatment for gender dysphoria as well. (*Id.*)

That same day, AHCA's then-Secretary Simone Marstiller purported to instruct by letter Deputy Secretary Tom Wallace to initiate a GAPMS process to review treatments for gender dysphoria. (Ex. 19, Letter from Marstiller to Wallace (ECF 175-19).) However, the process to create a report and adopt the Exclusion was already long underway. (*See* Ex. 273, April 11, 2022, email from Sheeran to Weida regarding a call with James Cantor (ECF 182-4); Ex. 274, April 14, 2022 email from Andrew Sheeran scheduling a call with Miriam Grossman (ECF 182-5); Ex. 275, April 18, 2022, email between Sheeran and Brignardello-Petersen about her role in

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v. Folwell, Case No. 1:19-CV-272, 2022 WL 3226731, *9 (M.D.N.C. Aug. 10, 2022). Others are affiliated with groups founded specifically to oppose gender-affirming care. For example, Dr. Brignardello-Petersen is affiliated with and "has conducted research for the Society for Evidence-Based Gender Medicine," which "is actually an activist group that opposes standard medical care for gender dysphoria" and is known for "present[ing] a cherry-picked collection of studies and narrative content that is full of scientific errors." (Ex. 324, Yale Public Comment, at 8-9 (ECF 183-27).)

the "GAPMS process" (ECF 182-6).) The letter also misstated that Florida Medicaid did "not have a policy on whether to cover" treatments for gender dysphoria, (Letter from Marstiller to Wallace (ECF 175-19)), when in fact it did—its policy was to cover these treatments on a case-by-case basis, when determined medically necessary. *See* Statement of Facts § VI(A), *supra*. Moreover, although AHCA had already reviewed puberty-delaying medications under a prior GAPMS and determined that they were not experimental, the agency embarked upon a new GAPMS process. (*See* Ex. 240, 2016 GAPMS for Puberty Suppression Therapy (ECF 181-4).) Notably, this was the first time the GAPMS process was used to review services already covered by Florida Medicaid. (ECF 120-6, Brackett Feb. 8 Dep. at 93:13-21; Br. Ex. 2, English Dep. at 41:6-14.).

2. The 2022 GAPMS Review Process and Proposed Rule

Also on April 20, 2023, AHCA formally tasked an agency employee named Matthew Brackett with conducting the GAPMS review, with assistance from two other employees, Devona Pickle and Nai Chen. (ECF 120-9, Dalton Dep. at 83:24-84:3; ECF 120-6, Brackett Feb. 8 Dep. at 96:6-15.) Brackett was not part of the normal GAPMS review team at the time. (ECF 120-9, Dalton Dep. at 84:11-85:19.) He and his two colleagues were part of the unrelated Canadian Prescription Drug Importation Plan team. (ECF 120-9, Dalton Dep. at 83:19-84:3.) In choosing Brackett, Pickle, and Chen, AHCA leadership entirely bypassed the AHCA

employees responsible for GAPMS determinations at the time, (ECF 120-9, Dalton Dep. at 85:7-19, 90:12-19; 24:5-14),[20] who are also the employees most knowledgeable about the GAPMS process. (*Id.* at 78:20-79:1; 151:9-13; *see also* Br. Ex. 2, English Dep. at 148:5-149:15 (Mr. English was kept off the project, despite being the "GAPMS guy," due to the understanding that he would be unwilling to participate because this "particular GAPMS was a conclusion in search of an argument.").) During this same time, AHCA staff worked with five of the agency's retained consultants—Cantor, Brignardello-Petersen, Van Meter, Lappert, and Donovan—to draft separate supporting reports that would be used as attachments. (ECF 120-6, Brackett Feb. 8 Dep. at 111:12-113:16; 110:5-10; 132:13-21.)

Aside from the fact that the GAPMS process had never before been used to

[20] Indeed, Van Mol appears to have been the true architect of the GAPMS Report that Brackett claims he solely drafted. (ECF 120-6, Brackett Feb. 8 Dep. at 97:16-19, 98:3-8). Brackett testified that he was the only one involved in reviewing the literature and writing the GAPMS Report, and that nobody else provided an outline or assisted with the drafting. He acknowledged only "verbal consultations" with the outside consultants. (*See* ECF 120-6, Brackett Feb. 8 Dep. at 96:11-97:19, 98:3-21; 104:8-20; 111:4-11, 145:14-146:24.) Van Mol wrote a document to be used in the GAPMS review process, which he sent to Weida and Brackett in early May. (Exs. 328, 328A 5/1/22 email from Van Mol with attachment (ECF 183-31 to 183-32).) AHCA used this document as guidance in drafting the main report. (*Compare* Ex. 328A, attachment to 5/1/22 email (ECF 183-32), *with* Ex. 18, June 2022 GAPMS Report report (ECF 175-18).) Van Mol also provided Brackett and Weida with additional sources throughout the process. (Exs. 284; 290; 347, emails from Van Mol to Weida (ECF 182-21, 182-29, 184-12).) And after the GAPMS report was drafted, Van Mol provided seven pages of corrections to the draft. (Exs. 286, 286A-B, email from Andre Van Mol dated May 13, 2022 with attachment (ECF 182-23 to 182-25).)

evaluate continued coverage of services already covered by Florida Medicaid, the GAPMS process and the June 2022 GAPMS Report that served as the basis for the Challenged Exclusion at issue in this case bore little resemblance to the GAPMS processes and reports that came before them. For one, the GAPMS process is typically used to analyze "a single service or good." (Ex. 321, Request Form authorizing payment to Van Mol (stating that service coverage analysis "requests *typically are for a single service or good,* this particular request called for a simultaneous analysis of three distinct services") (emphasis added) (ECF 183-24).) The June 2022 GAPMS process, however, reviewed three distinct treatments: "puberty blockers," "cross-sex hormones," and "sex reassignment surgery." (Ex. 18, AHCA GAPMS June 2022, at 39 (ECF 175-18).) The June 2022 GAPMS determination also differs from earlier GAPMS determinations in its consideration of the factors the Agency is required to consider in making its GAPMS Determination. *See* Fla. Admin. Code R. 59G-1.035(4); *see* Legal Argument § I, *infra*.

Indeed, the GAPMS process utilized to exclude coverage of gender affirming medication care "did not come through the traditional channels and was not handled through the traditional GAPMS process," and was so divergent from that the AHCA employee who was responsible for GAPMS determinations at the time, Jeff English, felt compelled to stand up for the "true credibility of the GAPMS process" by

informing the AHCA's Chief Medical Officer that the June 2022 GAMPS Report "does not present an honest and accurate assessment of the status of the current evidence and practice guidelines as I understand them to be in the existing literature." (Ex. 302, email from English to Cogle (ECF 183-4); *see also* Br. Ex. 2, English Dep. at 154:6-13 (the GAPMS process veered from process in terms of ""the quality of the studies included" and "the dismissal" of the "professional organizations and experts that we had frequently cited before."); *id.* at 137:11-138:17 (prior to the June 2022 GAPMS, the "relevant professional medical organizations" AHCA relied on included the American Academy of Pediatrics, American Psychological Association, and American Medical Association, among others); *id.* at 154:6-164:17 ("I would be hard-pressed to envision a scenario where I would second-guess [the Endocrine Society] without, you know, really. really good cause.").

Meanwhile, in addition to their work on the GAPMS Report and supporting documents, AHCA engaged these consultants to perform tasks related to publicizing and defending the agency's policy position. For example, on May 12, 2022, now-Secretary Weida asked Cantor to prepare a short video summarizing his position against gender-affirming care, which "would be posted on the Agency's website along with a copy of the Agency's GAPMS report and other resources on the topic." (Ex. 350, email between Weida and Cantor (ECF 184-15).) And ACHA paid two of

the other consultants, Van Mol and Grossman, not to write a report or review the GAPMS Report based on their knowledge and expertise, but instead to provide evidence and testimony to defend AHCA's position. (Ex. 290 (Weida asks Van Mol for help finding Florida-based people who would say that they regret gender-affirming treatment and doctors who will say they don't provide gender-affirming treatment anymore and reminds him to bill his time) (ECF 182-29); Ex. 303 (email from Grossman seeking feedback on remarks for July 8th hearing) (ECF 183-5); Ex. 307 (email from Grossman stating she expected to be challenged at the July 8th hearing) (ECF 183-9); Ex. 334 (email from Grossman to Van Mol regarding the July 8th hearing: "Can't wait to see you take them apart Andre." (ECF 183-38); Br. Ex. 2, Brackett 2/8/23 Dep., at 137:21-24 (stating that AHCA allocated $35,000 for each "consultant," for a total of $245,000).) Further, AHCA created a "slogan" for the rule promulgation process at issue here, which is something they have never done before. (ECF 120-6, Brackett Feb. 8 Dep. at 181:1-23; 184:9-11; Br. Ex. 2, English Dep., at 117:24-118:20.) The slogan, "Let Kids Be Kids," was featured on the website that was created specifically for the June 2022 GAPMS.[21]

Once the GAPMS report and the consultant reports were finalized, they had to be reviewed and approved by agency leadership. (Ex. 297, AHCA routing and

[21] The use of the phrase is peculiar given that the Challenged Exclusion applies across the board, excluding coverage for the treatments needed for transgender minors and adults. (ECF 120-6, Brackett Feb. 8 Dep. at 185:4-186:17.)

tracking form for June 2022 GAPMS (ECF 182-37).) All the reviewers approved the GAPMS report the day they received it, June 1, 2022. (*Id.*) On June 2, 2022, the GAPMS report was published, and on June 3, 2022, a proposed rule implementing the Challenged Exclusion was published, initiating a statutorily required 21-day comment period. *See* Notice of Proposed Rule, 59G-1.050 (June 3, 2022); *see* also Fla. Stat. 120.54(2).

3. Public Comment on the Proposed Rule

Upon receiving requests for public hearing from the public, AHCA scheduled the statutorily required public hearing, *see* Fla. Stat. § 120.54(3)(c), on the Proposed Rule that would become the Challenged Exclusion on July 8, 2022. This public hearing was the one and only occasion during which the public was able to engage with the agency promulgating this rule, ask questions, and provide oral input on the rule. (*See* ECF 120-9, Dalton Dep. at 118:22-119:3.)

The public hearing was presented before a panel of not only AHCA staff, Jason Weida, Cole Gearing, Matt Brackett, and Sheena Grant, but also outside counsel and consultants, Mohammad Jazil, Gary Perko, Dr. Andre Van Mol, Dr. Quentin Van Meter, and Dr. Miriam Grossman. (*See* Ex. 305, AHCA Rule 59G-1.050 Hearing Brief.) It was highly unusual for AHCA to rely on outside consultants not employed by AHCA, to pay those consultants to attend the public hearing, and to arrange and pay for their travel and transportation. (ECF 120-6, Brackett Feb. 8

Dep. at 177:14-20; *see also id.* at 180:12-25 (stating, when asked about the involvement of "consultants" like Grossman, Van Mol, and Van Meter, that "it was a unique experience for this case, but we generally don't have contracted consultants at our hearings.").) While AHCA is required by rule to have a "subject matter expert" at the public hearing, they had never before relied on outside individuals not employed by AHCA. (*See* ECF 120-9, Dalton Dep. at 120:13-121:10 (when asked about subject matter attendance at the public hearing, Dalton explained that "the subject matter expert for all of our coverage policies are individuals employed by the agency").) Moreover, at the hearing stickers featuring AHCA's slogan "Let Kids Be Kids" were handed out to all participants. (ECF 120-6, Brackett Feb. 8 Dep., 181:1-10). As an email from Grossman summarizing her experience at the July 8th hearing makes clear, this hearing was not an opportunity for AHCA to consider public comment, but rather a stage for AHCA's activist consultants to promote their views in opposition to gender affirming care (Ex. 307, 7/10/23 email from Grossman to to Weida, Van Mol, and Meter (ECF 183-9) ("I was prepared to be challenged and put on the spot but the clock ticked and ticked and…nothing. Where did all the opposition go? Weren't you expecting a bigger turnout? That one church really brought a lot of people! I was smiling ear to ear by the end.")

In addition to the oral public comments made at the hearing, AHCA accepted written comments. Indeed, thousands of written comments were submitted in

opposition to the Proposed Rule, including comments from the Endocrine Society (Ex. 323 (ECF 183-26)), the American Academy of Pediatrics (Ex. 325 (ECF 183-28)), and a team of legal and medical experts from various academic institutions. (Ex. 324 (ECF 183-27).) Together, these comments made it clear that: (1) the Proposed Rule would cause unnecessary harm and suffering; (2) the GAPMS Memo was significantly flawed and contrary to established standards of care; and (3) the Proposed Rule was illegal. (*See* Exs. 323-325 (ECF 183-26 to 183-28).)

Notwithstanding these comments, Defendants filed to adopt the Proposed Rule a mere three weeks after the close of the comment period. (*See* 59G-1.050, Rule History, *available at* https://www.flrules.org/gateway/ruleno.asp?id=59G-1.050.) The final version was identical to the Proposed Rule and went into effect on August 21, 2022. *Id.*

C. The Variance and Waiver Process Is Not Available to Obtain Coverage for Gender-Affirming Care

State statute and regulations provide a process by which a person can seek a variance and waiver from the "unreasonable, unfair, and unintended results" of agency rule requirements. Fla. Stat. § 120.542 (2022); *see also* Fla. Admin. Code R. 28-104.001-28.104.006. Under the statute, a variance is granted when: 1) "the person subject to the rule demonstrates that the purpose of the underlying statute will be or has been achieved by other means by the person;" and 2) "application of a rule would create a substantial hardship or would violate principles of fairness." Fla. Stat. §

120.542. Thus, by its own terms, the process cannot be used to request Medicaid coverage of a service that has been determined experimental under the regulations.

Defendants have provided no plausible explanation as to how Medicaid beneficiaries in need of services subject to the Challenged Exclusion could possibly satisfy the first requirement. Matthew Brackett, who testified as AHCA's corporate representative, suggested that a person could qualify for a waiver or variance by showing that the excluded services are not experimental to treat their gender dysphoria. (Br. Ex. 2, Brackett 2/8/23 Dep. at 42:19-43:18.) But that suggestion is nonsensical. AHCA made a categorical determination that the services are experimental – that determination is not dependent on the circumstances of a particular individual. (*See id.* at 41:22-42:4.)

And indeed, no variance has ever been granted for services that had been deemed experimental and categorically excluded from coverage (*Id.* at 240:1-241:18.) Brackett also acknowledged that this complex process was practically unavailable for pro se individuals, noting that due to "the complexities of request and legalities of it" a person would need legal assistance or representation to complete the process. (*Id.* at 241:19-242:13.) Accordingly, the variance and waiver process is not a viable option for individual Medicaid beneficiaries to obtain

coverage for gender-affirming care.[22]

LEGAL ARGUMENT AND AUTHORITIES

The Challenged Exclusion targets only transgender persons , including Plaintiffs Dekker, Rothstein, Doe, and K.F., and, accordingly, it violates the Fourteenth Amendment's Equal Protection Clause and Section 1557 of the Affordable Care Act, 42 U.S.C. § 18116. There is nothing experimental about the medical treatment (known as gender-affirming care) for gender dysphoria. To the contrary, gender-affirming care is supported by scientific evidence and recognized as safe, effective, and medically necessary. There is no rational basis, let alone the exceedingly persuasive justification or compelling interest, necessary for the implementation of the Challenged Exclusion. Defendants' abrupt deviation from the status quo has caused and will continue to cause irreparable harm to Plaintiffs, who will no longer be able to access medically necessary care, endangering their health and wellbeing.

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[22] Even if the variance process could result in coverage (which it cannot), requiring beneficiaries to use the process to obtain coverage of services subject to the Challenged Exclusion could run afoul of federal due process requirements. *See* 42 U.S.C. § 1396a(a)(3) (requiring states to grant an opportunity for a fair hearing before the state Medicaid agency to beneficiaries whose claim for services is denied); 42 C.F.R. §§ 431.200 to 431.246 (setting forth detailed notice and fair hearing requirements for states). (*Cf.* Ex. 229 (ECF 180-28) (template notice of adverse benefit determination providing no mention of the variance process); Ex. 231 (ECF 180-30) (sample AHCA final fair hearing order providing no mention of the variance process).)

I. Defendants' Determination That the Treatments at Issue Are Experimental Is Unreasonable

This Court, relying on *Rush v. Parham*, 625 F.2d 1150 (5th Cir. 1980), articulated as a controlling question in this case "whether, based on current medical knowledge, the state's determination that these [gender-affirming medical] treatments are experimental is reasonable."[23] AHCA's determination is not reasonable.

Here, Defendants' *own* regulations set forth the six specific criteria that govern whether a service is consistent with generally accepted professional medical standards, as opposed to experimental or investigational, for purposes of Medicaid coverage. *See* Fla. Admin. Code R. 59G-1.035(4); *see also K.G. ex rel. Garrido v.*

[23] Of note, the decision in *Rush* turns on the "reasonable standards" provision of the Medicaid Act, 42 U.S.C. § 1396a(a)(17), whereas Plaintiffs are claiming that the Challenged Exclusion violates the EPSDT and comparability provisions of the Medicaid Act. (*See* ECF No. 1, Compl., at ¶¶ 275-80.) Nevertheless, Plaintiffs agree that if the relevant treatments are experimental, the Challenged Exclusion does not violate the EPSDT requirements. (*See* Ex. 62, *EPSDT – A Guide for States*, at 24-25 (2014) (EPSDT does not require coverage of treatments, services, or items that are experimental or investigational. . . . The state's determination of whether a service is experimental must be reasonable and should be based on the latest scientific information available.").); *K.G. ex rel. Garrido v. Dudek*, 864 F. Supp. 2d 1314, 1321 (S.D. Fla. 2012), *aff'd in part, rev'd in part sub nom. Garrido v. Dudek*, 731 F.3d 1152 (11th Cir. 2013). That said, Plaintiffs contend the Exclusion could violate the Medicaid Act's comparability requirement, Section 1557 of the ACA, and the Equal Protection Clause even if Defendants' conclusion was reasonable, and the Court has acknowledged the possibility of such circumstances. (*See* ECF No. 64, at 4 (recognizing discrimination could occur where a state covers experimental services for some conditions and not others).)

Dudek, 864 F. Supp. 2d 1314, 1321 (S.D. Fla. 2012), *aff'd in part, rev'd in part sub nom. Garrido v. Dudek*, 731 F.3d 1152 (11th Cir. 2013). Consideration of each of these six factors clearly shows that the excluded services are not experimental.

AHCA's skewed and incomplete consideration of the GAPMS factors underscores that its determination otherwise was not reasonable.[24] *See K.G.*, 864 F.Supp.3d at 1322 (finding that AHCA's use of an "arbitrary, capricious, and unreasonable" process to determine whether a service is experimental shows that its conclusion was equally unreasonable).

A. Evidence-based clinical practice guidelines

Two long-standing professional medical associations – WPATH and the Endocrine Society – have published clinical practice guidelines recommending gender-affirming care, including puberty-delaying medications, hormone therapy, and surgery, for the treatment of gender dysphoria in adolescents and adults who meet specific criteria.[25] (*See* Ex. 34, WPATH Standards of Care 8 (ECF 175-34);

[24] The fact that AHCA even initiated the GAPMS process for these services reveals that the process was a sham, as the process is not used for services that the agency already covers. Ex. 30 (3/22/23 email from Pickle to English (ECF 175-30) (noting that per the state regulation, the GAPMS process is for requesting coverage, not disputing it); Br. Ex. 2, English Tr. at 41:6-41:14 (stating that the GAPMS process is not initiated to assess existing coverage of Medicaid services); (ECF 120-6, Brackett Feb. 8 Dep. at 93:13-93:21 (stating that the June 2022 GAPMS was the first time AHCA used the GAPMS process to eliminate coverage of a service).)

[25] In addition, the University of San Francisco Center for Excellence in Transgender Care has published Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People that recommend the use of the excluded

Ex. 123, Endocrine Soc. Guidelines (ECF 178-3).) These guidelines establish authoritative protocols for health care providers working with transgender patients. (Ex. 7, Karasic ¶ 39 (ECF 175-7); ¶ 39; Ex. 9, Shumer ¶¶ 48-49, 56 (ECF 175-9); Ex. 10, Schechter ¶ 24 (ECF 175-10); *see* Ex. 324, Yale Public Comment re: Proposed Medicaid Rule 59G-1.050(7) ("Yale Comment") (ECF 183-27), at 4.) Most major medical associations in the country, including the American Academy of Pediatrics, American Medical Association, the American Psychiatric Association, the American Psychological Association, the American College of Physicians, the American Academy of Family Physicians, and the American Academy of Child and Adolescent Psychiatry, among others, have endorsed these guidelines. *See* Statement of Facts § IV(B), n.14, *supra.* In reaching its conclusion, AHCA did not consider any of these views or positions and did not give any credit to any of them. (*See* Ex. 18, GAPMS Report, at Works Cited (ECF 175-18); ECF 120-6, Brackett Feb. 8 Dep. at 117:21-120:7.) There are no published clinical practice guidelines that recommend the use of psychotherapy alone to treat adolescents or adults with gender dysphoria, notwithstanding that AHCA presumably covers it. (*See* Ex. 9, Shumer Rebuttal ¶ 14 (ECF 175-9).)

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services. (*See* https://transcare.ucsf.edu/guidelines; Ex. 12, Olson Kennedy Rep. ¶ 12 (ECF 175-12); Ex. 7, Karasic Rep. ¶ 32 (ECF 175-7).)

Defendants' argument that the WPATH and Endocrine Society guidelines are biased and not evidence-based, *see* ECF 120 at 19-23, is without merit. First, it is *de rigeur* for professional medical associations to advocate on behalf of health care providers and their patients. (Ex. 14, Antommaria Rebuttal ¶¶ 54-56 (ECF 175-14).)[26] That does not undermine—let alone, invalidate—their published clinical practice guidelines. Second, the fact that members of WPATH drafted the Standards of Care does not reflect bias or a conflict of interest, but rather that clinicians and researchers with the requisite expertise in the field of transgender medicine drafted the guidelines. (*See* Ex. 12, Olson-Kennedy Rebuttal. ¶ 42 (ECF 175-12); Ex. 5, Antommaria ¶¶ 9-11 (ECF 175-5).) Third, the WPATH and Endocrine Society guidelines are based on a rigorous review of the peer-reviewed published literature, as well as extensive clinical experience. (*See* Ex. 17, Janssen Rebuttal ¶¶ 55-58 (ECF 175-17); Ex. 5, Antommaria ¶¶ 18-24, 29 (ECF 175-5); Ex. 7, Karasic ¶¶ 28, 33 (ECF 175-7); *see also* Ex. 34, WPATH Standards of Care 8 at Appx. A (ECF 175-34); Ex. 123, Endocrine Soc. Guidelines at 3872-73 (ECF 178-3).)

What is more, the guidelines themselves were published in medical journals and subjected to peer-review. "That the research is accepted for publication in a reputable scientific journal after being subjected to the usual rigors of peer review is

[26] *See, also, e.g.*, AMA, Health Care Advocacy, https://www.ama-assn.org/health-care-advocacy; American Society of Plastic Surgeons, Advocacy, https://www.plasticsurgery.org/for-medical-professionals/advocacy.

a significant indication that it is taken seriously by other scientists, i.e., that it meets at least the minimal criteria of good science." *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1318 (9th Cir. 1995).

And, as described more fully below, the level of evidence supporting the WPATH and Endocrine Society guidelines mirrors the level of evidence supporting many treatments that AHCA does not characterize as experimental. (*See* Ex. 10, Schechter ¶¶ 52-54 (ECF 175-10); Ex. 13, Schechter Rebuttal ¶¶ 7-10 (ECF 175-13); Ex. 17, Janssen Rebuttal ¶ 106 (ECF 175-17); Ex. 5, Antommaria ¶ 24 (ECF 175-5).)

Defendants' attempt to discredit the existing clinical practice guidelines for the treatment of gender dysphoria is even more remarkable in light of AHCA's usual treatment of such guidelines during GAPMS processes. When noting the presence of clinical practice guidelines and describing their recommendations, previous GAPMS reports do not even comment on the organization that developed the guidelines, much less delve into the inner workings of the organization to try to assess if the recommendations could be subject to bias. (*See, e.g.*, Ex. 330, Specially Modified Foods GAPMS (ECF 183-34); Ex. 331, Scleral Contact Lenses GAPMS (ECF 183-35); Ex. 332, Fractional Exhaled Nitric Oxide GAPMS (ECF 183-36); Ex. 333, Breast Pump GAPMS (ECF 183-37).). And indeed, AHCA has relied on guidelines and recommendations published by other organizations with an advocacy

mission to find that services are not experimental. (*See, e.g.*, Ex. 333, Breast Pump GAPMS (ECF 183-37) (referring to recommendations of AAP, AAFP, and others in determining that breast pumps are not experimental); Ex. 331 Scleral Contact Lenses GAPMS (ECF 183-35) (referring to retrospective review by American Academy of Ophthalmology in determining that scleral contact lenses are not experimental).) Tellingly, the 2016 GAPMS report on puberty suppression therapy included the Endocrine Society guidelines without any suggestion that they were somehow invalid. (*See* Ex. 240, 2016 GAPMS for Puberty Suppression Therapy (ECF 181-4).)

B. Published reports and articles in the authoritative medical and scientific literature

As detailed in Section IV(C), Statement of Facts, *supra*, there is an abundance of "peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations" examining the use of puberty delaying medications (GnRHa), hormone therapy, and surgery to treat gender dysphoria. *See* Fla. Admin. Code R. 59G-1.035(4)(b) (2022). The peer-reviewed literature on gender-affirming surgery dates back to the 1960s, and researchers have been evaluating the safety and efficacy of hormone therapy and puberty delaying medications for decades. *See, e.g.*, Statement of Facts § IV(C), *supra*.

In drafting the GAPMS Report, AHCA ignored virtually all of the large body of peer-reviewed literature on gender-affirming care. (*See* ECF 120-6, Brackett

2/8/23 Dep. at 147:12-147:25; ECF No. 84-1, Decl. of Matthew Brackett, at ¶ 4.) Indeed, Dr. Brignardello-Peterson and Dr. Wiercioch, the AHCA consultants who purported to conduct a review of the relevant literature, included just 27 studies published between 2020 and 2022 in their review. (*See* Ex. 324, Yale Comment, at 10-11, 31-32 (ECF 183-27).) They also only considered studies that included participants under age 25, while many patients who receive gender-affirming surgery are 25 or older. (Ex. 7, Karasic ¶ 81 (ECF 175-7).) In addition, they searched only one non-governmental organization website for research: the Society for Evidence-Based Gender Medicine, which is a small group founded recently specifically in opposition to gender-affirming care. (*Id.* ¶ 80 (noting that this decision "raises a concern for bias").) Their review of the relevant literature was far from comprehensive. (Ex. 324, Yale Comment, at 10-11 (ECF (183-27); Ex.7, Karasic ¶¶ 80-81 (ECF 175-7).)

The GAPMS Report and Defendants' experts attempt to discount the literature that they did consider, arguing that the studies are low quality. That claim is highly misleading, however. (Ex. 324, Yale comment at 11-12, 32-33 (ECF 183-27); *see also* Ex. 5, Antommaria ¶¶ 19-22 (ECF 175-5) (explaining how scientific evidence is rated).) While randomized trials are usually rated as high-quality evidence and observational studies as low-quality evidence (Ex. 5, Antommaria ¶20 (ECF 175-5)), for ethical and practical reasons, it is not possible to conduct randomized trials

involving the use of puberty delaying medications, hormone therapy, or surgery to treat gender dysphoria. (Ex. 8, Olson-Kennedy ¶¶ 74-85 (ECF 175-8); Ex. 10, Schechter ¶¶ 52-53 (ECF 175-10); Ex. 5, Antommaria ¶¶ 27-28 (ECF 175-5); Ex. 9, Shumer ¶ 17 (ECF 175-9); Ex. 7, Karasic ¶ 83 (ECF 175-7).)

The lack of randomized trials does not mean the existing research is insufficient to inform clinical decision making. (Ex. 14, Antommaria Rebuttal ¶ 30 (ECF 175-14); Ex., 10, Schechter ¶ 56 (ECF 175-10); Ex. 13, Schechter Rebuttal ¶ 8 (ECF 175-13); Ex. 8, Olson-Kennedy ¶¶ 73, 88-90 (ECF 175-8); *see also* Ex. 324, Yale Comment at 13, 33-34 (ECF 173-27).) In fact, the level of evidence supporting gender-affirming care is no different than the level of evidence supporting any number of very common medical interventions. (Ex. 10, Schechter ¶¶ 52-54 (ECF 175-10); Ex. 13, Schechter Rebuttal ¶¶ 7-11 (ECF 175-13); Ex. 17, Janssen Rebuttal ¶ 106 (ECF 175-17); Ex. 5, Antommaria ¶ 24 (ECF 175-5); Ex. 8, Olson-Kennedy ¶¶ 86, 124 (ECF 175-8); Ex. 7, Karasic ¶ 55 (ECF 175-7); *see also* Ex. 324, Yale Comment at 12-13, 34-36 (ECF 183-27) (noting that the evidence supporting the use of statins, screening mammograms, and routine surgical procedures have a similar evidence base).)

What is more, while the GAPMS Report and Defendants' experts criticize the methodology of individual studies, they fail to acknowledge that the entire body of literature, taken as a whole, provides strong evidence in support of puberty delaying

medications, hormone therapy, and surgery. (*See* Ex. 10, Schechter ¶¶ 73 (ECF 175-10); Ex. 8, Olson-Kennedy ¶¶ 98-99 (ECF 175-8); Ex. 16, Shumer Rebuttal ¶ 11 (ECF 175-16); Ex. 17, Janssen Rebuttal ¶¶ 26, 105 (ECF 175-17); *see also* Ex. 324, Yale Comment at 14-15, 36 (ECF 183-27).) Indeed, "the safety and efficacy in medicine is not and cannot be measured by any single study," as "*every study has limitations.*" (Ex. 12, Olson-Kennedy Rebuttal ¶ 73 (ECF 175-12).) "***To determine whether a treatment is safe and effective, and whether it is experimental or investigational, we look at the whole body of research and clinical experience.***" (*Id.*). "By this measure, gender-affirming medical care as treatment for gender dysphoria has been shown to be safe, effective, and is not experimental or investigational." (*Id.*).

Finally, while attempting to undermine the large body of peer-reviewed literature in support of gender-affirming care, Defendants rely on articles published in websites or other outlets – not peer-reviewed scientific literature. (*See* Ex. 18, GAPMS Report, at Works Cited (ECF 175-18); Ex. 324, Yale Comment at 13-15 (ECF 183-27).) This is not reliable evidence, which "means, in relevant part, 'only published reports and articles written in the authoritative medical and scientific literature.'" *K.G.*, 839 F.Supp.2d at 1265 (quoting Fla. Admin. Code R. 59G-1.010(84)(b)).

C. Effectiveness in improving prognosis or health outcomes

The peer-reviewed literature shows that puberty delaying medications, hormone therapy, and surgery are: 1) safe and effective for the treatment of gender dysphoria; and 2) when used for that purpose, are correlated additional positive health outcomes, including improved quality of life, mental health, and psychosocial functioning. *See* Statement of Facts § IV(C), *supra*. In determining whether a particular medical intervention is safe and effective, providers look at both the peer-reviewed literature and clinical experience and expertise. (Ex. 8, Olson-Kennedy ¶¶ 88-90 (ECF 185-8); Ex. 16, Shumer Rebuttal ¶ 21 (ECF 175-16); Ex. 10, Schechter ¶ 56 (ECF 175-10).) The clinical experience of providers who have treated thousands of patients with gender dysphoria supports the safety and effectiveness of gender-affirming medical care. (Ex. 9, Shumer ¶¶ 42, 46 (ECF 175-9); Ex. 8, Olson-Kennedy ¶¶ 30-31, 41 (ECF 175-8); Ex. 7, Karasic ¶¶ 26, 59 (ECF 175-7); Ex. 10, Schechter ¶ 36, 43 (ECF 175-10); Ex. 17, Janssen Rebuttal. ¶¶ 94-95, 101-102 (ECF 175-17).)

While Defendants argue that mental health services alone are equally effective in treating gender dysphoria, they provide absolutely no evidence to support that conclusion. *See* Statement of Facts § IV(D), *supra.* (*See also* Ex. 7, Karasic ¶ 37 (ECF 175-7); Ex. 11, Karasic Rebuttal ¶ 48 (ECF 175-11); Ex. 17, Janssen Rebuttal ¶ 91 (ECF 175-17); Ex. 8, Olson-Kennedy ¶ 112 (ECF 175-8); Ex. 10, Schechter ¶

58 (ECF 175-10).) In fact, research and clinical experience have proven that efforts to use talk therapy, and even aversive therapy, to try to "cure" transgender individuals are ineffective and harmful. (Ex. 17, Janssen Rebuttal ¶¶ 41-43 (ECF 175-17); Ex. 7, Karasic ¶¶ 30, 95 (ECF 175-7); Ex. 8, Olson-Kennedy at 10 ¶ 6, 13-15 ¶¶ 14-16 (ECF 175-8).) Similarly, while Defendants argue that many patients come to regret receiving gender-affirming care, the peer-reviewed literature, as well as the clinical experience of providers, demonstrates otherwise. (Ex. 10, Schechter ¶¶ 63-67 (ECF 175-10); Ex. 9, Shumer ¶ 75 (ECF 175-9); Ex. 7, Karasic ¶¶ 58, 62-64 (ECF 175-7).)

D. Utilization trends

The GAPMS Report makes no mention of this factor. There has been a notable increase in the utilization of gender-affirming medical care over the last three decades. (Ex. 5, Antommaria ¶¶ 39-40 (ECF 175-5).) AHCA's own data shows that the number of Medicaid beneficiaries accessing puberty-delaying medication (GnRHa), hormone therapy, and surgery has increased since 2017. (*See* Ex. 317, Coverage Data Charts (ECF 183-20); *see also* Ex. 6, Baker ¶ 59 (ECF 175-6).) Paradoxically, AHCA appears to view that rise in utilization as a reason to implement the Challenged Exclusion. (*See* Ex. 335, Juarez email 8/29/2022 re Medicaid data (ECF 183-39).) But, in fact, such data shows the opposite: that the services are commonly used and not experimental. *See Rush*, 625 F.2d at 1156 n.11

(contrasting a service that is "generally accepted by the professional medical community as an effective and proven treatment for the condition for which it is being used" with a service or treatment that "is rarely used, novel, or relatively unknown").

E. Other coverage policies

AHCA's coverage exclusion is an outlier among health plans. The vast majority of health plans, in Florida and elsewhere, do not have categorical transgender-specific exclusions. (*See* Ex. 6, Baker ¶¶ 40 (state employee plans), 41 (plans offered by private employers), 42 (federal employee plans), 44-46 (plans sold through the federal Marketplace, including in Florida) (ECF 175-6); *see also id*. ¶ 35 (highlighting that 25 states and D.C. prohibit such exclusions in state-regulated individual and group plans); Ex. 5, Antommaria ¶ 42 (ECF 175-5).) In drafting the GAPMS report, AHCA did not even review private insurance coverage policies. (ECF 120-6, Brackett Feb. 8 Dep. at 149:2-152:6.)

Likewise, Medicare has covered gender-affirming surgical care since 2014. (*See* Ex. 71, Dep't of Health & Human Servs., Departmental Appeals Bd., Appellate Div., Decision No. 2576 at 20 (May 30, 2014) (ECF 176-31) (invalidating the exclusion of gender-affirming surgery given the "consensus among researchers and mainstream medical organizations that [gender-affirming] surgery is an effective, safe and medically necessary treatment").) The 2016 decision memo that Defendants

rely on (*see* ECF 120 at 6, 7) did not change that policy. HHS simply declined to issue national standards governing when gender-affirming surgery is medically necessary, allowing local Medicare contractors to continue determining medical necessity on an individual basis. (Ex. 64, Ctrs. for Medicare & Medicaid Servs., Decision Memo for Gender Dysphoria and Gender Reassignment Surgery at 2 (Aug. 30, 2016) (ECF 176-24).) That decision was not unusual, as many widely accepted surgical procedures do not have national coverage standards under Medicare.[27] (Ex. 10, Schechter ¶ 79 (ECF 175-10).) Medicare also covers gender-affirming medications. (Ex. 5, Antommaria ¶ 41 (ECF 175-5).)

As for Medicaid, only 9 of the 56 states and territories operating a Medicaid program exclude coverage of gender-affirming care. (Ex. 6, Baker ¶¶ 54, 57 (ECF 175-6).) Even among those jurisdictions, Florida's exclusion stands apart for its breadth and scope.[28] (*Id.* ¶¶ 55-57 (noting that three of the exclusions are limited to

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[27] What is more, HHS only concluded that the evidence was "inconclusive for the Medicare population," which consists primarily of people over age 65. The conclusion is not transferable to other population groups. (Ex. 10, Schechter ¶ 79 (ECF 175-10).) For that reason, CMS has made clear that Medicare guidance is not determinative of whether a service is experimental for individuals under age 21. (Ex. 62, Ctrs. for Medicare & Medicaid Servs., *EPSDT – A Guide for States* 25 (2014) (ECF 176-22).)

[28] AHCA's evaluation of Medicaid coverage policies in the GAPMS report was flawed. It involved only an online search for state policies, (*see* ECF 120-6, Brackett Feb. 8 Dep. at 152:7-155:12), while a comprehensive evaluation would involve state statutes, regulations, operative guidance, managed care organizations' policies, and administrative and court decisions. (Ex. 6, Baker ¶ 56 (ECF 175-6).)

surgery, one is limited to minors, and one appears to be inoperative).) Perhaps most remarkably, Florida Medicaid covered puberty-delaying medications, hormone therapy, and surgical care prior as treatment for gender dysphoria prior to the implementation of the Challenged Exclusion. (Ex. 317, Coverage Data Charts (ECF 183-20); ECF 120-6, Brackett Feb. 8 Dep. at 74:18-75:9; 66:25-68:17, 81:14-84:18.) What is more, the insurers with which AHCA contracts to deliver services to Medicaid enrollees cover gender-affirming care under their own policies. (*See, e.g.*, Ex. 57 (Aetna Coverage of GnRHa) (ECF 176-17); Ex. 56 (Aetna Coverage of Gender Confirming Surgery) (ECF 176-16); Ex. 54 (Humana Coverage of Testosterone) (ECF 176-14); Ex 58 (Humana Coverage of Gender Confirming Surgery) (ECF 176-18); Ex 60 (Molina Coverage of Gender Confirming Surgery) (ECF 176-20); Ex 59 (Molina Coverage of Hormone Therapy) (ECF 176-19); Ex 61 (United Coverage of Gender Dysphoria Treatment) (ECF 176-21).)

While other nations' coverage policies have never before factored into the GAPMS process, Defendants argue that their determination regarding puberty delaying medications, hormone therapy, and surgery reflects an "international consensus" on the issue. (ECF 120, at 24-25.) But that is wrong. First, Defendants have not conducted a comprehensive review of other countries' policies regarding gender-affirming care. (*See* Ex. 18, GAPMS Report, at 35 (ECF 175-18) (citing to guidelines in only 3 European nations).) Second, the statements Defendants cite do

not even address treatment for adults, but Florida has excluded coverage of gender-affirming care for Medicaid beneficiaries of all ages. *Id.* Third, Defendants have misrepresented those nations' policies with respect to minors.[29] (Ex. 14, Antommaria Rebuttal ¶¶ 73-82 (ECF 175-14).) For example, Defendants ignore that the United Kingdom, Sweden, and Finland continue to provide gender-affirming care for minors in some cases, as do many other developed nations. (*See id*. ¶¶ 77-79; Ex. 7, Karasic ¶¶ 94-95.) Neither Australia nor New Zealand have changed their policies, and other countries like Denmark, Germany, Spain, and Mexico have adopted policies explicitly providing this care. (ECF 142-11, at 13-20.)

F. Recommendations or assessments by clinical or technical experts on the subject or field

This factor calls for the views "by clinical or technical experts *on the subject or field*." Fla. Admin. Code R. 59G-1.035(4)(f) (emphasis added). Recognized clinical and technical experts in the field of transgender medicine agree that gender-affirming medical care services in the form of puberty-delaying medications, hormone therapy, and surgery are safe and effective treatments for gender dysphoria. (Ex. 8, Olson-Kennedy ¶ 121 (ECF 175-8); Ex. 9, Shumer ¶ 89 (ECF 175-9); Ex. 7, Karasic ¶¶ 53-54, 100 (ECF 175-7); Ex. 17, Janssen Rebuttal ¶¶ 23, 133 (ECF 175-

[29] In the GAPMS report itself, AHCA included maps purporting to show the age at which an individual can receive hormone therapy or surgery "without consent of parents or of a public authority" in various European nations. (Ex. 18, GAPMS Report, at 37-38 (ECF 175-18).) That information is irrelevant.

17); Ex. 10, Schechter ¶¶ 23, 43, 81 (ECF 175-10); *see also* Ex. 324, Yale Comment at 4-5, 24-25 (ECF 183-27).) Because Defendants were determined to terminate Medicaid coverage for these services, AHCA did not seek recommendations or assessments from recognized experts or individuals with actual experience in the field of transgender medicine.

Instead, in preparing the GAPMS report, AHCA asked a handful of select, vocal opponents of gender-affirming care to serve as consultants. The process began with the Department of Health pointing AHCA staff to Dr. Michelle Cretella – a former President of the American College of Pediatricians, which has taken extreme positions on a number of LGBTQ issues and opposes the provision of gender-affirming care – who then pointed AHCA to other consultants. (ECF 120-6, Brackett Feb. 8 Dep. at 104:21-106:8, 110:5-110:25). Dr. Cretella then connected AHCA with Dr. Andre Van Mol, touting his credentials as "Chair of the Adolescent Sexuality Committee of the American College of Pediatricians and a spokesperson for the Christian Medical and Dental Associations." (Ex. 279, 4/21/22 email between Sheeran and Michelle Cretella (ECF 182-11).) Dr. Van Mol appears to promote fringe theories about gender-affirming care. (Ex. 284, 5/6/22 email from Van Mol to Weida (ECF 182-21) (sharing online articles about "financing the [transgender] movement and its tactics" including "Who Are the Rich, White Men Institutionalizing Transgender Ideology"); Ex. 285, 5/7/22 email from Van Mol to

Weida, Brackett and Pickle (ECF 182-22) (sharing additional online articles purporting to establish "the connection to big pharma/biotech/philanthropy profiteering in the clothes of being rights advocates").)

AHCA also retained Dr. Miriam Grossman as a consultant to assist with the GAPMS process. (ECF 120-6, Brackett Feb. 8 Dep. at 104:6-20, 111:4-11.) Dr. Grossman is a psychiatrist and transgender denier who "currently focuses on gender-confused young people and their parents" and "believes that every child is born in the right body." (Ex. 32, Grossman Biography (ECF 175-32).) She was very eager to support Defendants' efforts, as well as other similar restrictions. (*See, e.g.*, Ex. 334 7/7/22 Grossman email (ECF 183-38) (telling Dr. Van Mol before the July 8, 2022 hearing on the Challenged Exclusion that she "[c]an't wait to watch you take [AAP] apart Andre"); Ex. 307, 7/10/22 Grossman email (ECF 183-9) (after the hearing, stating that she "loved how [the people speaking in favor of the regulation] cheered each time de Santis was mentioned" and expressed her eagerness to see similar measures enacted in other states).)

It is no surprise then, that the so-called "experts" that AHCA retained to complete assessments to include in the GAPMS Report have no expertise in the field and have been shown to be unreliable or biased.

Romina Brignardello-Petersen. Despite claiming to have "no research interests in medical care for transgender youth," Dr. Brignardello-Peterson conducts

research for an organization (SEGM) that opposes gender-affirming care. (*See* Ex. 324, Yale Comment, at 8 (ECF 183-27).) That organization (SEGM) "is actually an activist group that opposes standard medical care for gender dysphoria" and is known for "present[ing] a cherry-picked collection of studies and narrative content that is full of scientific errors." (*Id.*, at 8-9.)

James Cantor. Dr. Cantor is a psychologist who has never diagnosed a child or adolescent with gender dysphoria nor treated a child or adolescent for the condition. *Eknes-Tucker v. Marshall*, 603 F. Supp. 3d 1131, 1142-43 (M.D. Ala. 2022) (giving "his testimony regarding the treatment of gender dysphoria in minors very little weight").

Quentin Van Meter. Dr. Van Meter is a pediatric endocrinologist who has never provided treatment for gender dysphoria, (ECF 144-3, Van Meter Dep. at 37:13-25), nor conducted any original, peer-reviewed research on gender identity, transgender people, or gender dysphoria. (*Id.* at 28:6-23.) The Past President of American College of Pediatricians,[30] he believes that being transgender is a choice

[30] The American College of Pediatricians ("ACPeds"), a Florida-headquartered group to which several of Defendants' experts and consultants belong (including Dr. Van Meter, Dr. Van Mol, Dr. Zanga, Dr. Hruz, and Michelle Cretella) is well-known for pushing anti-LGBTQ policies across the country and internationally. ACPeds was founded by "dissenting members of the AAP" who "disagree[d] with the AAP's point of view on gay parenting" and their "pro-homosexual stance," according to founding member Dr. Joseph Zanga. (ECF 117; *see also* ECF 112.) Since that time, ACPeds has campaigned widely against same-sex attraction (ECF 116 (claiming that "defenders and promoters of

and "is not normal," (*id*. at 197:24-198:2, 191:25-192:2), and considers gender affirmation to be "medical abuse." (*Id*. at 186:12-15.) (*See generally* ECF No. 144, Memo. in Support of Mot. to Exclude Expert Testimony of Dr. Quentin Van Meter.)

Patrick Lappert. Dr. Lappert, a retired surgeon, concedes that he has never provided and is not an expert in gender-affirming care. (*See* ECF 127-5, Lappert Dep. at 151, 168; ECF 127-4, *Brandt v. Rutledge* Trial Tr. at 1042:13-15.) He has characterized surgical treatment for gender dysphoria as an "intentional mutilation," (ECF 127-5, Lappert Dep. at 59-60), and "diabolical in every sense of the word." (*Id*. at 464-65; ECF 127-10 (Lifesite article).) *See also Kadel v. Folwell*, Case No. 1:19cv272, 2022 WL 3226731, *12 (M.D.N.C. Aug. 10, 2022) (finding "evidence that calls Dr. Lappert's "bias and credibility into serious question"). (*See generally* ECF 127, Mot. to Partially Exclude Expert Testimony of Dr. Patrick W. Lappert.)

G. Kevin Donovan. Dr. Donovan, a bioethicist and pediatric gastroenterologist, has never provided an ethical consult regarding the care of a transgender patient, has never treated a transgender patient, and is categorically

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homosexuality try to cover up the scientifically documented serious promiscuity...and psychological and medical illnesses associated with the lifestyle")), and even allege that "divorce and single parenting" are "harmful to children." (ECF 118.) Further, ACPeds has published official position statements endorsing conversion therapy for homosexual youth. (ECF 111; *see also,* ECF 116.) ACPeds founder, and Defendants' expert witness Dr. Zanga, has said "a child can no more make him or herself someone of the opposite sex than they could become a chimpanzee." (ECF 105.)

opposed to any gender-affirming medical treatment. (Br. Ex. 3, Donovan Dep. at 128:15-130:8, 118:6-120:14.) Despite proffering Donovan as an expert in their Rule 26(a)(2) disclosures, Defendants have elected not to call him as an expert, or even as a fact witness at trial. (ECF 197-2.)

The additional individuals that AHCA retained to serve as expert witnesses for this case are equally unqualified and unreliable. Like the consultants hired during the GAPMS process, their opposition to gender-affirming care is not based on the scientific and medical evidence, but rather their ideological views about sex and gender. (*See generally* ECF 136, Mot. to Exclude Expert Testimony of Dr. Paul W. Hruz; ECF 133, Mot. to Exclude Expert Testimony of Michael Laidlaw; ECF 119, Mot. to Exclude Expert Testimony of Sophie Scott, Ph.D.; ECF 138, 139, Mot. to Exclude Expert Testimony of Dr. Kristopher Kaliebe and Memo. in Support; ECF 142, Mot. to Exclude Expert Testimony of Joseph Zanga, M.D.)

In sum, a sober look at the GAPMS factors reveals that when used to treat gender dysphoria, puberty-delaying medication, hormone therapy, and surgery are consistent with generally accepted professional medical standards and are not experimental. Defendants' contrary conclusion is not reasonable.

II. The Challenged Exclusion Violates the EPSDT and Comparability Provisions of the Medicaid Act

A. The EPSDT and Comparability Provisions of the Medicaid Act Are Enforceable Pursuant to 42 U.S.C. § 1983.

The Court should reject Defendants' argument that Plaintiffs do not have a private cause of action to enforce their Medicaid Act claims. (*See* ECF 120, at 28.) For more than 20 years, the Supreme Court has required lower courts to apply a three-prong test to determine whether a statutory provision gives rise to a federal right under 42 U.S.C. § 1983. *See Gonzaga Univ. v. Doe*, 536 U.S. 273 (2002); *Blessing v. Freestone*, 520 U.S. 329 (1997). *Blessing* requires courts to evaluate three elements: first, Congress must intend the provision in question to benefit the plaintiff; second, the right contained in the provision must not be so "vague and amorphous" that its enforcement would strain judicial competence; and third, the statute must unambiguously impose a binding obligation on the state. 520 U.S. at 340-41 (citations omitted). *Gonzaga* clarified the first prong of the test, instructing that the provision in question must contain unambiguous "right- or duty-creating language," as opposed to language with an aggregate, rather than individual, focus. 536 U.S. at 284 n.3; *see also* 42 U.S.C. §§ 1320a(2), (10) (stating congressional intent that provisions of the Social Security Act, of which Medicaid is a part, are privately enforceable).[31]

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[31] Citing *Collins v. City of Harker Heights*, 503 U.S. 115, 119 (1992), Defendants argue that the EPSDT and comparability provisions do not create enforceable rights because § 1983 "does not provide a remedy for abuses that do not violate federal law." (ECF 120 at 28.) *Collins*, which did not involve a federal law, is inapposite. There, the Supreme Court held that even if the allegations in the complaint were true, there was no constitutional violation. 503 U.S. at 125-30. Defendants have made no such argument here, and in fact, this Court has found that if Defendants'

Blessing also instructs plaintiffs to plead their complaints in "manageable analytic bites" and courts to determine whether "each separate claim" satisfies the test. *Blessing*, 520 U.S. at 342; *id*. at 340. Here, Count III of Plaintiffs' complaint alleges that the Challenged Exclusion violates the EPSDT provisions, 42 U.S.C. §§ 1396a(a)(10)(A), 1396d(a)(4)(B), 1396d(r)(5), and 1396a(a)(43)(C), and Count IV alleges that the Challenged Exclusion violates the comparability requirements, 42 U.S.C. § 1396a(a)(10)(B). (*See* ECF 1, Compl., at ¶¶ 275-80.)

Every federal appellate court to have considered whether the EPSDT provisions are enforceable by Medicaid beneficiaries through section 1983 has applied the three-prong test and concluded that they are. *See S.D. ex rel. Dickson v. Hood*, 391 F.3d 581, 602-07 (5th Cir. 2004); *Pediatric Specialty Care, Inc. v. Ark. Dep't of Human Servs.*, 293 F.3d 472, 477-79 (8th Cir. 2002); *Miller v. Whitburn*, 10 F.3d 1315, 1319-20 (7th Cir. 1993). *See also Waskul v. Washtenaw Co. Cmty. Mental Health,* 979 F.3d 426, 445-48 (6th Cir. 2020) (finding § 1396a(a)(10)(A) enforceable in case involving coverage of services other than EPSDT); *Bontrager v. Ind. Fam. & Soc. Servs. Admin,* 697 F.3d 604, 606-07 (7th Cir. 2012) (same); *Watson v. Weeks*, 436 F.3d 1152, 1159-62 (9th Cir. 2006) (same).

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determination that the excluded treatments are experimental was unreasonable, Defendants have violated the Medicaid Act. (ECF 64, at 3-6.)

Defendants' argument that these courts failed to grasp the nature of a federal right under *Gonzaga* is unfounded. (*See* ECF 120, at 28.) Take, for example, *S.D. ex rel. Dickson v. Hood*. There, a teenage Medicaid beneficiary with spina bifida alleged that Louisiana's refusal to cover incontinence supplies necessary to help treat his condition violated the EPSDT provisions. Assessing the first *Blessing*/*Gonzaga* prong, the Fifth Circuit concluded that section 1396a(a)(10)(A) – which requires that the state plan "must provide for making medical assistance available, including at least the care and services listed in paragraph (1) through (5), (17) and (21) of section 1396d(a) of this title, to all individuals" who meet the eligibility criteria – contains "precisely the sort of 'rights-creating' language identified in *Gonzaga* as critical to demonstrating a congressional intent to establish a new right." *S.D.*, 391 F.3d at 603 (explaining that EPSDT services are listed in § 1396d(a)(4), which then refers to § 1396d(r)). The Court also found that the EPSDT provisions do not have an aggregate focus but rather are "'concerned with whether the needs of [particular individuals] have been satisfied.'" *Id*. at 604 (quoting *Gonzaga*, 536 U.S. at 275). Turning to the second prong of the test, the Court found that enforcement of the EPSDT provisions does not "'strain judicial competence;' it is the sort of work in which courts engage

every day." *S.D.*, 391 F.3d at 605.[32] As for the third prong, the Court concluded that the provisions impose binding requirements on participating states. *Id*. at 605-06.

Similarly, two circuits have addressed whether the comparability provision is enforceable through section 1983, and both concluded that it is.[33] *See Waskul*, 979 F.3d at 446-48; *Davis v. Shah*, 821 F.3d 231, 255 n.12 (2d Cir. 2016).[34] In *Waskul*, the Sixth Circuit found that the comparability provision – which requires that "the medical assistance made available to any individual described" must "not be less in

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[32] While Defendants claim otherwise (*see* ECF 120 at 30), district courts are clearly capable of determining whether particular health care services are "necessary" under section 1396d(r)(5). *See, e.g.*, *K.G.*, 981 F.Supp.2d at 1291-92 (concluding that applied behavioral analysis therapy "is necessary to correct or ameliorate the condition of Autism Spectrum Disorder" and AHCA violated EPSDT by excluding coverage of the therapy for beneficiaries under age 21 with ASD); *C.R. ex rel. Reed v. Noggle*, 559 F. Supp. 3d 1323, 1337 (N.D. Ga. 2021) (finding state denied plaintiff speech and feeding therapy services "that were medically necessary to ameliorate her conditions" in violation of EPSDT).

[33] In *Harris v. James*, 127 F.3d 993 (11th Cir. 1997), the Eleventh Circuit held that a federal regulation, standing alone, cannot create an enforceable right under section 1983. *Id.* at 1008. In reaching its decision, the Court looked at whether a Medicaid regulation requiring transportation to and from providers could be reasonably understood to be part of the content of various statutory provisions, including the comparability provision, and concluded that it could not. *Id*. at 1011-12. In reaching its decision, the Court made clear that it was not deciding the issue of whether the comparability provision could give rise to any other federal right. *Id*. at 1011. As such, *Harris* has no bearing on the issue before this Court. *See Doe v. Chiles*, 136 F.3d 709, 714-15 (11th Cir. 1998) (discussing limits of *Harris* holding).

[34] Following similar reasoning, a number of district courts have held that the comparability provision is enforceable under Section 1983. *See, e.g.*, *Cruz v. Zucker*, 116 F.Supp.3d 332, 345-46 (S.D.N.Y. 2015); *Women's Hosp. Found. v. Townsend*, 2008 WL 2743284 (M.D. La. July 10, 2008); *Michelle P. v. Holsinger*, 356 F.Supp.2d 763, 767-68 (E.D. Ky. 2005).

amount, duration, or scope than the medical assistance made available to any other such individual," 42 U.S.C. § 1396a(a)(10)(B) – contains "the kind of individually focused terminology that unambiguously confers an individual entitlement under the law." *Id.* at 447 (cleaned up). Turning to the second and third *Blessing* factors, the Court determined that the provision is "amenable to judicial remedy," as it "sets forth criteria for determining whether . . . services are equitably provided," and that the provision is "couched in mandatory rather than precatory language." *Id.* at 448 (cleaned up).

As this case law demonstrates, the EPSDT and comparability provisions create individual federal rights for Medicaid beneficiaries. Thus, these provisions are "presumptively enforceable by § 1983." *See Gonzaga Univ.*, 536 U.S. at 284. The State may rebut this presumption by making the "difficult showing" that Congress expressly prohibited reliance on section 1983 or that it provided a comprehensive remedial scheme intended to preclude individual suits. *See Blessing*, 520 U.S. at 346. Congress has not done so here. *See Wilder v. Va. Hosp. Ass'n*, 496 U.S. 498, 521-22 ("The Medicaid Act contains no . . . provision for private judicial or administrative enforcement . . . generalized powers . . . to audit and cut off federal funds [are] insufficient to foreclose reliance on § 1983 to vindicate federal rights."); *see also City of Rancho Palos Verdes v. Abrams*, 544 U.S. 113, 121-22 (2005)

(Scalia, J.) (citing *Wilder* and listing Medicaid as a statute whose enforcement is not foreclosed).

Finally, contrary to Defendants' argument, *Armstrong v. Exceptional Child Ctr., Inc.*, 575 U.S. 320 (2015), does not implicate Plaintiffs' ability to enforce Medicaid's EPSDT and comparability provisions pursuant to section 1983. *See* Defs.' Br. at 29-30. *Armstrong* concerned a Medicaid payment provision (not EPSDT or comparability) that health care providers (not Medicaid enrollees) were seeking to enforce under the Supremacy Clause (not section 1983). *See* 575 U.S. at 323-34. Unlike the provisions at issue in this case, the provision at issue in *Armstrong*, 42 U.S.C. § 1396a(a)(30)(A), had been found unenforceable pursuant to section 1983 by most courts, including this one. *See Fl. Pharmacy Ass'n v. Cook*, 17 F.Supp.2d 1293 (N.D. Fla. 1998). The relevant reasoning from *Armstrong* did not reflect a majority of the Court, but only a plurality, and it did not involve and certainly did not overrule the section 1983 enforcement test. *See, e.g.*, *BT Bourbonnais Care, LLC v. Norwood*, 866 F.3d 815, 820 (7th Cir. 2017) (concluding *Armstrong* does not preclude plaintiffs from enforcing the Medicaid Act through section 1983); *Legacy Cmty. Health Servs., Inc. v. Smith*, 881 F.3d 358, 373 (5th Cir. 2018), *as revised* (Feb. 1, 2018) (same); *see also*, *e.g.*, *O.B. v. Norwood*, 170 F. Supp. 3d 1186, 1090-93 (N.D. Ill. 2016) (holding EPSDT provisions enforceable under section 1983 and distinguishing *Armstrong*); *William v. Horten*, 2016 WL 6582682

(N.D. Ga. Nov. 7, 2016) (same, collecting cases); *J.E. v. Wong*, 125 F. Supp. 3d 1099, 1105-08 (D. Haw. 2015) (same).

The Court should hold that Plaintiffs have the right to enforce the EPSDT and comparability provisions of the Medicaid Act.

B. The Challenged Exclusion Violates the Medicaid Act's EPSDT Requirements.

As described in detail above, puberty delaying medications, hormone therapy, and surgery are not experimental. As such, Florida must cover the services when they are medically necessary for beneficiaries under age 21.

The fundamental purpose of the EPSDT requirements is to ensure that Medicaid recipients under age 21 receive the "health care they need when they need it." *M.H. v. Berry*, No. 15-cv-1427, 2021 WL 1192938, *6 (N.D. Ga. March 29, 2021) (quoting Ex. 62, Ctrs. for Medicare & Medicaid Servs., *EPSDT – A Guide for States* (2014) (ECF 176-22)). Specifically, the EPSDT provisions require each state Medicaid program to cover any service that is allowable under § 1396d(a) if "necessary . . . to correct or ameliorate" illnesses or conditions regardless of whether the state covers the service for adults. 42 U.S.C. §§ 1396d(r)(5), 1396a(a)(10)(A), 1396d(a)(4)(B); *see, e.g., Moore ex rel. Moore v.* Reese, 637 F.3d 1220, 1233-34 (11th Cir. 2011); *S.D. ex rel. Dickson v. Hood*, 391 F.3d 581, 589-593 (5th Cir. 2004). "The EPSDT obligation is thus extremely broad." *Katie A., ex rel. Ludin v. L.A. County*, 481 F. 3d 1150, 1154 (9th Cir. 2007); *see also Smith v. Benson*, 703 F.

Supp.2d 1262, 1269-70 ("the Centers for Medicare and Medicaid Services ("CMS"), has made the broad mandate of EPSDT program abundantly clear."). And "there is a very strong inference to be inclusive rather than exclusive" when determining the meaning of "correct or ameliorate." *Ekloff v. Rodgers*, 443 F.Supp.2d 1173, 1180 (D. Ariz. 2006). Further, states must take the proactive step of ensuring that services determined to be medically necessary for a particular beneficiary are actually arranged for. 42 U.S.C. § 1396a(a)(43)(C); *Katie A.*, 481 F. 3d at 1158-59.

Here, the EPSDT provisions require Defendants to cover the gender-affirming services that are the subject of the Challenged Exclusion. Puberty-delaying medications, hormone therapy, and surgery fall within the scope of benefits listed in § 1396d(a). *See* 42 U.S.C. § 1396d(a)(1) (inpatient hospital services), (2)(A) (outpatient hospital services), (5)(A) (physicians' services), (12) (prescribed drugs).[35] And, for many transgender young people, the services are "necessary . . . to correct or ameliorate" their gender dysphoria. *Id.* § 1396d(r)(5).

[35] While the Medicaid Act allows states to place certain limited restrictions on coverage of prescribed drugs for adults, *see* section III below, EPSDT requires coverage of all "prescribed drugs" for beneficiaries under age 21 when medically necessary. *See* 42 C.F.R. § 440.120 (defining prescribed drugs). (*See also* Ex. 63, Ctrs. for Medicare & Medicaid Servs., *CMCS Informational Bulletin* 2 (July 21, 2022) (ECF 176-23) (noting that "any prescribed drug covered under Medicaid EPSDT requirements is eligible for federal financial participation (FFP) regardless of the applicability of [42 U.S.C. 1396r-8]).

As described in detail above, there is broad consensus within the medical community that puberty-delaying medications (GnRHa), hormone therapy, and surgery may be medically necessary for transgender adolescents and young adults, based on their individual needs. *See* Facts § V, *supra.* Prior to implementing the Challenged Exclusion, AHCA reached the same conclusion, covering each of these services for a significant number of transgender Medicaid beneficiaries under age 21. (*See* Ex. 317, AHCA FY17-21 Gender Affirming Care Coverage Data Charts.) Indeed, the agency covered puberty delaying medications for K.F. and S.D. (ECF 120-6 (Brackett Feb.8 Dep.) at 247:9-247:20; ECF 11-8, Doe ¶ 19; ECF 11-9, Ladue ¶ 20), and hormone therapy for Mr. Rothstein. (ECF 120-6 (Brackett Feb.8 Dep.) at 246:15-247:6; ECF 11-7, Rothstein ¶ 12.)[36] While AHCA's policy regarding coverage of the services has changed, Plaintiffs' medical need for the services and the general consensus of the medical community regarding the services have not. *See* Statement of Facts §§ I(A), IV(B)-(C), *supra*.

Given that the services are not experimental, *see* Statement of Facts § IV(C), *supra*, AHCA cannot escape its obligation to cover them when necessary for a particular individual who is under age 21, including for Plaintiffs K.F., S.D., and Mr. Rothstein. *See S.D.,* 391 F.3d at 592 ("[T]he plain words of the [Medicaid Act] and

[36] AHCA also prior authorized coverage of a mastectomy for Mr. Rothstein. (*See* Ex. 319, List of Surgery Requests (showing Rothstein mastectomy approved).)

the legislative history make evident that Congress intended that the health care, services, treatment and other measures that must be provided under the EPSDT program be determined by reference to federal law, not state preferences.").

C. The Challenged Exclusion Violates the Medicaid Act's Comparability Requirement.

The Medicaid Act requires AHCA to ensure that the "medical assistance made available to any [categorically needy] individual . . . shall not be less in amount, duration, or scope than the medical assistance made available to any other such individual." 42 U.S.C. § 1396a(a)(10)(B); 42 C.F.R. § 440.240. Federal regulations make clear that states "may not arbitrarily deny or reduce the amount, duration, or scope of a required service . . . to an otherwise eligible beneficiary solely because of the diagnosis, type of illness, or condition." 42 C.F.R. § 440.230(c).

Courts repeatedly hold that the comparability requirement "prohibits discrimination among individuals with the same medical needs stemming from different medical conditions." *Davis v. Shah*, 821 F.3d 231, 258 (2d Cir. 2016) (finding state policy covering prescription orthopedic footwear and compression stockings for beneficiaries with certain listed conditions, but not for those with equal need for the services due to other conditions, violated comparability requirement); *see also White v. Beal*, 555 F.2d 1146, 1148 (3d Cir. 1977); *Cota v. Maxwell-Jolly*, 688 F. Supp. 2d 980, 993 (N.D. Cal. 2010).

With the Challenged Exclusion, however, AHCA is doing just that. For example, for many transgender people, various surgical procedures are medically necessary to treat their gender dysphoria. *See* Facts § IV(C)(3), *supra*. While AHCA refuses to cover these surgeries when necessary to treat gender dysphoria, the agency covers the same surgeries when necessary to treat other conditions. (*See* Ex. 1, Defs' Admissions Nos. 8-12 (ECF 175-1); Ex. 4, Pltfs' Reqs for Admissions at Definitions ¶ 13 (ECF 175-4).) Multiple federal courts have held that such a policy violates the comparability requirement by discriminating on the basis of diagnosis.[37] *Flack v. Wis. Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1019 (W.D. Wis. 2019); *Fain v. Crouch*, 618 F.Supp.3d 313 (S.D. W. Va. 2022), *appeal filed*, No. 22-1927, 2022 WL 3051015 (4th Cir. 2022), *reh'g en banc granted*, 2023 WL 2908815 (4th Cir. Apr. 12, 2023).

The same reasoning applies to the categorical exclusion of hormone therapy, which is medically necessary for many transgender people. *See* Statement of Facts § IV(C)(2), *supra*. For example, pursuant to the Challenged Exclusion, AHCA does not cover testosterone or estrogen when necessary to treat gender dysphoria but

[37] Defendants argue that there is no "equivalence between" a mastectomy performed to treat gender dysphoria and a mastectomy performed to treat breast cancer because in the breast cancer context, "diseased breast tissue is removed from the body." (ECF 120 at 28.) Defendants do not explain why that distinction is meaningful and ignore that a mastectomy is routinely performed (and covered by AHCA) in patients whose breast tissue is not "diseased." (*See* Ex. 13, Schechter Rebuttal ¶ 14, 24 (ECF 175-13).)

covers the same prescription drugs when necessary to treat other conditions. (*See* Ex. 1, Defs' Admissions ¶¶ No. 8 (ECF 175-1); Ex. 4, Pltfs' Reqs for Admissions at Definitions ¶ 13 (ECF 175-4).) While Defendants argue that these uses are not equivalent for purposes of Medicaid coverage, (*see* ECF 120, Defs.' Mot. for Summ. J. and Mem. of Law, at 28), the prescription drug provision of the Medicaid Act indicates otherwise. The statute requires states to cover all FDA-approved drugs when they are prescribed for a "medically accepted indication," subject to certain limited exceptions not at issue here.[38] 42 U.S.C. §§ 1396r-8(k)(2), 1396r-8(d)(1)(B). (*See* Ex. 63, Ctrs. for Medicare & Medicaid Servs., *CMCS Informational Bulletin* 2 (July 21, 2022) (ECF 176-23) ("covered outpatient drugs that are prescribed for a medically accepted indication must be covered" by Medicaid); *see also Edmonds v. Levine,* 417 F. Supp. 2d 1323, 1338 (S.D. Fla. 2006) (Congress designed a "statutory scheme, which sets forth very specific criteria and means by which a state may exclude coverage for specific drugs or use of such drugs"). A "medically accepted indication" is a use that is FDA-approved or "supported by one or more citations included or approved for inclusion in any of the compendia" listed in the Medicaid Act. 42 U.S.C. § 1396r-8(k)(6); *see also id*. § 1396r-8(g)(1)(B)(i) (listing three compendia, one of which is DRUGDEX). Thus, for purposes of determining

[38] Conversely, nothing in the Medicaid Act prohibits states from covering FDA-approved drugs when they are prescribed for a use that is not FDA-approved or supported by citation in a compendium.

medical need for a prescription drug under the Medicaid Act, a use that is FDA-approved stands on equal footing with a use that is supported by citation in a compendium. *See Edmonds v. Levine*, 417 F. Supp. 2d at 1337 (holding that AHCA cannot "substitute its own judgment for that of Congress" and deny coverage for uses of a prescription drug that are supported by citation in a compendium).

Here, citations in DRUGDEX support the use of various forms of testosterone (testosterone, testosterone cypionate, testosterone enanthate, and testosterone undecanoate) and estrogen (estradiol, estradiol cypionate, estradiol valerate) to treat gender dysphoria. (Ex. 25, DRUGDEX, Testosterone, at 18-21, 23-26, 29-36 (ECF 175-25); Ex. 26, DRUGDEX, Estradiol, at 23-25, 27-28, 34-35 (ECF 175-26).) *See Dobson v. Sec'y of Health & Hum. Servs.*, 2022 WL 424813 at *7 (11th Cir. 2022) (interpreting the phrase "supported by one or more citations" in § 1396r-8(k)(6) to mean a citation "tend[s] to show or help[s] prove the efficacy and safety of the prescribed off-label use"). But while that use is on par with any FDA-approved use for purposes of Medicaid coverage, Florida only covers testosterone for FDA-approved indications. (*See* Ex. 27, AHCA, *Prior Authorization Criteria, Testosterone (non-injectable formulations)* (revised March 13, 2023) (ECF 175-27) (limiting coverage to beneficiaries with hypogonadism); Ex. 25, DRUGDEX, Testosterone, at 10-11 (listing the FDA-approved indication as hypogonadism).) What is more, as a matter of practice, AHCA covers testosterone cypionate,

testosterone enanthate, and estrogen for ***absolutely any use*** – whether the use is FDA-approved, supported by citation in a compendium, or not – other than to treat gender dysphoria. (*See* AHCA, Preferred Drug List Effective Jan. 1, 2023, *available at* https://ahca.myflorida.com/content/download/8681/file/ PDL.pdf (indicating that AHCA does not require prior authorization for testosterone cypionate, testosterone enanthate, or any form of estradiol); Ex. 28, Agency Responses to Plaintiffs' Questions (3/1/2023) (ECF 175-28) (indicating that for drugs that do not require prior authorization, AHCA "does not verify the diagnosis" prior to providing coverage).) Thus, AHCA is excluding coverage for only one "medically accepted indication" (gender dysphoria) and providing coverage for every other indication, even those that are not medically accepted. By failing to provide "comparable services for individuals with comparable needs," AHCA is plainly violating the Medicaid Act. *Cota*, 688 F.Supp.2d at 993.

III. The Challenged Exclusion violates Section 1557 of the Affordable Care Act.

An "important component of the ACA's effort to ensure the prompt and effective provision of health care to all individuals . . . is the statute's express anti-discrimination mandate" in Section 1557. *Whitman-Walker Clinic, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 485 F.Supp.3d 1, 11 (D.D.C. 2020), *appeal dismissed*, No. 20-5331, 2021 WL 5537747 (D.C. Cir. Nov. 19, 2021). Accordingly, Section 1557 requires, in relevant part, that "[a]n individual shall not, on the ground

prohibited under … title IX of the Education Amendments of 1972 (20 U.S.C. 1681 *et seq.*), … be excluded from participation in, be denied the benefits of, or be subjected to discrimination under, any health program or activity, any part of which is receiving Federal financial assistance." 42 U.S.C. § 18116(a). It is "an affirmative obligation not to discriminate in the provision of health care." *Schmitt v. Kaiser Found. Health Plan of Wash.*, 965 F.3d 945, 955 (9th Cir. 2020).

"To state a claim under this provision, a plaintiff is required to show that he or she (1) was a member of a protected class, (2) qualified for the benefit or program at issue, (3) suffered an adverse action, and (4) the adverse action gave rise to an inference of discrimination." *Griffin v. Gen. Elec. Co.*, 752 F. App'x 947, 949 (11th Cir. 2019). Plaintiffs address each element in turn.

A. The Challenged Exclusion Discriminates Against Plaintiffs Based on Sex.

As noted above, Section 1557 prohibits discrimination "the ground prohibited under … title IX." 42 U.S.C. § 18116(a). Under Title IX, "[n]o person in the United States shall, on the basis of sex, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under … [a] program or activity receiving Federal financial assistance." 20 U.S.C. § 1681.

Here, the Challenged Exclusion discriminates based on sex in three distinct ways. First, the Challenged Exclusion speaks in explicit gendered terms and *facially discriminates* based on sex. Second, the Challenged Exclusion discriminates based

on sex stereotypes relating to a person's sex assigned at birth. And third, the Challenged Exclusion discriminates based on sex because it discriminates based on transgender status.

1. The Challenged Exclusion facially discriminates based on sex.

On its face, the Challenged Exclusion discriminates based on sex. The Challenged Exclusion explicitly precludes Medicaid coverage for "services for the treatment of *gender* dysphoria," including "*[s]ex* reassignment surgeries" and any "procedures that alter primary or secondary *sexual* characteristics." Fla. Admin. Code. R. 59G-1.050(7)(2022). "A facial inquiry is what it sounds like: a review of the language of the policy to see whether it is facially neutral or deals in explicitly racial or gendered terms.'" *Kadel v. Folwell*, 2022 WL 3226731, at *18 (M.D.N.C. Aug. 10, 2022) (cleaned up).

Here, one cannot "'try writing out instructions' for which treatments are excluded 'without using the word[] … sex (or some synonym).'" *Kadel*, 2022 WL 3226731, at *19 (quoting *Bostock*, 140 S. Ct. at 1746). "It can't be done." *Bostock*, 140 S. Ct. at 1746. It is impossible to determine whether a particular treatment is for "*gender* dysphoria,"[39] leads to ""*[s]ex* reassignment," or "alter[s] primary or secondary *sexual* characteristics"—and thus, whether the Exclusion applies—

[39] Gender dysphoria necessarily considers an individual's sex assigned at birth. *See* Statement of Facts § III(A)-(B)

without comparing the member's sex assigned at birth before the treatment to how it might be impacted by the treatment. *Kadel*, 2022 WL 3226731, at *19. Moreover, when "the trigger for application of the Exclusion and a denial of coverage [is] a diagnosis of 'gender dysphoria,'" the Exclusion facially discriminates based on sex. *C.P. by & through Pritchard v. Blue Cross Blue Shield of Illinois*, 2022 WL 17788148, at *6 (W.D. Wash. Dec. 19, 2022). "Gender dysphoria cannot be understood without referencing sex or a synonym." *Kadel v. Folwell*, 2022 WL 11166311, at *4 (M.D.N.C. Oct. 19, 2022).

This result is supported by a barrage of case law looking at similar exclusions. *See*, *e.g.*, *Fain v. Crouch*, 618 F.Supp.3d 313, 327 (S.D.W. Va. 2022); *Fletcher v. Alaska*, 443 F.Supp.3d 1024, 1027, 1030 (D. Alaska 2020); *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1019-22 (W.D. Wis. 2019); *Boyden v. Conlin*, 341 F.Supp.3d 979, 1002-03 (W.D. Wis. 2018). *Cf. Brandt by & through Brandt v. Rutledge*, 2022 WL 3652745, at *2 (8th Cir. Aug. 25, 2022) (finding a state law banning gender-affirming care for minors discriminates on the basis of sex).

Take *Kadel v. Folwell*, for example. In *Kadel*, the plan at issue "exclude[d] "[t]reatment or studies leading to or in connection with *sex* changes or modifications and related care." 2022 WL 3226731, at *19 (emphasis in original). As such, the court concluded that the plan's exclusion "facially discriminate[s] based on sex" and

"necessarily rests on a sex classification because it cannot be stated or effectuated without referencing sex." *Kadel*, 2022 WL 3226731, at *19.

Or *Fletcher v. Alaska*, 443 F.Supp.3d 1024 (D. Alaska 2020), for example. In *Fletcher*, the Court concluded that the "defendant's policy of excluding coverage for medically necessary surgery such as vaginoplasty and mammoplasty for employees, such a[s] plaintiff, whose natal sex is male while providing coverage for such medically necessary surgery for employees whose natal sex is female is discriminatory on its face and is direct evidence of sex discrimination." *Id.* at 1030. The court found that a health plan that covers one "surgery if it reaffirms an individual's natal sex, but denies coverage for the same surgery if it diverges from an individual's natal sex … is discrimination because of sex and makes … [the] policy … facially discriminatory." *Id.*

The court in *C.P.* came to a similar conclusion. There, the health plan excluded coverage "for treatment, drugs, therapy, counseling services and supplies for, or leading to, gender reassignment surgery." *C.P.*, 2022 WL 17788148, at *2. The court found that such policy constituted sex discrimination under Section 1557. *Id.* at *6.

The Eleventh Circuit's decision in *Adams by & through Kasper v. Sch. Bd. of St. Johns Cnty.*, 57 F.4th 791 (11th Cir. 2022) (en banc), does not affect this straightforward analysis. In *Adams*, the Eleventh Circuit was concerned not with

whether the policy at issue discriminated based on sex but "whether discrimination based on biological sex necessarily entails discrimination based on transgender status." *Id.* at 809. Indeed, in *Adams*, the Eleventh Circuit found that a "bathroom policy requir[ing] 'biological boys' and 'biological girls'—in reference to their sex determined at birth—to use either bathrooms that correspond to their biological sex or sex-neutral bathrooms," *id.* at 801, facially "classifie[d] on the basis of biological sex." *Id.* at 803.[40]

Because a Medicaid beneficiary's sex (however, one defines it) plays "an unmistakable and impermissible role in the" decision to deny Medicaid coverage under the Challenged Exclusion, the Exclusion facially discriminates based on sex. *Hammons v. Univ. of Maryland Med. Sys. Corp.*, No. CV DKC 20-2088, 2023 WL 121741, at *8 (D. Md. Jan. 6, 2023) (citing *Kadel*, 2022 WL 3226731, at *28).

2. The Exclusion discriminates based on sex because it discriminates based on sex stereotypes.

The Challenged Exclusion also discriminates based on sex because it is premised on the belief that a person's *sexual* characteristics must be aligned with the person's *sex* assigned at birth. In other words, "the Exclusion implicates sex

[40] Section 1557 only incorporated the grounds and enforcement mechanisms of Title IX, not any of its exemptions or carve-outs. *See Whitman-Walker Clinic, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 485 F.Supp.3d 1, 43 (D.D.C. 2020). Thus, unlike Title IX, Section 1557 lacks express statutory and regulatory carve outs. *Adams* firmly recognizes this textual distinction. 57 F.4th at 811.

stereotyping by limiting the availability of medical transitioning, if not rendering it economically infeasible, thus requiring transgender individuals to maintain the physical characteristics of their natal sex." *Boyden*, 341 F. Supp. 3d at 997.

But excluding coverage for gender-affirming medical care because it "*alter[s]* primary or secondary *sexual* characteristics," Fla. Admin. Code R. 59G-1.050(7)(a)(4), "entrenches" the sex-stereotyped "belief that transgender individuals must preserve the genitalia and other physical attributes of their [sex assigned at birth] sex over not just personal preference, but specific medical and psychological recommendations to the contrary." *Boyden*, 341 F.Supp.3d at 997. This is a "form of sex stereotyping where an individual is required effectively to maintain his or her natal sex characteristics." *Id.*; *see also Flack*, 328 F.Supp.3d at 951 ("the Challenged Exclusion feeds into sex stereotypes by requiring all transgender individuals … to keep … sex characteristics consistent with their natal sex no matter how painful and disorienting it may prove for some"). It "is textbook sex discrimination." *Kadel*, 2022 WL 3226731, at *19.

Accordingly, courts throughout the country have found similar discrimination against transgender people to be rooted in impermissible sex stereotyping. *See*, *e.g.*, *Kadel v. Folwell*, 446 F.Supp.3d 1, 14 (M.D.N.C. 2020) (exclusion "tethers Plaintiffs to sex stereotypes which, as a matter of medical necessity, they seek to reject"); *Toomey v. Arizona*, 2019 WL 7172144, at *6 (D. Ariz. Dec. 23, 2019)

("Discrimination based on the incongruence between natal sex and gender identity—which transgender individuals, by definition, experience and display—implicates … gender stereotyping.").

This principle is also in keeping with longstanding Eleventh Circuit precedent that "[a]ll persons, whether transgender or not, are protected from discrimination on the basis of [a sex stereotype]." *Adams,* 57 F.4th at 813 (quoting *Glenn v. Brumby,* 663 F.3d 1312, 1318-19 (11th Cir. 2011)). *Adams* does not change this result. In *Adams*, the Court found the sex stereotyping claim not viable because "bathroom policy does not depend in any way on how students act or identify" and the "bathroom policy separates bathrooms based on biological sex, which is not a stereotype." *Adams*, 57 F.4th at 809. Here, by contrast, the Challenged Exclusion hinges on prohibiting coverage for procedures that "*alter* primary or secondary *sexual* characteristics," Fla. Admin. Code R. 59G-1.050(7)(a)(4), and "services for the treatment of *gender* dysphoria," Fla. Admin. Code, *id.* at (7)(a), which by definition refers to the psychological distress that results from an *incongruence between one's sex assigned at birth and one's gender identity*. (See Ex. 7, Karasic ¶¶ 24-25 (ECF 175-7); Ex. 8, Olson-Kennedy at 10-11 ¶¶ 7-9 (ECF 175-8); Ex. 9, Shumer ¶ 36 (ECF 175-9); Ex. 10, Schechter ¶ ¶ 20-21 (ECF 175-10); *see also* Ex. 33, DSM 5 Gender Dysphoria (ECF 175-33).)

3. The Exclusion discriminates based on sex because it discriminates based on transgender status.

In *Bostock*, the Supreme Court explained that "it is impossible to discriminate against a person for being … transgender without discriminating against that individual based on sex." 140 S.Ct. at 1741. And it is settled law that a policy that discriminates based on conduct or characteristics that either define or are closely correlated with a particular group facially discriminates against that group. *See*, *e.g.*, *Christian Legal Soc'y v. Martinez*, 561 U.S. 661, 689 (2010) (holding that a club's exclusion of people because they engaged in same-sex conduct was discrimination based on sexual orientation); *Lawrence v. Texas*, 539 U.S. 558, 583 (2003) (O'Connor, J., concurring) (stating that a law targeting conduct "closely correlated with being homosexual" is "directed toward gay persons as a class").

Here, not only is gender dysphoria exclusively suffered by transgender people, *see* Statement of Facts § III(A)-(B), *supra*; *Fain*, 618 F. Supp. 3d at 325 ("[A] person cannot suffer from gender dysphoria without identifying as transgender."); *see also C.P.*, 2022 WL 17788148, at *6; *Kadel II*, 2022 WL 11166311, at *4, but the medical care singled out by the Exclusion—treatment to "*alter* primary or secondary *sexual* characteristics," Fla. Admin. Code R. 59G-1.050(7)(a)(4)—is medical care that only transgender people need or seek. *See Fain*, 618 F.Supp.3d at 327 ("Only individuals who identify as transgender would seek 'transsexual surgery'"); *Toomey*, 2019 WL 7172144, at *6 (finding that similar

exclusion "singles out transgender individuals for different treatment" because "transgender individuals are the only people who would ever seek gender reassignment surgery"); *Flack*, 328 F.Supp.3d at 950 ("expressly *singles out* and bars a medically necessary *treatment solely for transgender people*" (emphasis added)).

It should therefore come as no surprise that courts have held that "[d]iscrimination against individuals suffering from gender dysphoria is also discrimination based on sex and transgender status." *Kadel*, 2022 WL 3226731, at *20; *C.P.*, 2022 WL 17788148, at *6. Thus, the Challenged Exclusion discriminates based on transgender status and as such, discriminates based on sex.

B. As Medicaid beneficiaries, Plaintiffs qualified for the health program at issue: Medicaid.

Each plaintiff is enrolled in Medicaid and has received coverage for medically necessary gender-affirming medical services. (ECF 120-6, Brackett Feb. 8 Dep. at 243:16-245:10, 246:15-247:6, 247:9-20; ECF 11-6, Dekker ¶ 17; ECF 11-7, Rothstein ¶ 12; ECF 11-8, Doe ¶ 19; ECF 11-9, Ladue ¶ 20.) And lest there be any doubt, Section 1557 unquestionably applies to AHCA, who receives federal financial assistance from HHS. (ECF 197, at 6 ¶ 4.) Indeed, multiple courts have applied Section 1557 to state-administered Medicaid programs. *See, e.g.*, *Fain*, 618 F. Supp. 3d at 331; *Flack*, 328 F.Supp.3d at 949; *Cruz v. Zucker*, 195 F.Supp.3d 554, 571 (S.D.N.Y. 2016).

C. Plaintiffs have suffered an adverse action, that gives rise to an inference of discrimination.

As to the third element, Plaintiffs suffered an "adverse action" due to the Challenged Exclusion. Because of the Challenged Exclusion, Plaintiffs have lost Medicaid coverage for necessary medical treatment recommended by their doctors that would otherwise be covered. (*See* ECF 11-6, Dekker ¶ 23; ECF 11-7, Rothstein ¶¶ 19-20; ECF 11-8, Doe ¶ 29; ECF 11-9, Ladue ¶ 30.) *See also C.P.*, 2022 WL 17788148, at *6.

As to the fourth element, Defendants promulgated the Challenged Exclusion with discriminatory intent to achieve a discriminatory effect. The Challenged Exclusion bans coverage of medically necessary care for the treatment of gender dysphoria, which only transgender persons experience. *See also Kadel*, 2022 WL 3226731, at *20.

Moreover, where the state "intentionally penalizes a person identified as male at birth for . . . actions that it tolerates in [someone] identified as female at birth"—here, pursuing medical intervention to affirm a female identity—"sex plays an unmistakable and impermissible role." *Bostock*, 140 S.Ct. at 1741-42. Put another way, whether coverage is prohibited turns explicitly on a person's sex assigned at birth.

IV. Defendants' Challenged Exclusion Violates Equal Protection.

When government differentiates, as the State has done here, based on sex and/or transgender status, its line-drawing triggers heightened scrutiny.

A. The Challenged Exclusion Classifies Based on Sex.

As articulated above, the Challenged Exclusion (1) *facially discriminates* based on sex; (2) discriminates based on sex stereotypes relating to a person's sex assigned at birth; and (3) discriminates based on sex because it discriminates based on transgender status. *See* Legal Argument § III(A), *supra*.

The fact that one sex is not categorically treated worse than another does not change the fact that the law discriminates based on sex for purposes of equal protection. "[T]he Equal Protection Clause, extending its guarantee to 'any person,' reveals its concern with rights of individuals, not groups." *J.E.B.* v. *Alabama ex rel. T.B.*, 511 U.S. 127, 152 (1994) (Kennedy, J., concurring) (cleaned up); *see also Loving v. Virginia*, 388 U.S. 1, 8 (1967) (rejecting "the notion that the mere 'equal application' of a statute containing racial classifications is enough to remove the classifications from the Fourteenth Amendment's proscription of all invidious racial discriminations"); *Waters v. Ricketts*, 48 F.Supp.3d 1271, 1282 (D. Neb. 2015) ("The 'equal application' of [bans on same-sex marriage] to men and women as a class does not remove them from intermediate scrutiny"), *aff'd on other grounds*, 798 F.3d 682 (8th Cir. 2015).

Defendants have argued that the law does not facially classify on the basis of sex or transgender status, citing the Supreme Court's decision in *Geduldig* v. *Aiello*, 417 U.S. 484 (1974). But Defendants' reliance on *Geduldig* is misplaced for three distinct reasons:

First, the Exclusion explicitly and facially classifies based on sex. *See Fletcher*, 443 F.Supp.3d at 1027, 1030; *see also Whitaker v. Kenosha Unified Sch. Dist. No.1 Bd. of Educ.*, 858 F.3d 1034, 1051 (7th Cir. 2017). Every person to whom the Challenged Exclusion applies is therefore discriminated against because of sex.

Second, *Geduldig* only held that an exclusion of pregnancy from a disability benefits program with no showing of "pretext" is not *per se* "discrimination against the members of one sex." 417 U.S. at 496 n.20. But "[s]ome activities may be such an irrational object of disfavor that, if they are targeted, and if they also happen to be engaged in exclusively or predominantly by a particular class of people, an intent to disfavor that class can readily be presumed." *Bray v. Alexandria Women's Health Clinic*, 506 U.S. 263, 270 (1993). Here, the Exclusion was designed to categorically exclude gender-affirming care from coverage—care "which is only sought by transgender individuals." *Brandt v. Rutledge*, 2021 WL 3292057, at *2 (E.D. Ark. Aug. 2, 2021). That is precisely what *Geduldig* and *Bray* prohibit: a pretextual classification designed to effectuate discrimination.

Third, the centrality of gender transition to transgender identity distinguishes this case from *Geduldig*. Unlike the pregnancy exclusion in *Geduldig*, the Exclusion here is based on a characteristic that defines membership in the excluded group. Pregnancy is not the defining characteristic of a woman. Living in accord with one's gender identity rather than birth-assigned sex is the defining characteristic of a transgender person. *See*, *e.g.*, *Glenn*, 663 F.3d at 1316.

Defendants have also argued that that *Adams* held that "sex-based discrimination is discrimination based on biological sex" and that the Exclusion "does not make a distinction based on biological sex." (ECF 120 at 32.) Not so, *see supra*. But even when viewed in that (incorrect) framing, the Exclusion discriminates based on sex. That is because the Exclusion prohibits coverage of procedures that ""*alter* primary or secondary *sexual characteristics*." Fla. Admin. Code R. 59G-1.050(7). Such characteristics are biological.

Defendants further argue that rational basis applies because the Exclusion purportedly discriminates not based on sex, but on "medical diagnosis." (ECF 120 at 32.) But this does not save the Challenged Exclusion, either. Federal courts have rejected Defendants' attempt "to frame the Exclusion as one focused on medical diagnoses, not … gender." *Kadel*, 446 F.Supp.3d at 18. And only transgender people need coverage for "services and treatment for *gender dysphoria*" because

only transgender people are diagnosed with gender dysphoria. *See C.P.*, 2022 WL 17788148, at *6; *Kadel II*, 2022 WL 11166311, at *4; *Fain*, 618 F.Supp.3d at 325.

B. The Challenged Exclusion Classifies Based on Transgender Status and Therefore Independently Triggers Heightened Scrutiny.

As articulated above, the Challenged Exclusion discriminates based on transgender status. *See* Legal Argument § III(A)(3), *supra*. Such discrimination based on transgender status is separately entitled to, at least, heightened scrutiny. *See Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 607 (4th Cir. 2020), as amended (Aug. 28, 2020); *see also Karnoski v. Trump*, 926 F.3d 1180, 1200 (9th Cir. 2019).

In identifying whether a classification is suspect or quasi-suspect, courts consider whether: (a) the class has historically been "subjected to discrimination," *Bowen v. Gilliard*, 483 U.S. 587, 602 (1987); (b) the class's defining characteristic "bears [any] relation to ability to perform or contribute to society," *City of Cleburne,* 473 U.S. at 440-41; (c) the class exhibits "obvious, immutable, or distinguishing characteristics that define them as a discrete group," *Gilliard*, 483 U.S. at 602; and (d) the class is "a minority or politically powerless." *Id.*

All indicia are present for transgender people. "[T]ransgender people as a class have historically been subject to discrimination or differentiation; … they have a defining characteristic that frequently bears no relation to an ability to perform or contribute to society; … as a class they exhibit immutable or distinguishing

characteristics that define them as a discrete group; and … as a class, they are a minority with relatively little political power." *Evancho v. Pine-Richland Sch. Dist.*, 237 F.Supp.3d 267, 288 (W.D. Pa. 2017).[41]

History of discrimination. "There is no doubt that transgender individuals historically have been subjected to discrimination on the basis of their gender identity, including high rates of violence and discrimination in education, employment, housing, and healthcare access." *Grimm*, 972 F.3d at 611 (citation omitted). As the Fourth Circuit detailed in *Grimm*, there is extensive data documenting the staggering discrimination that transgender people face in all aspects of life. *Id.* at 611-12. This pattern of discrimination is long-standing, including through formal governmental action. Expression of a person's transgender identity was criminalized for much of the nineteenth and twentieth centuries through cross-dressing laws. *See* Jennifer Levi & Daniel Redman, *The Cross-Dressing Case for Bathroom Equality*, 34 SEATTLE U. L. REV. 133, 152-53, 171 (2010). More recently, Congress explicitly excluded transgender people from protection under four civil rights statutes over the past thirty years. *See* Kevin M. Barry et al., *A Bare Desire to*

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[41] Although there is record evidence related to some of these factors, when courts decide the legal question of what level of equal protection scrutiny applies to a classification, they are not confined to record evidence presented by the parties. *See, e.g., Frontiero v. Richardson*, 411 U.S. 677, 684-86 (1973) (referencing diverse sources including history books and law review articles in its analysis supporting its conclusion that classifications based on sex are inherently suspect); *Grimm*, 972 F.3d at 611-12 (referencing congressional records and law review articles).

Harm: Transgender People and the Equal Protection Clause, 57 B.C. L. REV. 507, 556-57 (2016). The record is replete with evidence of this discrimination. *See* Statement of Facts § II, *supra*.

Defining characteristic that bears no relation to the ability to contribute to society. Transgender people have a defining characteristic that "bears no relation to ability to perform or contribute to society." *See Cleburne*, 473 U.S. at 441. The relevant question is not whether every person in the class is the same but rather whether they share a characteristic that "tend[s] to be irrelevant to any proper legislative goal." *Plyler* v. *Doe*, 457 U.S. 202, 216 n.14 (1982). Transgender people share the defining characteristic of having a gender identity that does not align with their birth-assigned sex. *See* Statement of Facts, § III(A)-(B), *supra*. And "[s]eventeen of our foremost medical, mental health, and public health organizations agree that being transgender implies no impairment in judgment, stability, reliability, or general social or vocational capabilities." *Grimm*, 972 F.3d at 612 (quotation marks omitted). (*See also* Ex. 7, Karasic ¶¶ 26, 35 (ECF 175-7).)

Obvious, immutable, or distinguishing characteristics. There is no requirement that a characteristic be immutable in a literal sense in order to trigger heightened scrutiny. For example, heightened scrutiny applies to classifications based on alienage and "illegitimacy" even though both classifications are subject to change. *Windsor*, 699 F.3d at 183 n.4; *see Nyquist* v. *Mauclet*, 432 U.S. 1, 9 n.11

(1977) (rejecting argument that alienage did not deserve strict scrutiny because it was mutable). "Rather than asking whether a person *could* change a particular characteristic, the better question is whether the characteristic is something that the person *should* be required to change [in order to avoid government discrimination] because it is central to a person's identity." *Wolf* v. *Walker*, 986 F.Supp.2d 982, 1013 (W.D. Wis. 2014) (emphasis in original), *aff'd sub nom*, *Baskin* v. *Bogan*, 766 F.3d 648 (7th Cir. 2014); *see also Latta* v. *Otter*, 771 F.3d 456, 464 n.4 (9th Cir. 2014). "A transgender person's awareness of themselves as male or female is no less foundational to their essential personhood and sense of self than it is for those [who are not transgender]." *Grimm*, 972 F.3d at 624 (Wynn, J., concurring). A person's gender identity is a core part of who they are is not something that can be changed voluntarily or by external forces. (*See* Ex. 8, Olson-Kennedy at 8 ¶¶ 1-2 (ECF 175-8); Ex. 9, Shumer ¶ 29-33 (ECF 175-9); Ex. 7, Karasic ¶ 23 (ECF 175-7).)

Political powerlessness. The final factor concerns whether the class of persons is "in a position to adequately protect themselves from the discriminatory wishes of the majoritarian public." *Windsor*, 699 F.3d at 185. As evidenced by the over 500 legislative bills targeting them for discrimination in the first few months of 2023 alone,[42] transgender people are not in such a position.

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[42] Trans Legislation Tracker, 2023 anti-trans bills tracker, https://translegislation.com/ (last visited Apr. 28, 2023).

As such, numerous courts have reached the conclusion that classifications based on transgender status are subject to, at least, heightened scrutiny. *See, e.g.*, *Grimm*, 972 F.3d at 607; *Karnoski*, 926 F.3d at 1200; *Flack*, 328 F.Supp.3d at 951–53; *M.A.B. v. Bd. of Educ. of Talbot Cnty.*, 286 F.Supp.3d 704, 718–22 (D. Md. 2018); *Evancho*, 237 F.Supp.3d at 288; *Norsworthy v. Beard*, 87 F.Supp.3d, 1104, 1119 (N.D. Cal. 2015).

Defendants argue that *Adams* precludes this conclusion. They are wrong. Defendants misconstrue the reach of the *Adams* case again in their assertion that the court "explained what constitutes unconstitutional discrimination based on transgender status." (Mot. at 32.) But the *Adams* court did no such thing. True, the *Adams* court expressed in *dicta* "doubt that transgender persons constitute a quasi-suspect class" because "the Supreme Court has rarely deemed a group a quasi-suspect class." 57 F.4th at 803 n.5. But that does not mean that "[t]ransgender individuals [] aren't entitled to heightened constitutional review per se." (ECF 120 at 33.)

"The novelty of an issue does not doom it to failure," however. *Nonhuman Rts. Project, Inc. v. Breheny*, 197 N.E.3d 921, 937 (2022) (Wilson, J., dissenting). Indeed, "a novel habeas case freed an enslaved person" and "a novel habeas case removed a woman from the subjugation of her husband." *Id.* The argument "'this has never been done before' … is an argument against all progress, one that flies in

the face of legal history." *Id.* "The correct approach is not to say, 'this has never been done' and then quit, but to ask, 'should this now be done even though it hasn't before, and why?'" *Id.*

C. Defendants Engaged in Purposeful Discrimination.

Defendants must "treat all persons similarly situated alike" or "avoid all classifications that … that reflect a 'bare desire to harm a politically unpopular group.'" *Glenn*, 663 F.3d at 1315 (quoting *City of Cleburne v. Cleburne Living Ctr., Inc.*, 473 U.S. 432, 446-47 (1985)).

While a showing of intentional discrimination is unnecessary in this case given that the Challenged Exclusion is facially discriminatory, *see Cmty. Servs., Inc. v. Wind Gap Mun. Auth.*, 421 F.3d 170, 177 (3rd Cir. 2005), here, the Challenged Exclusion purposefully discriminates against transgender people.

Determining discriminatory intent is guided by an eight-factor test. *See League of Women Voters of Fla., Inc. v. Fla. Sec'y of State*, 32 F.4th 1363, 1373 (11th Cir. 2022) (cleaned up). Here, most of the factors are either met or there is a genuine dispute of material fact as to their presence.

- *The impact of the challenged law*: "[T]he Exclusion impacts only transgender individuals—that provides some circumstantial evidence of intentional discrimination." *Lange v. Houston Cnty., Georgia*, 608 F.Supp.3d 1340, 1355 (M.D. Ga. 2022) ("*Lange II*"). *See also supra*.

- *The historical background:* Here, Florida Medicaid covered medical treatment for gender dysphoria, until 2022, when Florida's government enacted or adopted a blizzard of anti-LGBTQ laws. This includes restrictions on the coverage and provision of gender-affirming care, "Don't Say or Trans" laws, banning of books discussing LGBTQ identities, bans on drag performances, and more. *See* Statement of Facts § II, *supra*. (ECF 1, Compl. at ¶¶126(a)-(f).)
- *The specific sequence of events leading up to its passage:* Plaintiffs have laid out circumstantial evidence concerning this factor, including the coordination with the Governor's Office, FDOH, and anti-transgender activists. *See* Statement of Facts § VI(B), *supra*;
- *Procedural and substantive departures:* Plaintiffs have documented a litany of procedural and substantive departures, including but not limited to AHCA: (1) hiring of outside consultants, which AHCA had never done for a GAPMS (ECF 120-6, Brackett Feb. 8 Dep., at 137:10-12, 139:17-138:3), and all of the consultants retained opposed gender-affirming care (Ex. 324, Yale Comment, at 7-9 (ECF 183-27); (2) not enlisting or even considering any consultant supporting the provision of gender-affirming care (ECF 120-9, Dalton Dep., at 112:5-23); (3) employing a GAPMS process for a treatment already covered, which was unprecedented (ECF

120-6, Brackett Feb. 8 Dep. at 93:13-21); (4) bypassing the employees typically tasked with conducting GAPMS processes (ECF 120-9, Dalton Dep. at 85:16-19); (5) "dismiss[ing] the professional organizations and experts that [AHCA] frequently cited before" (Br. Ex. 2, English Dep. at 154:6-13); and (6) closely coordinating with and having the process originate from other agencies like FDOH and the Governor's Office. (ECF 120-6, Brackett Feb. 8 Dep., at 89:18-19, 90:25-91:1, 92:2-4; Br. Ex. 2, English Dep. at 154:8-19; Ex. 302, 6/27/2022 email from English to Cogle (ECF 183-4).)

- *The contemporary statements and actions of key legislators:* Plaintiffs have pointed to some of these disturbing and offensive statements. Statement of Facts § II, *supra*. (ECF 1, Compl., ¶126(g).)
- *The foreseeability of the disparate impact and knowledge of that impact:* Not only was the impact on transgender Medicaid beneficiaries foreseeable, but it was also communicated to Defendants during the notice-and-comment process. (Ex. 323, Endocrine Soc. Comment, at 6 (ECF 183-26); Ex. 324, Yale Comment, at 2 (ECF 183-27); Ex. 325, AAP Public Comment, at 3-4 (ECF 183-28).)[43]

[43] *See also* NHELP Public Comment, *available at* https://static1.squarespace.com/static/6283b20d7013340d81fd360f/t/644c7c3e38b786135741e3f0/1682734142446/FHJP+%2B+NHeLP+Comments+on+Rule+59G-1050.pdf; Lamba Legal Public

- *The availability of less discriminatory alternatives*: "There is no evidence [Defendants] considered less discriminatory alternatives." *Lange II*, 608 F.Supp.3d at 1356.

Thus, when it comes to whether Defendants engaged in purposeful discrimination, "the facts are hotly disputed," at least. *Lange II*, 608 F.Supp.3d at 1356.

D. The Challenged Exclusion Cannot Survive Heightened Scrutiny

The Challenged Exclusion targeting transgender Medicaid beneficiaries demands meaningful review. Arguably, it is subject to the onerous strict scrutiny standard, wherein Defendants must show that the Challenged Exclusion is narrowly tailored to advance a compelling state interest. *Adarand Constructors, Inc. v. Peña*, 515 U.S. 200, 227 (1995). Even under the heightened scrutiny required for all sex-based classifications, Defendants carry the heavy burden of showing that the Challenged Exclusion is substantially related to an important government interest, and that they had an "exceedingly persuasive" justification for it. *Glenn*, 663 F.3d at 1321; *see also, e.g.*, *VMI*, 518 U.S. at 533. Under both standards, the "burden of justification is demanding and [] rests entirely on the State," and constitutionality is

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Comment, *available at* https://static1.squarespace.com/static/6283b20d7013340d81fd360f/t/644c7c560af479331dbb642b/1682734166584/Lambda+Legal+Comments+Regarding+Changes+to+Florida+Medicaid+Coverage+2022.07.08+-+Copy.pdf ; Southern Legal Counsel Public Comment, *available at* https://static1.squarespace.com/static/6283b20d7013340d81fd360f/t/644c7c11c861fa5a60881a4d/1682734097281/SLC+Final+Comment+-+Medicaid+Proposed+Rule.pdf.)

judged based on the "the actual state purposes, not rationalizations for actions in fact differently grounded." *VMI*, 518 U.S. at 533, 535-36.

Here, the Challenged Exclusion cannot meet either standard. To the extent that Defendants contend the Challenged Exclusion is justified because gender-affirming care is allegedly "experimental" and "investigational," that conclusion is contradicted by the evidence. *See* Statement of Facts § IV(C), *supra*; Legal Argument § I, *supra*. The Court cannot simply accept Defendants' *ipse dixit* that gender-affirming medical treatments are "experimental" and "investigational" because "[t]he Court retains an independent constitutional duty to review factual findings where constitutional rights are at stake." *Gonzales* v. *Carhart*, 550 U.S. 124, 165 (2007).

As articulated above (Facts § IV(C)(4), *supra*), Defendants cannot carry their burden to justify the Challenged Exclusion based on purported concerns about the quality of the evidence concerning treatment. While Defendants baldly assert that this well-established treatment is "experimental," the medical and scientific evidence in the record shows the opposite and Plaintiffs refer the Court to Section I of the Argument where they articulate why under *Rush*.

Defendants rely on a claimed absence of long-term longitudinal studies and randomized clinical trials assessing safety and efficacy of gender-affirming care. These kinds of studies are not the only type of studies upon which the medical

profession relies on to determine the safety and efficacy of treatments. (Ex. 12, Olson-Kennedy ¶¶ 70-90 (ECF 175-12).) In the context of pediatric medicine, the body of research is less likely to use randomized trials than is clinical research for adults, and, at times, it is unethical to conduct such randomized trials.[44] (Ex. 5, Antommaria, ¶¶ 24-27 (ECF 175-5); Ex. 12, Olson-Kennedy, ¶¶ 74-77 (ECF 175-12).) For similar reasons, researchers rarely use randomized clinical trials for surgical treatments. (Ex. 13, Schechter ¶ 8 (ECF 175-13).) Thus, if AHCA were to exclude from Medicaid coverage all treatment unsupported by randomized clinical trials, it would have to exclude much of pediatric medicine and many surgical procedures.

If limiting Medicaid coverage to treatments supported by certain kinds of medical research, such as randomized clinical trials, somehow advanced a government interest in individual patients' well-being, then Defendants would have to require that standard to be met for all treatments, but it does not. *See Eisenstadt*, 405 U.S. at 452. AHCA cannot provide any rational explanation—much less an

[44] Requiring use of randomized trials to justify a medical intervention would be unethical because it would require doctors to disregard substantial evidence demonstrating the safety and efficacy of medical treatments and deny patients treatments that are known to provide relief for their medical conditions. Moreover, even if this demand were legitimate, an exclusion of coverage for treatment would prohibit any additional research, thereby undermining any purported desire for further study.

"exceedingly persuasive" one—to justify subjecting only gender-affirming care to this unique burden. *VMI*, 518 U.S. at 533.

Indeed, Defendants cannot establish any reputable scientific or medical support for the Challenged Exclusion, let alone an "exceedingly persuasive" justification, *VMI*, 518 U.S. at 531, or one "narrowly tailored to a compelling state interest." *Adarand*, 515 U.S. at 235.

The Challenged Exclusion cannot even withstand deferential "rational basis" review. Under rational basis, the classification must be rationally related to a legitimate state interest. *City of Cleburne*, 473 U.S. at 440. States must "avoid all classifications that are arbitrary or irrational and those that reflect a bare … desire to harm a politically unpopular group." *Glenn*, 663 F.3d at 1315 (cleaned up). Here, as articulated in Section IV(C) of the Argument, Defendants have chosen to exclusively single out transgender Medicaid beneficiaries for exclusion of coverage. The Challenged Exclusion targets only transgender beneficiaries and their medical care alone for unequal treatment. *See Kadel*, 2022 WL 3226731, at *20 ("Discrimination against individuals suffering from gender dysphoria is also discrimination based on sex and transgender status."); *Toomey*, 2019 WL 7172144, at *6 (noting exclusion "singles out transgender individuals for different treatment" because "transgender individuals are the only people who would ever seek gender reassignment surgery").

As such, the Challenged Exclusion violates the Equal Protection Clause.

CONCLUSION

For the foregoing reasons, the record shows that Plaintiffs should prevail on the merits of each of their statutory and constitutional claims and are entitled to a declaratory judgment and permanent injunctive relief against the Challenged Exclusion.

Respectfully submitted this 28th day of April 2023.

/s/ Chelsea Dunn
Chelsea Dunn

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CERTIFICATE OF SERVICE

I hereby certify that on this 28th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Chelsea Dunn
Counsel for Plaintiffs

TAB 199-1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION
CASE NO.: 4:22-CV-00325-RH-MAF

AUGUST DEKKER, et al.,

Plaintiff,

vs.

JASON WEIDA, et al.,

Defendant.
_____/

REMOTE ZOOM-RECORDED DEPOSITION OF

AUGUST DEKKER

VOLUME 1
Pages 1 through 35

Thursday, January 26, 2023

10:02 a.m. - 10:54 p.m.

Location: Phipps Reporting
20 N. Orange Avenue, Suite 700
Orlando, Florida 32801

STENOGRAPHICALLY REPORTED BY
SANDRA NARUP
RPR, RSA, FPR-C

Job No.: 291657

Q. And have you taken Prednisone?
A. Yes.
Q. You still take it?
A. No.
Q. What about tocilizumab, T-O-C-I-L-I-Z-U-M-A-B?
MR. CHARLES: Sorry. Gary, can you spell that again more slowly?
MR. PERKO: Sure. T-O-C-I-L-I-Z-U-M-A-B.
A. I believe that's my Actemra, so, yes.
BY MR. PERKO:
Q. You still take it?
A. Yes.
Q. Did the provider at Metro Inclusive Health, or whoever prescribed these drugs, advise you of any essential adverse effects of taking these medications at the same time as testosterone?
A. No. But I worked closely with my rheumatologist to avoid these risks.
Q. So your rheumatologist explained the risks associated with taking these medications at the same time as testosterone?
A. Yes, I was made aware of it.
Q. Have you been told by any of your healthcare providers that celecoxib increases the risk of cardiovascular disease?

A. I believe so.
Q. Do you happen to know the M.D.'s name?
A. No, I do not.
Q. When you were prescribed -- first prescribed testosterone, were you advised of the risks and benefits of taking that hormone?
MR. CHARLES: Objection. Asked and answered.
You can answer.
A. Yes, I was.
BY MR. PERKO:
Q. Had you been informed by any of your healthcare providers that the warning label for testosterone says that it may cause liver problems?
A. No.
Q. Do you know if your liver tests are being monitored by the prescriber of testosterone?
A. They're being monitored by my rheumatologist every eight weeks.
Q. Have you been told that doses of testosterone used to treat gender dysphoria can lead to high red blood cell counts?
MR. CHARLES: Sorry. Can you say that again, Gary? I couldn't hear you.
MR. PERKO: Sure.
BY MR. PERKO:

A. Benefits included increased body hair, deepened voice, enlargement of the clitoris, increased body and facial hair, increased muscle tone. Probably a few other things I'm forgetting.

Q. Okay. What benefits have you experienced from taking testosterone?

A. My mental health has significantly improved since I -- well, whenever I'm on testosterone, I no longer have any suicidal ideations, I am generally the most stable and happy I have ever been.

Q. Earlier today, Mr. Perko asked about a hospital visit in January of 2019. Is that correct?

A. Yes.

Q. And you responded -- I'm paraphrasing here -- that that was related to an unsupportive, abusive partner. Is that correct?

A. Yes.

Q. Were there other reasons that caused your experience of suicidal ideation at that time?

A. My situation was complicated by the fact that I -- this was the same partner who convinced me to stop my testosterone treatment, and I was experiencing mental health issues due to not having my medication.

Q. By medication, are you referring to testosterone?

A. Yes.

Q. Earlier today -- I'm paraphrasing here -- you told Mr. Perko that there were negative effects to stopping testosterone. Is that correct?

A. Yes.

Q. Were there negative mental health effects that you experienced as well?

A. Yes.

Q. And what were some of those?

A. My social anxiety specifically was very, very high. I did not want to go outside or to leave the house because, afraid of being perceived as female.

My depression also worsened significantly, and that contributed to me not wanting to interact with the outside world.

MR. CHARLES: Okay. Unless you have anything else, Gary, I think we're okay.

MR. PERKO: I don't have anything else.

Mr. Dekker, you have the right to review the transcript of the deposition to identify any transcription errors. Would you like to do that?

THE WITNESS: Yes.

MR. PERKO: I have nothing further. Thank you for your time, Mr. Dekker.

THE CERTIFIED STENOGRAPHER: Okay. And --

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
VOLUME 9 OF 10 (Tabs 199-2 – 230-4)

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TAB 199-2

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA

CASE NO. 4:22-cv-00325-RH-MAF

AUGUST DEKKER, et al.,
Plaintiffs,
vs.
SIMONE MARSTILLER, et al.,
Defendants
_____/

DEPOSITION OF:	JEFFREY ENGLISH
AT THE INSTANCE OF:	THE PLAINTIFF
DATE:	JANUARY 23, 2023
TIME:	COMMENCED: 10:00 A.M.
LOCATION:	AGENCY FOR HEALTH CARE ADMINISTRATION 2727 MAHAN DRIVE TALLAHASSEE, FLORIDA 32308
REPORTED BY:	DANA W. REEVES Court Reporter and Notary Public in and for State of Florida at Large

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PLAINTIFF'S INDEX TO EXHIBITS

DEFENDANT'S INDEX TO EXHIBITS

NO.	DESCRIPTION	MARKED
Exhibit D1	Computer-assisted musculoskeletal surgical navigational orthopedic GAPMS	166
Exhibit D2	Blue Cross Blue Shield of Rhode Island document	167

*Uh-uh is a negative response
*Uh-huh is a positive response

that is on our fee schedule and it is --

Q Can I stop you there? When you say multiple things checked off, do you mean yes or no?

A Yes -- well, let me double-check that. Yeah. You know, if something gets checked off as a yes, you know, especially overwhelmingly so, then that would be something that we would, you know, give a really serious consideration of coverage for. And if we looked at it, and it was, you know, potentially experimental investigational, and then that's the GAPMS. And if it's, you know, yes, we should cover this, what -- you know, why don't we have this on our fee schedule kind of thing, then that would be a decision point.

Q Okay. Does a yes answer to any of these questions imply that a service is not experimental?

MR. PERKO: I'm going to object to form. You can answer.

THE WITNESS: Do answer or --

MR. PERKO: Do answer.

THE WITNESS: Okay. Well, through this form, we would discover that it's -- you know, if it's something that's already on the fee schedule that we already covered, then that would -- that would end the process immediately and we would just notify the provider, hey, we already pay for this

and move on to the next thing.
BY MS. DeBRIERE::
Q So if it was on AHCA's fee schedule --
A Then it's not and then someone -- I guess the presumption is that someone or someone somewhere along the way determined that AHCA would cover it, and that it was not a -- you know, it was not experimental investigational.
Q I'm sorry, Mr. English. Hold on one second. Just a real basic question. I see here an email address, healthserviceresearch@AHCA.myflorida.com inbox?
A Yes. That's a -- that's a -- the requesters will send in -- that's the email address to inquire about making a GAPMS request or a coverage request.
Q Who can submit a GAPMS request via the email?
A Anybody, I believe.
Q Okay. Other than the three entities you listed that typically trigger a traditional GAPMS --
A I would think of it other than the weird one with Beth and the bionic pancreas, most of the other requests would come in through health service research, you know, the provider or the manufacturer. And from time to time, you would get a phone call, usually from a salesperson and they'd want to set up a meeting. And they -- you know, they have sort of regional travel

schedules, they want to hit you up on their way through. But health service research is sort of, I guess, the basic -- getting the process started way of contacting us.

Q To your knowledge, have you ever had a request to initiate come from another state agency?

A I do not -- I'll just point out, again, I inherited a queue and I don't necessarily know where all the projects that I inherited originated.

Q So, to your knowledge --

A No.

Q And to your knowledge, has a request ever come from a member of the public?

A I'm unclear how you define that.

Q Fair.

A I mean, technically, isn't everyone a member of the public?

Q Yes. Absolutely. Have you ever had a request come in from a Medicaid recipient, to your knowledge?

A I can't say for certain. It sounds familiar, but I can't say for certain. And what I might actually be remembering is a provider requesting on behalf of Medicaid patient.

Q Okay. How about request from a political figure?

A No. That's bill analysis. That's a -- that's a different -- that's a different task.

Q Okay. To your knowledge, have you ever not used the decision tree for a traditional GAPMS request?

A When I first started, you know, but I only have -- it might have been one or two. There was a stretch where I was working with what was already in the queue, and so I don't know that this had been performed for those. I think some of them because I think Chris -- Christina, like, in order to sort of workshop this, we went through and we're like, well, this one would, you know, and this one, but it was pretty much like the newer requests going forward, and then Nick was assigned with backtracking with this, and I don't know if he got every single one in the queue or not, so that's theoretical there are GAPMS that -- for which this was not performed.

Q After the checklist was developed and it was consistently -- after December of 2020 --

A Yes.

Q -- when traditional GAPMS request was received by AHCA, did you ever not use the checklist?

A It was part of the -- it was part of the standard process. I can't say for sure that, you know, when we were working from home -- I think I had meetings

with supervisors for them, but I don't know for certain that every single request that came in went through that or not. I can't say.

Q You said it was the standard process?

A It is.

Q Okay. Is GAPMS ever initiated with respect to services that AHCA is covering -- already covering?

A In my experience, no, that would -- that would be determined through the checklist and that would be deemed not a GAPMS.

Q Kind of the same question asked a little differently. Is it ever initiated to assess existing coverage of Medicaid services?

A Not in my experience.

Q I asked some of these. I don't want to ask them again, so I'm going to blow through them real quick.

MR. PERKO: Would now be time for a break?

MS. DeBRIERE: Yeah, let's do it.

(Brief recess.)

BY MS. DeBRIERE::

Q So did you speak to anybody during the break about the deposition?

A I did not.

Q Okay. And I just want to go back quickly to

what I believe we marked as Exhibit 2. Is that -- no, Exhibit 3, excuse me, which is the GAPMS decision tree checklist. I needed to ask one more question about that. If something was -- so when you receive the request, and you're going through the checklist, if something was on Medicaid's fee schedule, and therefore covered by Florida Medicaid, would you initiate the GAPMS process?

A No.

Q What types of Medicaid services are assessed using the GAPMS process?

A Treatments, I guess, for lack of a better way for shorthand. Typically, it's -- can I answer the question by giving you an example of GAPMS?

Q Absolutely. You can answer the question however you would like to?

A There's, you know, specially modified low-protein foods for inborn errors of metabolism. There's negative-pressure wound therapy, which is a medical device for wound healing. There's low-intensity pulsed ultrasound, which is a medical device for healing fractures. There's a procedure with sort of a proprietary technology called transcervical fibroid ablation that's kind of a cross between a procedure and the type of bead that's used in the procedure that

Q Who's involved in the -- who was involved in the GAPMS process when you were doing it?

A Primarily myself. There was, from time to time if we got it -- you know, if I got along in the process and was determining that, you know, this had a potential, that it would be recommending coverage -- because everything has to be budget-neutral, we would -- I would reach out to Medicaid, the fiscal folks, and they would put together a fiscal analysis of what the cost would be, or any potential cost savings. So from time to time, not every GAPMS, if I didn't reach out to them, if it was something that it was clear that we weren't going to cover, because the time wasn't -- it's pointless to take up their time. My supervisor -- I had weekly regular weekly meetings with my immediate supervisor, you know, to go over what was in the queue, what was I working on, what was the status.

I frequently had scheduled meetings with the Bureau Chief, but those didn't often come off, but it was understood that, you know, typically, along, you know, the course of time, you know, they would get, you know, an update on what was going on, and if it was one where, you know, I had written it, my supervisor had signed off on it, and then the next step was, you know, to get the bureau chief to sign off on it in order for

it to go to the Medicaid director. And then Nick -- Nick was doing the checklist. But I mean, it was -- it was kind of a joke with my, you know, with my co-workers, I was kind of like the one-end game.

Q Okay. Okay. So can you describe that line of approval. So it started with you.

A It started with me. I would write a report. I would submit it to either, at the time Christina, or Jesse, whoever was my immediate supervisor. They would review it, they may or may not have some edits to send back, and then it would -- once they had, you know, signed off on it and said, you know, this can advance to the bureau chief, and then, you know, the bureau chief would sign off on it, yay or nay, and then the next step is to go to the Medicaid director.

Q Okay. And who currently is the Medicaid director?

A Tom Wallace.

Q And who's the bureau chief for Medicaid policy?

A Ann Dalton.

Q And I know you just said this, and I apologize, but the final decision maker then in the GAPMS process is the Medicaid director. Is that correct?

A Yes. I mean, it typically requires his or her signature.

Q Is that different from being a decision maker?

A A decision point? Yes.

Q No, a decision maker. Sorry.

A That's linguistics, sort of. I mean, it -- I can't reach out to the requester and say yay or nay until Tom has signed or, you know, whoever -- Beth has signed off on the report.

Q Does the Medicaid director review the report and reach an independent conclusion?

MR. PERKO: Object to form. You can answer.

THE WITNESS: I don't know.

BY MS. DeBRIERE::

Q In the GAPMS process you just described from you to your supervisor, to the bureau chief, to the Medicaid director, does AHCA ever rely on individuals outside the agency in the process?

A Not in my experience, no.

Q How many GAPMS reports are issued per year?

A That's kind of a loaded question.

Q I don't mean it to be.

A Okay. In my -- you know, if I can round up three years of doing GAPMS reports, there were a couple of expedited GAPMS that kind of made it all the way

medical necessity?

A I've read it before.

Q I have a copy of it. Do you want to see it?

A Sure.

MS. DeBRIERE: Sorry. It's on page seven, Gary. And what the witness is reviewing -- I think I needed more coffee at lunch -- what the witness is reviewing is 59G-1.010, and it's the definition of medically necessary medical necessity at 2.83 in the policy.

THE WITNESS: Yes.

(Whereupon, Exhibit No. 6 was marked for identification.)

BY MS. DeBRIERE::

Q Do you know what AHCA uses this definition for?

A I mean, I've had -- it's been in literature or in, you know, in reference to the GAPMS process. Beyond that, I don't know how its utilized.

Q How does it relate to the GAPMS process?

A As I understand it, if a GAPMS is approved, as you know, something that Medicaid is going to cover, then it's considered under the blanket definition of that term or phrasing. It's been deemed medically necessary, I guess.

Q If what?
A If it's passed GAPMS.
Q If AHCA determines the service is experimental and will not be covered by Medicaid, would there be any reason to determine whether the service is medically necessary under any other portion of the medical necessity definition?
A That question might come up around the EPSDT consideration, but otherwise, I don't know.
Q You don't know or --
A I can't -- I don't believe so, you know.
Q When the agency decides to exclude a Medicaid service as experimental, does AHCA communicate that information to the public?
A Not in my experience. I've only ever communicated to -- well, I mean, there have been -- there have been requests that have come in that didn't reach the level of a GAPMS, because they didn't even get to that point. It was like, no, we don't cover that, because it's so obvious that we don't cover that. So we would explain to them, you know, these are the things when -- we explain the process to them, and these are things -- but, you know, that's kind of the gist of it.
Q So, in your experience, after determining that a service would be excluded as experimental, does AHCA

notify the general public?

A No, we would notify the requester and then move on to the next project.

Q Would AHCA typically publish that decision on a website?

A Not that I'm aware of, no.

Q Would they provide the general public with the expert reports they relied on during the GAPMS process?

A Not that I'm aware of, no.

Q Does AHCA typically draft a press release about the conclusion that's reached in GAPMS?

A Not in my experience, no.

Q Is the Governor of Florida typically involved in the dissemination of a GAPMS conclusion?

A Not that I'm aware of, no.

Q Any other political figures, are they typically involved?

A Not that I'm aware of, no.

Q Other state agency heads?

A No.

Q Does AHCA publish the exclusion of a service being experimental in a coverage policy or coverage and limitation handbook?

A If they do, I'm not aware of it.

Q If through the GAPMS process a service is

were with her. We shelved it until we got the results. So that -- it's this big study about pregnant women and asthma because the preliminary results were very favorable, and it would have been sort of the -- it would have been a very narrow coverage determination, a very narrow call, but if I remember correctly, the results of that study did not pan out.

Q Okay. Looking at this particular GAPMS --

A No. It was managing asthma in pregnancy. Sorry. Not FMAP.

Q Yeah, especially when you're on state plan, right.

A Yeah.

Q Let's move to one I know you're familiar with, specially-modified low-protein foods. We'll mark as Exhibit 8 -- 9.

(Whereupon, Exhibit No. 9 was marked for identification.)

THE WITNESS: See, this one predates me.

BY MS. DeBRIERE::

Q So what happened there?

A Things didn't move forward. So it was basically starting over and starting from scratch. And so the report that I wrote for -- especially I wrote multiple versions of that report -- looks very different

from that one.

Q Do you remember what organizations on which you relied to write this report?

MR. PERKO: He said he didn't write this report, counsel.

MS. DeBRIERE: I'm sorry. You're right. I strike the question.

BY MS. DeBRIERE::

Q Do you remember on what organizations you relied to write your report on specially-modified low-protein foods?

A I know I consulted organizations concerned with inborn errors of metabolism. And the two, we were directing it specifically to one called phenylketonuria, but there's another one called -- something to the effect of maple syrup disease, so it was organizations that were focused on those two conditions primarily.

Q Do you remember what organizations those were?

A Off the top of my head, I do not.

Q Were you looking -- were you assessing it as to children or as to adults?

A The way, after discussion with my supervisors, the way we were going about it was the argument sort of dictated that we -- that condition requires children to stay on a very strict low-protein diet. It's a lifelong

diet. It's a diet for life. And so what we were able to determine in the research was that, which makes sense, children, you know, when you're a kid, your parent controls your diet, and so you eat what they gave you and parents could keep the children on the diet, but when they started to reach their teenage years, they wanted more autonomy. Nobody wanted to go with their friends to Burger King, while they just sat and had a shake, you know, low-protein, a special shake. And that the research indicated that when children -- in the time of life when people either continue to adhere to the diet or drop off was in their teenage years. So we were targeting under age 21, and with the goal of trying to keep them diet-adherent so that they could progress on to adulthood with good habits and protect their health.

Q Do you remember if one of the organizations you looked at was the American Academy of Pediatrics, or relied on?

A Almost certainly.

Q Why are you -- why are you almost certainly?

A They're kind of a name brand organization.

Q Is it one that you find trustworthy in terms of their opinion?

A I have.

Q Can you look at this document and tell me if

this is -- the reason I ask is that -- skip to the front page, to page three. Do you know if it's complete? If you see there's a page number at the corner there.

A Yeah. Yeah, there's -- there should be a page. Yeah, there's a page there.

Q You don't think it's a typo?

A No, it's -- because on the second page, it picks up with, like, mid-paragraph.

Q Okay. Thank you for that. Were you involved in anything related to the GAPMS for scleral contact lenses?

A I was not.

Q So just going over the GAPMS process generally, in summary, to determine whether a service is experimental under GAPMS, you look at professional literature. And then the most persuasive professional literature is going to be, that's peer review?

A Ideally, sure.

Q You look at whether other state Medicaid programs cover?

A Yes.

Q And you look whether health insurance in the private market covers?

A Yes.

Q And if the majority of states cover, that's

going to be in the favor of finding it not experimental?
A It's hard -- it would be -- make it harder for us to justify that it's experimental.
Q And you look at whether Medicare covers?
A Yes.
Q And, again, whether Medicaid covers favors a finding of not being experimental?
A Yes.
MR. PERKO: Object to form.
BY MS. DeBRIERE::
Q And you look at whether evidence-based clinical practice guidelines exist?
A Yes.
Q And you look at whether the service is accepted by relevant professional medical organizations?
A Yes.
Q How do you -- would the American Medical Association be considered an organization on which AHCA would rely for GAPMS?
MR. PERKO: Object to form.
THE WITNESS: Yes.
BY MS. DeBRIERE::
Q How about the American Psychological Association?
MR. PERKO: Same objection.

THE WITNESS: Yes.
BY MS. DeBRIERE::
Q The American Academy of Child and Adolescent Psychiatry?
MR. PERKO: Same objection.
THE WITNESS: I am not familiar with that organization.
BY MS. DeBRIERE::
Q The American College of Obstetricians and Gynecologists?
MR. PERKO: Same objection.
THE WITNESS: Yes.
BY MS. DeBRIERE::
Q In the past GAPMS, organizations on which you've relied include the American Academy of Pediatrics?
A Yes.
Q You undertake a cost analysis for potential cost-saving to Florida Medicaid when you're doing GAPMS?
A Yeah. I mean, if it's not budget-neutral, it's almost certainly not going to be covered.
Q You do not typically enlist outside medical experts during the GAPMS process?
A I have not.
Q You do not pay outside individuals?

A I don't.
Q You don't ask outside individuals to write a report?
A No.
MR. PERKO: Asked and answered, counsel.
BY MS. DeBRIERE::
Q You do not typically codify your conclusions reached during the GAPMS process into rule?
A I don't believe so.
Q You do not typically develop a website and slogan to advertise a GAPMS conclusion?
A I have not.
Q Generally, other agency heads or political figures not involved in the initiation -- are not involved in the initiation of the GAPMS process?
A Not in my experience.
Q In disseminating its conclusion?
A No.
(Whereupon, Exhibit No. 10 was marked for identification.)
BY MS. DeBRIERE::
Q Let's go to Exhibit 10, is the 2016 GAPMS memo, and this is going to be DEF_000288776 to DEF_00028 8785. Are you familiar with this document, Mr. English?
A I am not.

imagine this is a very large agency. Have you been involved in any conversation around AHCA's coverage of cross-sex hormone therapy?

A I am not.

Q Okay. Do you have any idea as to why, even though you were the GAPMS guy during these dates, that you would not be involved in these decisions?

MR. PERKO: Object to form.

THE WITNESS: I do. What I was explained by Jesse, my supervisor, his version of how -- and I don't know if the same person that wrote the gender dysphoria GAPMS wrote this -- Jesse's explanation for how that author was chosen, he said that it was a meeting between he and Jason and Ann, and Jason had come and asked who they might recommend to write the report, and when my name was brought up, Jesse said no, that he -- I guess he didn't want me working on that. And Ann offered up the actual author, eventual author, and Jesse concurred.

BY MS. DeBRIERE::

Q How do you know that this meeting happened?

A He told me.

Q Jesse told you?

A Uh-huh.

Q Why did Jesse say no? Did he say to you?

A Yes. He -- I believe his perception of it was that it was -- he said that he didn't want me involved with it. He didn't want to be supervising the person who was, and he didn't think that it was something that I would have been willing to do.

Q Was he right?

A Yes.

Q Why?

A Because my perception was that that particular GAPMS was a conclusion in search of an argument.

Q Did Jesse agree with you?

A You'd have to ask him.

Q Why don't you think Jesse wanted to supervise the project?

A We're all sitting here right now.

Q Fair.

A And on top of that, I mean, he was pretty new in his position, too. He had been promoted after Christina left.

Q How long had he been in that position?

A Not super, super long. I mean, God, I think Christina was -- actually, I don't know. She left -- one of the December's during the pandemic, but I don't remember. She went out on maternity leave and never came back, and then he ended up filling her position.

Could have been 2021, or it could have been 2022. I don't honestly recall.

Q Who was the author of the report you're referring to?

A Matt Brackett.

Q Do you know why Mr. Brackett was chosen?

MR. PERKO: Object to form.

THE WITNESS: Jesse told me that he -- he told Jason that Matt would do any assignment that he was given.

BY MS. DeBRIERE::

Q Had Mr. Brackett ever done a GAPMS memo before?

A He had. He was -- he wrote GAPMS prior to my arrival.

Q Why didn't they keep Mr. Brackett in that position? Why did they hire someone new?

MR. PERKO: Object to form.

THE WITNESS: When I arrived, Matt was over the -- I believe he was over durable medical equipment. And I think, just based on conversations he and I had had, there's a kind of a bit of frustration built into the GAPMS position because it's not a priority, you know, outside of a pandemic, even it's just not a priority. And so he

was -- you know, he would tell me, you know, look, I didn't get a lot, you know, through either -- it's kind of a thankless job, but it's important, you know, that kind of thing. So it -- I think he wanted to go do -- he's been here -- you know, I don't know how much longer though, at least a little bit, or maybe more than that longer than me, and I think he just wanted to go do something else.

BY MS. DeBRIERE::

Q Okay. Why do you think it mattered to Mr. Boucher that you not be a part of the gender dysphoria GAPMS?

MR. PERKO: Object to form.

THE WITNESS: My belief is that he didn't see -- he didn't believe that it would be something that I would -- I would be willing to do and he, I believe, was possibly trying to save himself, a hassle as well.

BY MS. DeBRIERE::

Q Let's turn back to the email between you and Mr. Cogle, which is Exhibit 5. On the second page, you have a paragraph that starts, if you will, excuse me, I feel obligated to include this information.

A Yes.

Q Are you familiar with what you wrote there?

A I am.

Q Would you say that's a reason why you didn't want to be involved in the gender dysphoria GAPMS process?

A Yes and no, indifferent all at the same time. I mean, part of why this paragraph was written was out of frustration. Again, I was -- you know, my co-worker's, it was the -- you know, we joked I was the GAPMS guy. That report came out. I read the report. It was not something I felt like I would have produced and because there were a lot of people around inside the agency and my personal life that thought that I wrote the report, because it said, GAPMS, you know. So I had grown tired of -- you know, and at the same time, it's like, you know, my friends are seeing reports about it on television and things like that, or in the newspaper or whatever, it was a news story, a prominent news story with, you know, debate and politics and all these things, and I was a bit frustrated that that was occurring. And combined with the fact that Dr. Cogle was someone I respect, and I kind of in response to the emotion I'd received in his initial email, I wanted to assure him that that wasn't me.

Q I just want to make the record clear by entering in Exhibit 14. And this exhibit is entitled

Florida Medicaid generally accepted professional medical standards determination on the treatment of gender dysphoria. It's dated June 2022.

(Whereupon, Exhibit No. 14 was marked for identification.)

BY MS. DeBRIERE::

Q Is the report we've been talking about that Mr. Brackett authored?

A Yes.

Q And this is the report that Jesse said you would not author, is that correct?

A Correct.

Q And it's the report that you did not want to author?

A Correct. I mean, keep in mind, I found out about it after the project already started. And then I went and asked Jesse about it. I was like, you know, and I wasn't like, you know, who's doing the GAPMS. I was just like, hey, what's going on, you know. And he explained, you know, how Matt was chosen and why I was not, and I was thankful for that and went from there.

Q And you said in your response to my questions about your email to Dr. Cogle that this report did not reflect the level of work that you would do, is that correct?

A Well, that's a -- that's a loaded question. I mean, it's a 45-page report, which is very different from the -- what I was dealing with, which was the push for the trend for tighter cleaner, smaller reports that took less time to read. What was the --

Q Yeah. Why isn't this GAPMS report on gender dysphoria reflective of your work?

A It veers a bit from process.

Q In what ways?

A Well, in terms of the quality of the studies included, the dismissal, the professional organizations and experts that we had frequently cited before, the length of the report, where it originated from.

Q Where did it originate from?

A I would say the executive. Came from they said, you know, Secretary Marstiller, she's part of the executive.

Q Anybody else in the executive?

A Oh, sure. Governor. Yeah.

Q I cut you off.

MR. PERKO: I meant to object to form on that last question.

BY MS. DeBRIERE::

Q You said it dismissed the opinions of professional organizations, where it was initiated was

off, the length of the report was off. Anything else?

A Keep in mind that the people who prepared the report, or Matt and a guy Ni -- I don't remember Ni's last name -- they were not discreet about what they were working on or why, and it seemed to be impacting morale a little bit among some co-workers, and it was kind of an immature sort of approach or attitude or something to it that was off-putting a bit, I suppose, for folks.

Q Are folks in the agency generally aware of things that GAPMS is working on?

A Frankly, most people don't really care or pay attention. You know, everyone has -- just the way everything's set up here, you, you know, everyone has their own little corner of the piece of the puzzle of Medicaid, and it's a big learning curve for everything, and so you want to focus on your little piece of the puzzle and try and grow your puzzle into, you know, understanding how it fits into the main thing. Certain topics sometimes, I had to do one on transanal irrigation, and I caught a lot of grief from some of my co-workers on that one, you know, silly stuff, you know, office banter, that kind of thing, but that one was -- it was just kind of altogether a different thing.

Q You described it as immature.

A Well, certain behavior was.

Q What?

A There was a -- I don't remember the person's name. I was told that they were a trans person. I knew him as this guy who had an office nearby Matt and I, and it was after the report had come out, I believe, and they were, like, kind of whooping it up, yelling back and forth across the hallway, because about -- like the number of views it was getting on Twitter and things like that. And so that employee had to get up and go over and tell them, you know, look, it's -- you know, congratulations on your report, but I feel like you're being somewhat insensitive. And, you know, that was awkward.

Q Yeah. You mentioned that Mr. Brackett was not in -- Mr. Chen -- Dr. Chen?

A He's -- I think he's pharmacist, yeah.

Q Mr. Brackett and Mr. Chen were not discreet about it, what they were working on. How did they characterize what they were working on?

A Just what the topic was. It was actually -- Ni's the one that told me that -- he's who told me that it was -- I was wholly unaware of the assignment, and Ni's the one that told me about the assignment.

Q Is this the first time you've ever been -- since being the GAPMS guy, was the first time you'd ever

been excluded from the GAPMS process?

A Well, I mean, this other one here predates the publication of that one, but --

Q And that --

A -- in April, and this one probably began in April or March or something like that. So, yeah, whichever. The chicken or the egg, whichever one came first. I was unaware of both of those.

Q The title that you were just referencing that is Exhibit 13, I think? Is that right?

A Yes.

Q And do you think that report was a precursor to the Exhibit 14?

MR. PERKO: Object to form.

THE WITNESS: I wouldn't know.

BY MS. DeBRIERE::

Q How many Medicaid services does this GAPMS memo Exhibit 14 analyze, do you know?

A Maybe three.

Q Is that typical?

A No. Well -- I mean, no, I've looked at GAPMS where it was two devices, two different devices at the same time, but never like two different treatments, same time.

Q Do you know why AHCA used that approach here?

A I do not.
Q Would you recommend that approach in a GAPMS process?
A I can't outright say I would or would not. It would depend on the circumstance and how closely related I perceive the procedures or services to be.
Q Do you know if this is supposed to apply to children or adults or both?
A My understanding is both, or to children and -- most of the discussion has been around children. Children.
Q So you don't -- having reviewed this, you can't say?
A I don't recall. I mean, I read it back in, like, June.
Q Okay?
MR. PERKO: About ready for a break, counsel?
MS. DeBRIERE: Mr. English, do you think you can do like 10 more minutes?
THE WITNESS: I can do whatever's good for the order.
MS. DeBRIERE: Is that okay, Gary?
MR. PERKO: Yeah.
BY MS. DeBRIERE::
Q Do you know if AHCA enlisted outside medical

experts to do a literature review for this report?

A That's my understanding.

Q Is that typical for GAPMS?

A Not in my experience.

Q Do you know if they paid these professionals to do the report?

A My understanding is they did.

Q Is that typical?

A Not in my experience.

Q Do you know why AHCA used that approach here?

A I do not.

Q Have you ever -- I'm sorry. Did they attach the expert reports to the final GAPMS report? Did AHCA attach the expert reports to the final GAPMS report?

A I don't know if I saw, like, a copy with attachments or if it's -- I don't recall if it was referenced or included in their report like -- but I remember seeing those when I was looking at it, you know?

Q Is that typical?

A Well, no, I mean, I've never had outside reports to attach to it, were included with the GAPMS.

Q When you mentioned that -- one issue you took with the report is they dismissed professional organizations' opinions. Would those professional

organizations include the Endocrine Society's position?

MR. PERKO: Object to form.

BY MS. DeBRIERE::

Q If you don't remember, that's okay.

A I know who the Endocrine -- who they are. I would be hard-pressed to envision a scenario where I would second-guess them -- and without, you know, really, really good cause.

Q What about the American Academy of Pediatrics?

MR. PERKO: Object to form.

THE WITNESS: No.

BY MS. DeBRIERE::

Q No, you --

A I would be deferential to their recommendations.

Q Are you aware of the coverage of the treatment for gender dysphoria under other Medicaid programs?

A I want to say that things could have changed because I haven't really looked at some of that stuff since last year.

Q Why were you looking at it last year?

A When I --

Q Go ahead.

A If I recall, it's somewhere between maybe 30 and 40 states or something that provide coverage for it.

Q When you undertake GAPMS, how would that factor into your ultimate conclusion?

A If it were 30 states, that would -- it could be a factor. If it were 40 states or more, it would be -- it'd be harder to dismiss. It's something that my supervisor would have been making an inquiry about if I were recommending against coverage.

Q Because that many states covering indicates that it's not experimental?

MR. PERKO: Form.

THE WITNESS: It indicates that there is existing widespread coverage for it.

BY MS. DeBRIERE::

Q How does that factor into whether the service is experimental?

MR. PERKO: Form.

THE WITNESS: It makes an argument for coverage for something easier to make, assuming that they meet the threshold on all the other categories, you know, then that's, you know --

BY MS. DeBRIERE::

Q Do you know if they did a decision tree checklist for the services listed in the June 2022 memo?

A I do not.

Q Do you know if AHCA undertook an Analysis

of -- to determine how excluding coverage of treatment for gender dysphoria would affect the Florida Medicaid budget?

A I do not.

Q Does anything else stand out to you about this memo that we haven't discussed?

MR. PERKO: Object to form.

THE WITNESS: It's frankly unlike anything I've experienced in the process, but I mean, just the sort of -- you know, we're all sitting here, the publicity about it, everything that sort of comes with it. It's unusual, in my limited time here.

BY MS. DeBRIERE::

Q Do you agree with the conclusion?

MR. PERKO: Object to form.

THE WITNESS: I think it's two different issues.

BY MS. DeBRIERE::

Q Yeah.

A I'm not sure that it matters what I believe about the question of whether or not Florida Medicaid should pay for transgender services. I view it as a process issue, and I believe that everyone should have the same -- the same opportunity for review and a consistent process.

Q Was this consistent with the other opportunities people have had for review of a Medicaid service?

A I do not -- I do not believe it was.

Q Do you know how AHCA implemented the conclusions found in this memo?

A I do not. I know they had to write a rule, and I know they had a hearing. That's all I know.

Q Have they talked to you about implementation regarding state amendment at all?

A They have not.

Q Throughout this deposition, I got the sense that you were really good at your job, as the GAPMS guy.

A It's not for me to say. I feel like I put forth some effort.

Q Yeah, and you got a certificate for doing one in eight hours.

A Just a couple of friends, but I think my performance is reflected in my performance reviews.

Q Yeah. And why do you think they moved you from GAPMS to the state plan?

A I asked to be moved.

Q Okay. Why did you ask to be moved?

A Because I felt like the GAPMS process had lost some integrity and I didn't want to be associated with

it. I didn't want the blowback from the requesters out there who were going to wonder why their report wasn't -- I mean, every month it got harder and harder and harder to justify those reports not moving. And I was just, you know, kind of burned out. If you're in a position where you're working on something and they tell you, you know, slow down and stop, you know, then let's go learn something else. And, honestly, I thought leaving would protect me from some of this.

Q You had mentioned that they had to adopt a rule to implement this decision. Is that typical of a conclusion reached through the GAPMS process?

A Not that I'm aware of.

Q The same question with having a hearing. Is that something typically related to a conclusion in the GAPMS process?

A Not that I'm aware of.

Q Has it ever been done, that you're aware of, for any GAPMS conclusions?

A I was never asked to attend a rule hearing or anything related to any of the GAPMS I worked on. So, not that I'm aware of.

MS. DeBRIERE: Are you okay with taking like a 10 minute break?

THE WITNESS: Sure.

TAB 199-3

IN THE UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.)
)
Plaintiffs,)
)
vs.) NO. 4:22-CV-00325-RH-MAF
)
)
JASON WEIDA, et al.,)
)
Defendants.)

VIDEOCONFERENCE DEPOSITION OF
G. KEVIN DONOVAN, M.D., M.A.
LOCATED IN SAND SPRINGS, OKLAHOMA
TAKEN ON BEHALF OF THE PLAINTIFFS
ON MARCH 22, 2023

REPORTED BY: JANA C. HAZELBAKER, CSR

web page of the Catholic Medical Association?

A I don't think so.

Q So the website states that, "The following are resolutions accepted as positions at the Catholic Medical Association."

And we're going to jump to the resolutions that are listed in the topic of "Family and Sexual Education." Specifically I'm going to look at Resolution 8-12, which is a resolution on transgender treatments.

Resolution 8-12 reads that, "The Catholic Medical Association does not support the use of any hormones, hormone-blocking agents, or surgery in all human persons for the treatment of gender dysphoria."

Were you aware of this resolution of the Catholic Medical Association?

A No. As I've mentioned, I'm not a member of the Catholic Medical Association.

Q And if you --

A I wasn't aware of this.

Q You weren't aware of this?

A No.

Q If you had been aware of this, would it have changed your decision to publish in the Catholic Medical Association's official journal?

A Well, I -- I imagine that I would probably be pleased if anybody agrees with me.

Q So are your beliefs aligned with this resolution?

A I don't know because I haven't seen the full text of it. I just see a title there.

Q So this is the full text of the resolution. The title is "8-12: Resolution on Transgender Treatments." And then it says "Be it resolved."

A Well, then, that does sound reasonable.

Q Okay. And then if we move down to Resolution 8-13, which is the "Resolution on Gender Dysphoria," it reads, "Be it resolved that the Catholic Medical Association and its members reject all policies that condition all persons with gender dysphoria to accept as normal a life of chemical and surgical impersonation of the opposite sex. Further, that the use of puberty-blocking hormones and cross-sex hormones and surgical reassignment surgery be rejected."

Were you aware of this resolution of the Catholic Medical Association?

A No. Like I said, I've never seen this page before and I don't know if any of these were ever adopted.

Q These are on the website of the Catholic Medical Association as adopted resolutions.

A Okay.

Q I'll represent that to you. And so if you had been aware of this resolution, would it have impacted your decision to publish in The Linacre Quarterly, the Catholic Medical Association's official publication?

A No.

Q And are your beliefs around the treatment of gender dysphoria aligned with this Resolution 8-13?

A I would not have used this language, but I don't have severe disagreements with it.

Q Okay. At this point we're going to turn back to what has been marked as Plaintiffs' Exhibit 1. And that is your report, which is not on my screen anymore, so I'm going to have to stop that share again.

(Document is displayed).

This, we already identified, as the expert declaration that was provided, written by you and provided to plaintiffs by the defendants in the lawsuit that brings us here today, Dekker versus Weida.

by your terminology. So you say that you "have studied issues surrounding transgender patients." Specifically, what issues related to transgender patients have you studied?

A Well, I think that the things that I have read about and been concerned about exactly parallel those that you see in the younger patients, as well, in terms of the concept, the diagnosis and the treatment and the results.

Q So can you estimate how many times you've been consulted on issues specific to transgender patients?

A No. I mean, these are not formal consultations, these are discussions.

Q I'm sorry. So going back to your role providing ethical consultations, either -- I guess at Georgetown would have been primarily the period of time we're talking about. Can you estimate how many of those ethical consults would have related to transgender patients?

A None of the hospital consults related to transgender patients as transgender patients.

Q So you've not given an ethical consult with regard to patient care for a patient that was transgender?

A Not for an individual patient, no.
Q And that extends to both children and adults?
A Correct.
Q Moving on to Paragraph 11 where you say, "For ethical as well as medical reasons, I have never prescribed medications nor referred for surgery any patients that consider themselves transgender."
These medical reasons you reference -- going back to your specialty, you're a pediatric gastroenterologist. We've established that. That's right, right? Is that right?
A Yes.
Q Did any of your pediatric gastroenterology patients identify as transgender, to your knowledge?
A No --
Q To your knowledge --
A -- not to my knowledge.
Q Oh, I'm sorry, I cut you off again. I apologize.
What were you saying?
A I just said "not to my knowledge."
Q To your knowledge, have any of your pediatric gastroenterology patients been diagnosed with gender dysphoria?

A Not to my knowledge.

Q Have you ever prescribed a medication to a patient in your role as a bioethicist?

A That's not the role of a bioethicist.

Q Okay. I just wanted to confirm that.

Do bioethicists treat medical conditions with surgical referrals?

A That's not the role of the bioethicist.

Q Okay. When you -- so turning back to Paragraph 11, when you refer to ethical reasons that you don't prescribe medications, is that because your activities as a bioethicist are informed by your Catholic faith?

A No, it's because I think that it's unethical.

Q Do you think that it's unethical because it's not consistent with the ERDs that we talked about as Plaintiffs' Exhibit 4?

A No, I think it's unethical on the face of it. I don't think you have to be Catholic, Muslim, Jewish, or none of the above to come to the same conclusions.

Q In Paragraph 12 you say that, "None of your opinions are biased by professional income."

The entirety of your career in medicine

TAB 200

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MEMORANDUM OF LAW IN OPPOSITION TO DEFENDANTS' MOTION FOR SUMMARY JUDGMENT

I. INTRODUCTION

While Defendants correctly acknowledge that a primary question in this case is whether, "based on current medical opinion," Florida's Exclusion and "determination" that medical treatments for gender dysphoria are "experimental is reasonable," *Rush v. Parham*, 625 F.2d 1150, 1157 n.13 (5th Cir. 1980), Defendants' Motion is otherwise a masterclass in misinformation and disinformation.

In addition to misstating facts, Defendants ignore that single most material fact in this case—whether medical treatment for gender dysphoria is experimental—is genuinely disputed, particularly given the overwhelming record evidence that such medical treatment is *not* experimental or investigational, but rather *necessary*, *safe*, and *effective*. This alone warrants denying Defendants' Motion, as "[t]he party

seeking summary judgment bears the exacting burden of demonstrating that there is no dispute as to any material fact in the case." *Warrior Tombigbee Transp. Co. v. M/V Nan Fung*, 695 F.2d 1294, 1296 (11th Cir. 1983).

Take Defendants' opening paragraph. Defendants reference a handful of countries that have purportedly restricted the provision of gender-affirming care in a manner that is both misleading and false.[1] Defendants "ignore European countries where access to trans care has recently expanded (Spain, Portugal, and France)." (Opp. Ex. A.)[2] Indeed, "in France, the use of hormone blockers or hormones of the opposite sex is possible with parental authorization at any age," and surgical treatment for gender dysphoria is likewise available, including "mastectomy, which is authorized … from the age of 14."[3] New Zealand also has not restricted the provision of gender-affirming medical care. (Opp. Ex. B; Opp. Ex. C.)

Defendants argue that because some outlier doctors go against the grain, the Exclusion and their determination is "reasonable" under *Rush*. Not so. Under *Rush*, "whether the state's determination 'is' reasonable, [is] controlled … by 'current

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[1] How countries with nationalized health care systems provide medical care has little bearing here.

[2] Exhibits referred to as "Ex.#" refer to Plaintiffs' trial exhibits filed at ECF 175-184. Exhibits referred to as "Opp. Ex. [letter]" are exhibits attached to this memorandum.

[3] https://www.academie-medecine.fr/wp-content/uploads/2022/03/22.2.25-Communique-PCRA-19-Gender-identity-ENG.pdf.

medical opinion.'" Doc.64 (quoting *Rush*, 625 F.2d at 1157 n.13). "Defendants attempt to create scientific controversy in [an otherwise] uniform agreement through experts who mix their scientific analysis with hypothetical speculation and political hyperbole." *Kadel v. Folwell*, 2022 WL 3226731, at *32 (M.D.N.C. 2022). But "Defendants' belief that gender affirming care is ineffective and unnecessary is simply not supported by the record." *Id.*

Here, Plaintiffs have presented copious evidence demonstrating that gender-affirming care is *not* experimental or investigational, but *necessary*, *safe*, and *effective* medical care that has been provided and studied *for decades*. Each of Plaintiffs' experts completely undermine the State's position, and at minimum, create a genuine issue of material fact. And unlike Defendants' experts (with one exception), Plaintiffs' experts *all* have experience treating or studying gender dysphoria, and its medical treatment. Their testimony shows that gender-affirming care is safe, effective, and widely accepted. Defendants ignore this evidence.[4]

Defendants also fail to contend with the plethora of case law showing that exclusions of medical treatments for gender dysphoria from coverage are unlawful

[4] Defendants reference an expert report from Dr. Brignardello-Petersen, one of AHCA's consultants on the GAPMS Report. Defendants never disclosed Dr. Brignardello-Petersen as an expert in this case and refused to accept service of Plaintiffs' subpoena for her as she is based in Canada. To the extent Defendants seek to introduce Dr. Brignardello-Petersen's report in support of the GAPMS Report or to reference it as expert opinion, Plaintiffs move to strike such references.

and violate the Medicaid Act's comparability and EPDST requirements, Section 1557 of the ACA, and the Fourteenth Amendment's Equal Protection Clause.

Because there are material facts genuinely in dispute and a barrage of case law supports Plaintiffs' claims, the Court should deny Defendants' Motion.

II. STATEMENT OF THE CASE AND FACTS

Correcting every misstatement in Defendants' statement of the case and facts would exceed permitted word limits, so Plaintiffs refer the Court to their Trial Brief and present the following facts.

A. Gender Dysphoria

Gender dysphoria is a serious medical condition, experienced only by transgender people, characterized by the significant distress caused by the incongruence between their sex assigned at birth and their gender identity. (Ex.8, at 10 ¶7; Ex.10, ¶20; Ex.7, ¶24.) Without appropriate treatment, gender dysphoria can cause debilitating anxiety, severe depression, self-harm, and even suicidality. (Ex.7, ¶¶26, 36, 68; Ex.9, ¶41; Ex.10, ¶21.)

B. Treatment for Gender Dysphoria

Gender dysphoria is treatable, and interventions are supported by well-established evidence-based guidelines, for which decades of research and clinical practice provide support. (Ex.9, ¶ 41; Ex.5, ¶ 17; Ex.8, at 12-13 ¶¶ 10-12; Ex.10, ¶¶24-26; Ex.7, ¶¶27-28, 33, 56-59; Ex.142.)

Treatment seeks to eliminate the distress of gender dysphoria by aligning an individual's body and presentation with their internal sense of self. (Ex.7, ¶36; Ex.10, ¶22.) The medical community does not consider these treatments to be experimental or investigational. (Ex.5, ¶¶32-33; Ex.14, ¶¶21-36; Ex.17, ¶23; Ex.8, ¶73; Ex.10, ¶¶ 44-46; Ex.9, ¶89.).

1) The treatment protocols for gender dysphoria

Gender-affirming medical care dates back almost a century. (Ex.5, ¶32, Ex.10, ¶46.) The first gender-confirming surgeries were performed in the 1920s. (Ex.143, at 48-49.) Hormone treatment for gender dysphoria began after estrogen and testosterone became commercially available in the 1930s. (Ex.5, ¶32; Ex.11, ¶32; Ex.2, ¶ 27; Ex.143, at 49.) Puberty-delaying medications have been used to treat gender dysphoria since the late 1990s. (Ex.5, ¶32; Ex.8, ¶24; Ex.142, at 364.)

WPATH first established standards of care for the treatment of gender dysphoria in 1979, which have been continuously maintained and are now in their eighth version ("WPATH SOC8") (Ex.7, ¶27; Ex.8, at 12 ¶10; Ex.9, ¶48; Ex.10, ¶ 24; Ex.17, ¶55; Ex.142, at 361; *see also* Ex.34.) The WPATH SOC8 are based on the best available evidence and professional consensus. (Ex.5, ¶29; Ex.7, ¶28; Ex.8, at 12 ¶10; Ex.9, ¶48; Ex.10, ¶¶ 8, 24; Ex.17, ¶56; Ex.142, at 361; *see also* Ex.34, at S8, S247-S251.)

The Endocrine Society's Clinical Practice Guidelines are largely consistent with the WPATH SOC8 and were developed using rigorous scientific methods. (Ex.5, ¶¶17-18; Ex.7, ¶¶31-33; Ex.8, at 13 ¶12; Ex.9, ¶53; Ex.10, ¶26; Ex.17, ¶¶57-58; Ex.142, at 361; *see also* Ex.123; Doc.193-24.)

The WPATH SOC8 and the Endocrine Society Guidelines provide for medical interventions that are individualized based on patient needs and may include puberty-delaying medications, hormone therapy, or surgeries. (Ex.8, at 12 ¶10; Ex.7, ¶40; Ex.9, ¶57; Ex.10, ¶ 25; *see generally* Ex.34; Ex.123; Doc.193-24.) Treatment protocols differ for adolescents (minors who have started puberty) and adults. (Ex.17, ¶59; *see also* Ex.34, at S32, S48, S111, S129; Ex.123, at 3878, Table 5.) No medical or surgical treatments are provided to any patient until *after the onset of puberty*. (Ex.8, at 17 ¶18; Ex.7, ¶41; Ex.9, ¶44; Ex.17, ¶¶25, 59; *see also* Ex.34, at S69; Ex.123, at 3870.)

America's major medical organizations agree gender-affirming medical care is necessary for people with gender dysphoria. (Ex.5, ¶30; Ex.7, ¶34; Ex.8, at 12 ¶¶10-11, ¶48; Ex.9, ¶¶54-55; Ex.10, ¶27; Ex.17, ¶60; Ex.142, at 361.)

a) Puberty-delaying medications

For adolescents with gender dysphoria who experience severe distress with the onset of puberty, puberty-delaying medications may be indicated. (Ex.7, ¶42; Ex.8, ¶¶22-23; Ex.9, ¶46; Ex.17, ¶89.) Such interventions afford the adolescent time

to better understand their gender identity while delaying the development of secondary sex characteristics, which can cause severe distress when incompatible with an adolescent's gender identity. (Ex.8, ¶¶23-24; Ex.12, ¶81; Ex.9, ¶66; Ex.17, ¶92.) The treatment is reversible if an adolescent discontinues the treatment, puberty will resume. (Ex.7, ¶42; Ex.8, ¶¶24; Ex.9, ¶65.)

Puberty-delaying medications do not have any long-term implications on fertility or sexual function, and there is no evidence that they impact brain development, emotional regulation, or cognition. (Ex.15, ¶¶21-33; Ex.12, ¶¶17-23; Ex.9, ¶73.) The medical and scientific literature has established that puberty-delaying medications are safe and effective to treat gender dysphoria in adolescents. (Ex.5, ¶32; Ex.9, ¶¶63, 78-82; Ex.8, ¶¶25-29, 99-101; Ex.16, ¶¶51-54; Ex.12, ¶¶73-74; *see also*, *e.g.*, Exs. 141, 163, 165, 167, and 168.)

b) Hormone therapy

For some adolescents and adults with gender dysphoria, hormone therapy may be medically necessary. (Ex.17, ¶96; Ex.8, ¶32; Ex.7, ¶43, Ex.9, ¶¶46, 72.) Gender-affirming hormone therapy is a partially reversible treatment, meaning some of the hormones' effects are reversible, while others are not. (Ex.7, ¶43; Ex.8, ¶32.) Hormone therapy allows for a physical development more closely aligning with a person's gender identity, helping alleviate gender dysphoria. (Ex.9, ¶¶60, 71.)

The scientific literature shows that hormone treatment is safe and effective to treat gender dysphoria in adolescents and adults. (Ex.9, ¶¶86-88; Ex.8, ¶¶ 34-40; Ex.17, ¶¶101-102; *see also*, *e.g.*, Ex.166; Ex.180; Ex.221; Ex.156; Ex.197; Ex.176; Ex.195; Ex.164; Ex.212.)

c) Surgery

Gender-confirming surgery may be indicated for some transgender adults and older adolescents to align their primary and secondary sex characteristics with their gender identity. (Ex.8, ¶42; Ex.10, ¶22.) Surgeons regularly perform these procedures to treat conditions other than gender dysphoria. (Ex.10, ¶38.) The scientific literature shows that surgery is a safe and effective treatment for gender dysphoria. (Ex.10, ¶¶40-42, 46; Ex.8, ¶¶44-45; Ex.5, ¶32; *see also*, *e.g.*, Ex.202, Ex.208; Ex.178; Ex.192; Ex.198; Ex.193.)

2) The quality of the evidence

The quality of the evidence supporting these gender-affirming medical interventions is comparable to studies supporting other, well-established treatments and procedures. (Ex.8, ¶¶70-90; Ex.5, ¶¶18-28; Ex.11 ¶¶55, 83; Ex.10, ¶52-54; Ex.17, ¶106.) Scientific ratings of evidence generally employ stringent standards that are not satisfied for many commonly prescribed treatments. As one recent scientific article concluded, "only a minority of outcomes for health care interventions are supported by high-quality evidence." (Ex.182.) The fact that a

treatment is not supported by "high-quality" evidence does not mean that the treatment is unsupported in the literature and clinical practice, that it is experimental or investigational, or that it is not medically necessary. (Ex.14, ¶75.) That is because "[t]o determine whether a treatment is safe and effective, and whether it is experimental or investigational, we look at the whole body of research and clinical experience." (Ex.12, ¶73.) "By this measure, gender-affirming medical care as treatment for gender dysphoria has been shown to be safe, effective, and is not experimental or investigational." (*Id.*)

3) Psychotherapy alone is not an effective treatment for gender dysphoria.

There is no established safe and effective alternative to gender-affirming medical care for treating gender dysphoria. (Ex.10, ¶58; Ex.7, ¶37; Ex.11, ¶¶23-24, 47.) Defendants present psychotherapy alone as an alternative but have offered no evidence to support that claim. (Opp. Ex. D (Weida), 88:18-22.) None exists. While behavioral health interventions are an important component of gender-affirming care for many, the literature has established for decades that mental health interventions alone are insufficient to treat gender dysphoria. (Ex.7, ¶37; Ex.11, ¶48; Ex.17, ¶91; Ex.8, ¶112; Ex.10, ¶58; Ex.158, at 13.)

III. ARGUMENT

A. Defendants' determination that gender-affirming medical treatments are experimental is unreasonable, or at least, genuinely disputed.

This Court, relying on *Rush*, 625 F.2d 1150, articulated as a controlling question in this case "whether, based on current medical knowledge, the state's determination that these treatments are experimental is reasonable."[5] Here, AHCA's determination was not reasonable, or at minimum, there is a genuine issue of material fact on that point.

Defendants' own Medicaid regulations set forth six specific criteria that govern whether a service is consistent with generally accepted professional medical standards, as opposed to experimental or investigational. Fla. Admin. Code ("FAC") 59G-1.035(4); *see also K.G.*, 864 F.Supp.2d at 1321. These GAPMS factors show that the excluded services are not experimental. AHCA's skewed and incomplete

[5] Of note, *Rush* turns on the "reasonable standards" provision of the Medicaid Act, 42 U.S.C. §1396a(a)(17), whereas Plaintiffs claim that the Exclusion violates the EPSDT and comparability provisions. (Doc.1, at ¶¶275-80). Nevertheless, Plaintiffs agree that if the treatments are experimental, the Exclusion does not violate EPSDT requirements. Ex.62; *K.G. ex rel. Garrido v. Dudek*, 864 F.Supp.2d 1314, 1321 (S.D. Fla. 2012), *aff'd in part, rev'd in part sub nom. Garrido v. Dudek*, 731 F.3d 1152 (11th Cir. 2013). Regardless, Plaintiffs contend the Exclusion could violate the Medicaid Act's comparability requirement, Section 1557, and the Equal Protection Clause even if Defendants' conclusion was reasonable. The Court has acknowledged that possibility. (Doc.64, at 4.)

consideration thereof underscores that its determination was not reasonable.[6] *See K.G.*, 864 F.Supp.3d at 1322.

1) Evidence-based clinical practice guidelines

Two professional medical associations – WPATH and the Endocrine Society – have published clinical practice guidelines recommending gender-affirming care for the treatment of gender dysphoria in persons meeting specific criteria. (Ex. 34; Ex.123; Doc.193-24.) These guidelines establish the authoritative protocols for health care providers working with transgender patients. (Ex.7, ¶39; Ex.9, ¶¶48-49, 56; Ex.10, ¶24; Ex.324, at 4.) And no published clinical practice guidelines recommend the use of psychotherapy alone to treat gender dysphoria. (Ex.9, ¶14.)

Defendants' argument that the WPATH and Endocrine Society guidelines are biased and not evidence-based is without merit. First, it is *de rigeur* for professional medical associations to advocate on behalf of health care providers and patients. (Ex.14, ¶¶54-56.) That does not undermine—let alone, invalidate—their published clinical practice guidelines. Second, the fact that WPATH members drafted the Standards of Care reflects not bias or a conflict of interest, but that clinicians and researchers with the requisite expertise in transgender medicine drafted them. (Ex.12, ¶42; Ex.5, ¶¶9-11.) Third, the WPATH and Endocrine Society guidelines

[6] That AHCA even initiated the GAPMS process for these services reveals that the process was a sham, as it is not used for already-covered services. (Ex.30; Doc.120-6, 93:13-93:21.)

are based on rigorous reviews of the peer-reviewed scientific literature, as well as extensive clinical experience. (Ex.34, at App'x A; Ex.123, at 3872-73; Ex.17, ¶¶55-58; Ex.5, ¶¶18-24, 29; Ex.7, ¶¶28, 33.)

Moreover, the guidelines themselves were peer-reviewed and published in medical journals. "That the research is accepted for publication in a reputable scientific journal after being subjected to the usual rigors of peer review is a significant indication that it is taken seriously by other scientists, i.e., that it meets at least the minimal criteria of good science." *Daubert v. Merrell Dow Pharms., Inc.*, 43 F.3d 1311, 1318 (9th Cir. 1995).

Defendants' attempt to discredit these clinical practice guidelines is even more remarkable considering AHCA's prior reliance on these very guidelines during GAPMS processes. For example, the 2016 GAPMS report on puberty suppression therapy included the Endocrine Society guidelines without any suggestion that they were somehow invalid. (Ex. 240.)

2) Published reports and articles in the authoritative medical and scientific literature

Abundant "peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations" examines the use of puberty delaying medications, hormone therapy, and surgery to treat gender dysphoria. FAC 59G-1.035(4)(b).

In drafting the GAPMS Report, AHCA ignored most of the body of peer-reviewed literature on gender-affirming care. (Doc.120-6, at 147:12-147:25; Doc.84-1, ¶4.) The "assessment" by Dr. Brignardello-Peterson and Dr. Wiercioch included just 27 studies published between 2020 and 2022 (Ex.324, at 10-11.)—hardly a comprehensive review. (Ex.324, at 10-11; Ex.7, ¶¶80-81.)

The GAPMS Report and Defendants' experts attempt to discount the supportive literature they did consider as "low quality." That claim is highly misleading and at minimum surfaces a factual dispute. (Ex.324, at 11-12; Ex.5, ¶¶19-22.) While randomized trials are rated as high-quality evidence and observational studies as low-quality evidence (Ex. 5, ¶20), for ethical and practical reasons, it is not possible to conduct randomized trials involving medical treatments for gender dysphoria. (Ex.8, ¶¶74-85; Ex.10, ¶¶52-53; Ex.5, ¶¶27-28; Ex.9, ¶17; Ex.7, ¶83.) The lack of randomized trials does not render the existing research insufficient to inform clinical decision making. (Ex.324, at 13; Ex.14, ¶30; Ex.10, ¶56; Ex.13, ¶8; Ex.8, ¶¶73, 88-90.)

3) Effectiveness in improving prognosis or health outcomes

The peer-reviewed literature shows that puberty-delaying medications, hormone therapy, and surgery are: 1) safe and effective for the treatment of gender dysphoria; and 2) when used for that purpose, correlated with additional positive

health outcomes, including improved quality of life, mental health, and psychosocial functioning. (Section II.B, *supra*.)

4) Utilization trends

The GAPMS Report makes no mention of this factor. There has been a notable increase in the utilization of gender-affirming medical care over the last three decades, and AHCA's own data reflects this increase. (Ex.5, ¶¶39-40; Ex. 317; *see also* Ex.6, at ¶59.) Paradoxically, AHCA appears to view that rise in utilization as a reason to implement the Exclusion. (Ex.335.) But what it shows is that the services are commonly used and not experimental. *See Rush*, 625 F.2d at 1156, n.11 (contrasting service that is "generally accepted by the professional medical community as an effective and proven treatment for the condition for which it is being used" with a one that "is rarely used, novel, or relatively unknown").

5) Other coverage policies

AHCA's coverage exclusion is an outlier among health insurance plans. Most health plans, in Florida and elsewhere, do not have categorical transgender-specific exclusions. (Ex.6, ¶¶40-46; *id.* ¶35 (highlighting that 25 states and D.C. prohibit such exclusions in state-regulated individual and group plans); Ex.5, ¶42.) In drafting the GAPMS report, AHCA did not even review private insurance policies. (Doc.120-6, at 149:2-152:6.)

Only 9 of the 56 states and territories operating a Medicaid program exclude coverage of gender-affirming medical care. (Ex.6, ¶¶54, 57.) Even among those jurisdictions, Florida's exclusion stands apart for its breadth and scope. (Ex.6, ¶¶ 55-57.) And Florida Medicaid itself covered this care until the Exclusion was adopted. (Doc.120-6, at 66:25-68:17, 74:18-75:9, 84:2-18, 243:7-15; Ex.257; Ex.317.)

While other nations' coverage policies have never factored into the GAPMS process, Defendants argue that their determination regarding puberty-delaying medications, hormone therapy, and surgery reflects an "international consensus" on the issue. (Mot. at 24-25.) That is wrong and misleading. Defendants have not conducted a comprehensive review of other countries' policies regarding gender-affirming care. And Defendants have misrepresented those nations' policies. (Ex.14, ¶¶73-82; Doc.142-11.)

6) Recommendations or assessments by clinical or technical experts on the subject or field

Recognized clinical and technical experts in the field of transgender medicine agree that puberty-delaying medications, hormone therapy, and surgery are safe and effective treatments for gender dysphoria. (Ex.8, ¶121; Ex.9, ¶89; Ex.11, ¶¶53-54, 100; Ex.17, ¶¶23, 133; Ex.10, ¶¶23, 43, 81; Ex.324, at 4-5.) But AHCA did not seek recommendations or assessments from recognized experts; it consulted a handful of vocal opponents of gender-affirming care.

B. Plaintiffs' Medicaid Act Claims Are Viable.

1) The EPSDT and Comparability Provisions of the Medicaid Act Are Enforceable Pursuant to 42 U.S.C. § 1983.

The Court should reject Defendants' argument that Plaintiffs have no private cause of action to enforce their Medicaid Act claims. For more than 20 years, the Supreme Court has required lower courts to apply a three-prong test to determine whether a statutory provision gives rise to a federal right under 42 U.S.C. § 1983. *See Gonzaga Univ. v. Doe*, 536 U.S. 273 (2002); *Blessing v. Freestone*, 520 U.S. 329 (1997). Under *Blessing*, courts must evaluate three elements: first, Congress must intend the provision in question to benefit the plaintiff; second, the right contained in the provision must not be so "vague and amorphous" that its enforcement would strain judicial competence; third, the statute must unambiguously impose a binding obligation on the state. 520 U.S. at 340-41 (citations omitted). *Gonzaga* clarified the first prong of the test, instructing that the provision in question must contain unambiguous "right- or duty-creating language," as opposed to language with an aggregate, rather than individual, focus. 536 U.S. at 284 n.3; *see also* 42 U.S.C. §§ 1320a(2), (10) (congressional intent that provisions of the Social Security Act, of which Medicaid is a part, are privately enforceable).[7]

[7] Citing *Collins v. City of Harker Heights*, 503 U.S. 115, 119 (1992), Defendants argue that the EPSDT and comparability provisions do not create enforceable rights because § 1983 "does not provide a remedy for abuses that do not violate federal law." (Mot. at 28.) *Collins*, which did not involve a federal law, is inapposite. There,

Blessing also instructs plaintiffs to plead their complaints in "manageable analytic bites" and courts to determine whether "each separate claim" satisfies the test. *Blessing*, 520 U.S. at 342; *id*. at 340. Here, Count III of Plaintiffs' complaint alleges that the Exclusion violates the EPSDT provisions, 42 U.S.C. §§ 1396a(a)(10)(A), 1396d(a)(4)(B), 1396d(r)(5), and 1396a(a)(43)(C), and Count IV alleges that the Exclusion violates the comparability requirements, 42 U.S.C. § 1396a(a)(10)(B). (Doc.1, at ¶¶275-80.)

Every federal appellate court to have considered whether the EPSDT provisions are enforceable by Medicaid beneficiaries through section 1983 has concluded that they are. *See S.D. ex rel. Dickson v. Hood*, 391 F.3d 581, 602-07 (5th Cir. 2004); *Pediatric Specialty Care, Inc. v. Ark. Dep't of Human Servs.*, 293 F.3d 472, 477-79 (8th Cir. 2002); *Miller v. Whitburn*, 10 F.3d 1315, 1319-20 (7th Cir. 1993); *see also Waskul v. Washtenaw Co. Cmty. Mental Health,* 979 F.3d 426, 445-48 (6th Cir. 2020) (finding § 1396a(a)(10)(A) enforceable in non-EPSDT case); *Bontrager v. Ind. Fam. & Soc. Servs. Admin,* 697 F.3d 604, 606-07 (7th Cir. 2012) (same); *Watson v. Weeks*, 436 F.3d 1152, 1159-62 (9th Cir. 2006) (same).

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the Supreme Court held that even if the allegations in the complaint were true, there was no constitutional violation. *Id*. at 125-30. Defendants make no such argument, and this Court has found that if Defendants' determination that the excluded treatments are experimental was unreasonable, Defendants have violated the Medicaid Act. (Doc.64, at 3-6.)

Defendants' argument that these courts failed to grasp the nature of a federal right under *Gonzaga* is unfounded. Take, for example, *S.D. ex rel. Dickson v. Hood*, in which a Medicaid beneficiary sought to enforce the EPSDT provisions. Assessing the first *Blessing*/*Gonzaga* prong, the Fifth Circuit concluded that section 1396a(a)(10)(A)—which requires that the State "must provide for making medical assistance available, including at least the care and services listed in paragraph (1) through (5), (17) and (21) of section 1396d(a) of this title, to all individuals" who meet the eligibility criteria—contains "precisely the sort of 'rights-creating' language identified in *Gonzaga* as critical to demonstrating a congressional intent to establish a new right." *S.D.*, 391 F.3d at 603. The Court also found that the EPSDT provisions do not have an aggregate focus but rather are "'concerned with whether the needs of [particular individuals] have been satisfied.'" *Id*. at 604 (quoting *Gonzaga*, 536 U.S. at 275). Turning to the second prong, the Court found that enforcement of the EPSDT provisions does not "strain judicial competence; it is the sort of work in which courts engage every day." *S.D.*, 391 F.3d at 605 (quotations omitted).[8] And third, the Court concluded that the provisions impose binding requirements on participating states. *Id*. at 605-06.

[8] While Defendants claim otherwise, district courts are clearly capable of determining whether health care services are "necessary" under section 1396d(r)(5). *See, e.g.*, *K.G.*, 981 F.Supp.2d at 1291-92; *C.R. ex rel. Reed v. Noggle*, 559 F.Supp.3d 1323, 1337 (N.D. Ga. 2021).

Similarly, two circuits have concluded that the comparability provision is enforceable through section 1983.[9] *See Waskul*, 979 F.3d at 446-48; *Davis v. Shah*, 821 F.3d 231, 255 n.12 (2d Cir. 2016).[10] In *Waskul*, the Sixth Circuit found that the comparability provision – which requires that "the medical assistance made available to any individual described" must "not be less in amount, duration, or scope than the medical assistance made available to any other such individual," 42 U.S.C. § 1396a(a)(10)(B) – contains "the kind of individually focused terminology that unambiguously confers an individual entitlement under the law." *Id*. at 447 (cleaned up). The Court further determined that the provision is "amenable to judicial remedy," as it "sets forth criteria for determining whether . . . services are equitably provided," and that the provision is "couched in mandatory rather than precatory language." *Id*. at 448 (cleaned up).

These cases establish that the EPSDT and comparability provisions create individual federal rights for Medicaid beneficiaries and are thus "presumptively

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[9] In *Harris v. James*, 127 F.3d 993 (11th Cir. 1997), the Eleventh Circuit held that a federal regulation itself cannot create an enforceable right under section 1983. *Id.* at 1008. The Court made clear that it was not deciding whether the statutory comparability provision could give rise to a federal right. *Id*. at 1011. Thus, *Harris* has no bearing on the issue before this Court. *See Doe v. Chiles*, 136 F.3d 709, 714-15 (11th Cir. 1998).

[10] Multiple district courts have reached the same conclusion. *See, e.g.*, *Cruz v. Zucker*, 116 F.Supp.3d 332, 345-46 (S.D.N.Y. 2015); *Women's Hosp. Found. v. Townsend*, 2008 WL 2743284 (M.D. La. July 10, 2008); *Michelle P. v. Holsinger*, 356 F.Supp.2d 763, 767-68 (E.D. Ky. 2005).

enforceable by § 1983." *Gonzaga*, 536 U.S. at 284. Defendants cannot make the "difficult showing" that Congress expressly prohibited reliance on section 1983 or that it provided a comprehensive remedial scheme intended to preclude individual suits to rebut this presumption. *Blessing*, 520 U.S. at 346. Congress has not done so. *See Wilder v. Va. Hosp. Ass'n*, 496 U.S. 498, 521-22; *see also City of Rancho Palos Verdes v. Abrams*, 544 U.S. 113, 121-22 (2005).

Finally, *Armstrong v. Exceptional Child Ctr., Inc.*, 575 U.S. 320 (2015), does not implicate the enforceability of Medicaid's EPSDT and comparability provisions pursuant to section 1983. *Armstrong* concerned a Medicaid payment provision (not EPSDT or comparability) that health care providers (not Medicaid enrollees) were seeking to enforce under the Supremacy Clause (not section 1983). 575 U.S. at 323-34. Unlike the provisions at issue here, the provision at issue in *Armstrong*, 42 U.S.C. § 1396a(a)(30)(A), had been found unenforceable pursuant to section 1983 by most courts, including this one. *See Fl. Pharmacy Ass'n v. Cook*, 17 F.Supp.2d 1293 (N.D. Fla. 1998). The plurality's reasoning in *Armstrong* did not involve and certainly did not overrule the section 1983 enforcement test. *See*, *e.g.*, *BT Bourbonnais Care, LLC v. Norwood*, 866 F.3d 815, 820 (7th Cir. 2017); *Legacy Cmty. Health Servs., Inc. v. Smith*, 881 F.3d 358, 373 (5th Cir. 2018).

2) The Exclusion Violates the Medicaid Act's EPSDT Requirements.

The EPSDT requirements' fundamental purpose is to ensure that Medicaid recipients under age 21 receive the "health care they need when they need it." *M.H. v. Berry*, 2021 WL 1192938, *6 (N.D. Ga. 2021) (cleaned up). Specifically, they require each state Medicaid program to cover any service allowable under § 1396d(a) if "necessary . . . to correct or ameliorate" health conditions regardless of whether the state covers the service for adults. 42 U.S.C. §§ 1396d(r)(5), 1396a(a)(10)(A), 1396d(a)(4)(B); *see, e.g., Moore ex rel. Moore v.* Reese, 637 F.3d 1220, 1233-34 (11th Cir. 2011); *S.D*, 391 F.3d at 589-93. "The EPSDT obligation is thus extremely broad." *Katie A., ex rel. Ludin v. L.A. County*, 481 F. 3d 1150, 1154 (9th Cir. 2007); *see also Smith v. Benson*, 703 F.Supp.2d 1262, 1269-70 (S.D. Fla. 2018). And "there is a very strong inference to be inclusive rather than exclusive" when determining the meaning of "correct or ameliorate." *Ekloff v. Rodgers*, 443 F.Supp.2d 1173, 1180 (D. Ariz. 2006). Further, states must take the proactive step of ensuring that services determined to be medically necessary for a particular beneficiary are actually arranged for. 42 U.S.C. § 1396a(a)(43)(C); *Katie A.*, 481 F. 3d at 1158-59.

Here, the EPSDT provisions require Defendants to cover the gender-affirming services barred by the Exclusion. Puberty-delaying medications, hormone therapy, and surgery fall within the scope of benefits listed in § 1396d(a). *See* 42 U.S.C. §

1396d(a)(1) (inpatient hospital services), (2)(A) (outpatient hospital services), (5)(A) (physicians' services), (12) (prescribed drugs). And, for many transgender young people, the services are "necessary . . . to correct or ameliorate" their gender dysphoria. *Id*. § 1396d(r)(5).

Broad consensus within the medical community recognizes that these treatments can be medically necessary for transgender adolescents and young adults, based on their individual needs. Prior to implementing the Exclusion, AHCA reached the same conclusion, covering each of these services for a significant number of transgender Medicaid beneficiaries under age 21. (Ex.317.) Indeed, AHCA covered puberty-delaying medications for K.F. and S.D. (Doc.120-6, at 247:9-247:20), and hormone therapy for Mr. Rothstein (*id*. at 246:15-247:6).

3) The Exclusion Violates the Medicaid Act's Comparability Requirement.

The Medicaid Act requires AHCA to ensure that the "medical assistance made available to any [categorically needy] individual . . . shall not be less in amount, duration, or scope than the medical assistance made available to any other such individual." 42 U.S.C. § 1396a(a)(10)(B); 42 C.F.R. § 440.240. Federal regulations make clear that states "may not arbitrarily deny or reduce the amount, duration, or scope of a required service . . . to an otherwise eligible beneficiary solely because of the diagnosis, type of illness, or condition." 42 C.F.R. § 440.230(c).

Courts regularly hold that the comparability requirement "prohibits discrimination among individuals with the same medical needs stemming from different medical conditions." *Davis*, 821 F.3d at 258; *see also White v. Beal*, 555 F.2d 1146, 1148 (3d Cir. 1977); *Cota v. Maxwell-Jolly*, 688 F.Supp.2d 980, 993 (N.D. Cal. 2010).

While AHCA refuses to cover various surgical procedures necessary to treat gender dysphoria, the agency covers the same surgeries when necessary to treat other conditions. (Ex.4 at Definitions ¶ 13; Ex.1, at ¶¶ 8-12.) Multiple federal courts have held that such a policy violates the comparability requirement by discriminating based on diagnosis.[11] *See*, *e.g.*, *Flack v. Wis. Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1019 (W.D. Wis. 2019); *Fain v. Crouch*, 2022 WL 3051015, *13 (S.D. W. Va. 2022).

The same reasoning applies to the categorical exclusion of hormone therapy. AHCA does not cover testosterone or estrogen when necessary to treat gender dysphoria but covers the same prescription drugs when necessary to treat other conditions. (Ex.4, ¶13; Ex.1, ¶8.) While Defendants argue that these uses are not

[11] Defendants argue that there is no "equivalence between" a mastectomy performed to treat gender dysphoria and a mastectomy performed to treat breast cancer because in the breast cancer context, "diseased breast tissue is removed from the body." (Mot. at 28.) Defendants do not explain why that distinction is meaningful and ignore that a mastectomy is routinely performed (and covered by AHCA) in patients whose breast tissue is not "diseased." (Ex.10, ¶¶14, 24.)

equivalent for purposes of Medicaid coverage, the prescription drug provision of the Medicaid Act indicates otherwise. The statute requires states to cover all FDA-approved drugs when they are prescribed for a "medically accepted indication," subject to certain limited inapplicable exceptions.[12] 42 U.S.C. §§ 1396r-8(k)(2), 1396r-8(d)(1)(B); Ex.63, at 2; *see also Edmonds v. Levine,* 417 F.Supp.2d 1323, 1338 (S.D. Fla. 2006). A "medically accepted indication" is a use that is FDA-approved or "supported by one or more citations included or approved for inclusion in any of the compendia" listed in the Medicaid Act. 42 U.S.C. § 1396r-8(k)(6); *see also id.* § 1396r-8(g)(1)(B)(i) (listing three compendia, including DRUGDEX). Thus, under the Medicaid Act, a use that is FDA-approved stands on equal footing with a use that is supported by citation in a compendium. *See Edmonds*, 417 F.Supp.2d at 1337 (holding that AHCA cannot "substitute its own judgment for that of Congress" and deny coverage for uses of a prescription drug that are supported by citation in a compendium).

Here, citations in DRUGDEX support the use of various forms of testosterone and estrogen to treat gender dysphoria. Ex.25, at 18-21, 23-26, 29-36; Ex.26at 23-25, 27-28, 34-35. *See Dobson v. Sec'y of Health & Hum. Servs.*, 2022 WL 424813 at *7 (11th Cir. 2022) (interpreting the phrase "supported by one or more citations"

[12] Conversely, nothing in the Medicaid Act prohibits states from covering FDA-approved drugs when they are prescribed for a use that is not FDA-approved or supported by citation in a compendium.

in § 1396r-8(k)(6) to mean a citation "tend[s] to show or help[s] prove the efficacy and safety of the prescribed off-label use"). But while that use is on par with any FDA-approved use for purposes of Medicaid coverage, Florida only covers testosterone for FDA-approved indications. (Ex.27; Ex.25, at 10-11.) Moreover, as a matter of practice, AHCA covers testosterone cypionate, testosterone enanthate, and estrogen for ***absolutely any use*** – whether the use is FDA-approved, supported by citation in a compendium, or not – other than to treat gender dysphoria. (Ex.28.)[13] Thus, AHCA is excluding coverage for only one "medically accepted indication" (gender dysphoria) and providing coverage for every other indication, even those that are not medically accepted.

C. The Exclusion Violates Section 1557 of the ACA.

Section 1557 creates "an affirmative obligation not to discriminate in the provision of health care." *Schmitt v. Kaiser Found. Health Plan of Wash.*, 965 F.3d 945, 955 (9th Cir. 2020). Section 1557 requires, in relevant part, that "[a]n individual shall not, on the ground prohibited under … title IX of the Education Amendments of 1972 (20 U.S.C. 1681 *et seq.*), … be excluded from participation in, be denied the benefits of, or be subjected to discrimination under, any health program or activity, any part of which is receiving Federal financial assistance." 42

[13] https://ahca.myflorida.com/content/download/8681/file/PDL.pdf.

U.S.C. § 18116(a). Title IX prohibits discrimination "on the basis of sex." 20 U.S.C. § 1681.

"To state a claim under [Section 1557], a plaintiff is required to show that he or she (1) was a member of a protected class, (2) qualified for the benefit or program at issue, (3) suffered an adverse action, and (4) the adverse action gave rise to an inference of discrimination." *Griffin v. Gen. Elec. Co.*, 752 F.App'x 947, 949 (11th Cir. 2019). Plaintiffs address each element in turn.

1) The Exclusion discriminates against Plaintiffs based on sex.

The Exclusion discriminates based on sex in three distinct ways. First, the Exclusion speaks in explicit gendered terms and *facially discriminates* based on sex. Second, the Exclusion discriminates based on sex stereotypes relating to a person's sex assigned at birth. And third, the Exclusion discriminates based on sex because it discriminates based on transgender status.

a) The Exclusion facially discriminates based on sex.

On its face, the Exclusion discriminates based on sex. The Exclusion explicitly precludes Medicaid coverage for "services for the treatment of *gender* dysphoria," including "*[s]ex* reassignment surgeries" and any "procedures that alter primary or secondary *sexual* characteristics." FAC 59G-1.050(7). "A facial inquiry is what it sounds like: a review of the language of the policy to see whether it is facially neutral or deals in explicitly racial or gendered terms.'" *Kadel*, 2022 WL

3226731, at *18 (cleaned up).

Here, one cannot "'try writing out instructions' for which treatments are excluded 'without using the word[] … sex (or some synonym).'" *Kadel*, 2022 WL 3226731, at *19 (quoting *Bostock*, 140 S. Ct. at 1746). "It can't be done." *Bostock*, 140 S. Ct. at 1746. It is impossible to determine whether a particular treatment is for "*gender* dysphoria,"[14] leads to ""*[s]ex* reassignment," or "alter[s] primary or secondary *sexual* characteristics"—and thus, whether the Exclusion applies—without comparing the member's sex assigned at birth to how it might be impacted by the treatment. *Kadel*, 2022 WL 3226731, at *19.

A barrage of case law examining similar exclusions supports this conclusion. *See*, *e.g.*, *Fain*, 2022 WL 3051015, at *8; *Fletcher v. Alaska*, 443 F.Supp.3d 1024, 1027, 1030 (D. Alaska 2020); *Flack v. Wisconsin Dep't of Health Servs.*, 395 F.Supp.3d 1001, 1019-22 (W.D. Wis. 2019); *Boyden v. Conlin*, 341 F.Supp.3d 979, 1002-03 (W.D. Wis. 2018).

The Eleventh Circuit's decision in *Adams by & through Kasper v. Sch. Bd. of St. Johns Cnty.*, 57 F.4th 791 (11th Cir. 2022) (en banc), does not affect this straightforward analysis. In *Adams*, the Eleventh Circuit was concerned not with whether the policy at issue discriminated based on sex but "whether discrimination based on biological sex necessarily entails discrimination based on transgender

[14] Gender dysphoria necessarily considers an individual's sex assigned at birth.

status." *Id.* at 809. Indeed, the court found that a "bathroom policy requir[ing] 'biological boys' and 'biological girls'—in reference to their sex determined at birth—to use either bathrooms that correspond to their biological sex or sex-neutral bathrooms," *id.* at 801, facially "classifie[d] on the basis of biological sex." *Id.* at 803.[15]

Because a beneficiary's sex (however, one defines it) plays "an unmistakable and impermissible role in the" decision to deny Medicaid coverage under the Exclusion, the Exclusion facially discriminates based on sex. *Kadel*, 2022 WL 3226731, at *28.[16]

b) The Exclusion discriminates based on sex because it discriminates based on sex stereotypes.

Excluding coverage for gender-affirming medical care because it "*alter[s]* primary or secondary *sexual* characteristics," FAC 59G-1.050(7), "entrenches" the sex-stereotyped "belief that transgender individuals must preserve the genitalia and other physical attributes of their [sex assigned at birth] sex over not just personal preference, but specific medical and psychological recommendations to the

[15] Section 1557 only incorporated the grounds and enforcement mechanisms of Title IX, not any of its exemptions or carve-outs. *See Whitman-Walker Clinic, Inc. v. U.S. Dep't of Health & Hum. Servs.*, 485 F.Supp.3d 1, 43 (D.D.C. 2020).

[16] The holding in *Lange v. Houston County, Georgia*, 499 F.Supp.3d 1258, 1275 (M.D. Ga. 2020) ("*Lange I*"), is unavailing. (Doc.137 at 2-3.) *Lange I* is particularly unpersuasive for Plaintiffs' statutory claims, where Congress has directly renounced *Geduldig*'s reasoning.

contrary." *Boyden v. Conlin*, 341 F.Supp.3d 979, 997 (W.D. Wis. 2018). This is a "form of sex stereotyping where an individual is required effectively to maintain his or her natal sex characteristics." *Id.*; *see also Flack*, 328 F.Supp.3d at 951. It "is textbook sex discrimination." *Kadel*, 2022 WL 3226731, at *19.

Accordingly, courts throughout the country have found similar discrimination against transgender people to be rooted in impermissible sex stereotyping. *See*, *e.g.*, *Kadel v. Folwell*, 446 F.Supp.3d 1, 14 (M.D.N.C. 2020); *Toomey v. Arizona*, 2019 WL 7172144, at *6 (D. Ariz. Dec. 23, 2019).

This principle accords with longstanding Eleventh Circuit precedent that "[a]ll persons, whether transgender or not, are protected from discrimination on the basis of [a sex stereotype]." *Adams,* 57 F.4th at 813 (quoting *Glenn v. Brumby,* 663 F.3d 1312, 1318-19 (11th Cir. 2011)). *Adams* does not change this result. Unlike in *Adams*, the Exclusion hinges on prohibiting coverage for procedures that "*alter* primary or secondary *sexual* characteristics," FAC 59G-1.050(7), and "services for the treatment of *gender* dysphoria," FAC 59G-1.050(7), which by definition refers to the psychological distress that results from an *incongruence between one's sex assigned at birth and one's gender identity*. (Ex.33).

c) The Exclusion discriminates based on sex because it discriminates based on transgender status.

In *Bostock*, the Supreme Court explained that "it is impossible to discriminate against a person for being … transgender without discriminating against that

individual based on sex." 140 S.Ct. at 1741. And it is settled law that a policy that discriminates based on conduct or characteristics that either define or are closely correlated with a particular group facially discriminates against that group. *See*, *e.g.*, *Christian Legal Soc'y v. Martinez*, 561 U.S. 661, 689 (2010); *Lawrence v. Texas*, 539 U.S. 558, 583 (2003) (O'Connor, J., concurring).

Here, only transgender people have gender dysphoria. *See Fain*, 2022 WL 3051015, at *6; *see also C.P.*, 2022 WL 17788148, at *6; *Kadel*, 2022 WL 11166311, at *4; Section II(A), *supra*. Thus, the medical care singled out by the Exclusion is medical care that only transgender people need or seek. *See Fain*, 2022 WL 3051015, at *8; *Toomey*, 2019 WL 7172144, at *6; *Flack*, 328 F.Supp.3d at 950.

2) Plaintiffs have suffered an adverse action giving rise to an inference of discrimination.

Plaintiffs suffered an "adverse action" due to the Exclusion. Because of the Exclusion, Plaintiffs have lost Medicaid coverage for necessary medical treatment recommended by their doctors that would otherwise be covered. Defendants promulgated the Exclusion with discriminatory intent to achieve a discriminatory effect. The Exclusion bans coverage of medically necessary care for the treatment of gender dysphoria, which only transgender persons need. *See also Kadel*, 2022 WL 3226731, at *20.

Moreover, where the state "intentionally penalizes a person identified as male

at birth for . . . actions that it tolerates in [someone] identified as female at birth"—here, pursuing medical intervention to affirm a female identity—"sex plays an unmistakable and impermissible role." *Bostock*, 140 S.Ct. at 1741-42. Put another way, whether coverage is prohibited turns explicitly on a person's sex assigned at birth.

D. The Exclusion Triggers Heightened Scrutiny Under the Equal Protection Clause and Defendants Have Not Met Their Burden.

None of Defendants' arguments undermine the triable issue that Defendants' Exclusion violates Equal Protection because it discriminates based on sex and transgender status. And because the Exclusion discriminates based on sex and transgender status, Defendants must show that an "exceedingly persuasive justification" supports the Exclusion. *United States v. Virginia*, 518 U.S. 515, 531 (1996).

1) <u>The Exclusion discriminates based on sex, triggering heightened scrutiny.</u>

As outlined above, the Exclusion (1) *facially discriminates* based on sex; (2) discriminates based on sex stereotypes relating to a person's sex assigned at birth; and (3) discriminates based on sex because it discriminates based on transgender status.

Defendants argue that *Adams* held that "sex-based discrimination is discrimination based on biological sex" and that the Exclusion "does not make a

distinction based on biological sex." (Mot. at 32.) Not so, *see supra*. But even viewed in that (incorrect) framing, the Exclusion discriminates based on sex because the Exclusion prohibits coverage of procedures that ""*alter* primary or secondary *sexual characteristics*." FAC 59G-1.050(7). Such characteristics are biological.

Defendants further argue that rational basis applies because the Exclusion purportedly discriminates not based on sex, but on "medical diagnosis." (Mot. at 32.) But this does not save the Exclusion, either. Federal courts have rejected identical arguments. *Kadel*, 446 F.Supp.3d at 18. Only transgender people need coverage for "services and treatment for *gender dysphoria*" because only transgender people are diagnosed with gender dysphoria.

Defendants also argue that because the Exclusion is applied to both transgender people who were assigned female at birth and those who were assigned male at birth, it does not discriminate "based on sex." (Mot. at 32.) But that one group of transgender people are not treated worse than another does not change the fact that the Exclusion discriminates based on sex. "[T]he Equal Protection Clause, extending its guarantee to any person, reveals its concern with rights of individuals, not groups." *J.E.B. v. Alabama ex rel. T.B.*, 511 U.S. 127, 152 (1994) (Kennedy, J., concurring) (cleaned up); *see also Loving v. Virginia*, 388 U.S. 1, 8 (1967).

Finally, Defendants' reliance on *Geduldig v. Aiello*, 417 U.S. 484 (1974), is unavailing.

First, the Exclusion explicitly and facially classifies based on sex. *See Fletcher*, 443 F.Supp.3d at 1027, 1030; *see also Whitaker v. Kenosha Unified Sch. Dist. No.1 Bd. of Educ.*, 858 F.3d 1034, 1051 (7th Cir. 2017). Every person to whom the Challenged Exclusion applies is therefore discriminated against because of sex.

Second, *Geduldig* only held that an exclusion of pregnancy from a disability benefits program with no showing of "pretext" is not *per se* "discrimination against the members of one sex." 417 U.S. at 496 n.20. But "[s]ome activities may be such an irrational object of disfavor that, if they are targeted, and if they also happen to be engaged in exclusively or predominantly by a particular class of people, an intent to disfavor that class can readily be presumed." *Bray v. Alexandria Women's Health Clinic*, 506 U.S. 263, 270 (1993). Here, the Exclusion categorically excludes gender-affirming care from coverage, "which is only sought by transgender individuals." *Brandt v. Rutledge*, 2021 WL 3292057, at *2 (E.D. Ark. Aug. 2, 2021). That is precisely what *Geduldig* and *Bray* prohibit.

Third, the centrality of gender transition to transgender identity distinguishes this case from *Geduldig*. Unlike the pregnancy exclusion in *Geduldig*, the Exclusion here is based on a characteristic that defines membership in the excluded group. Pregnancy is not the defining characteristic of a woman. Living in accord with one's gender identity rather than birth-assigned sex is the defining characteristic of a transgender person. *See*, *e.g.*, *Glenn*, 663 F.3d at 1316.

2) The Exclusion discriminates based on transgender status and therefore independently triggers heightened scrutiny.

Defendants misconstrue the reach of the *Adams* case again in their assertion that the court "explained what constitutes unconstitutional discrimination based on transgender status." (Mot. at 32.) But the *Adams* court did no such thing. True, the *Adams* court expressed in *dicta* "doubt that transgender persons constitute a quasi-suspect class" because "the Supreme Court has rarely deemed a group a quasi-suspect class." 57 F.4th at 803 n.5. But that does not mean that "[t]ransgender individuals [] aren't entitled to heightened constitutional review per se." (Mot. at 33.)

Discrimination based on transgender status is separately entitled to, at least, heightened scrutiny because transgender people meet all of the indicia required. *See Grimm v. Gloucester Cnty. Sch. Bd.*, 972 F.3d 586, 607 (4th Cir. 2020); *see also Karnoski v. Trump*, 926 F.3d 1180, 1200 (9th Cir. 2019). "[T]ransgender people as a class have historically been subject to discrimination or differentiation; … they have a defining characteristic that frequently bears no relation to an ability to perform or contribute to society; … as a class they exhibit immutable or distinguishing characteristics that define them as a discrete group; and … as a class, they are a minority with relatively little political power." *Evancho v. Pine-Richland Sch. Dist.*, 237 F.Supp.3d 267, 288 (W.D. Pa. 2017).

3) There is a genuine dispute of material fact as to whether Defendants engaged in purposeful discrimination.

Defendants must "treat all persons similarly situated alike" or "avoid all classifications that … that reflect a bare desire to harm a politically unpopular group." *Glenn*, 663 F.3d at 1315 (cleaned up). That said, because the Exclusion is facially discriminatory, a showing of intentional discrimination is unnecessary. *See Cmty. Servs., Inc. v. Wind Gap Mun. Auth.*, 421 F.3d 170, 177 (3rd Cir. 2005).

Determining discriminatory intent is guided by an eight-factor test. *See League of Women Voters of Fla., Inc. v. Fla. Sec'y of State*, 32 F.4th 1363, 1373 (11th Cir. 2022) (cleaned up). Here, these factors are met.

- *The impact of the challenged law*: "[T]he Exclusion impacts only transgender individuals—that provides some circumstantial evidence of intentional discrimination." *Lange v. Houston Cnty., Georgia*, 608 F.Supp.3d 1340, 1355 (M.D. Ga. 2022) ("*Lange II*"). *See also supra*.
- *The historical background:* Here, Florida Medicaid covered medical treatment for gender dysphoria, until 2022, when Florida's government adopted a blizzard of anti-LGBTQ laws. This includes restrictions on the coverage and provision of gender-affirming care, "Don't Say or Trans" laws, banning of books discussing LGBTQ identities, bans on drag performances, and more. (Opp. Ex. E; Doc.1, ¶¶126(a)-(f).)

- *The specific sequence of events leading up to its passage:* Plaintiffs have laid out circumstantial evidence concerning this factor, including the coordination with the Governor's Office, FDOH, and anti-transgender activists.
- *Procedural and substantive departures:* Plaintiffs have documented a litany of procedural and substantive departures, including AHCA's: (1) hiring of outside consultants, which AHCA had never done for a GAPMS (Doc.120-6, at 137:10-12, 139:17-138:3), all of whom opposed gender-affirming care (Ex.324, at 7-9); (2) not enlisting or even considering any consultant supporting the provision of gender-affirming care (Doc.120-6, 135:10-15; Doc.120-9, 112:5-23); (3) employing an unprecedented GAPMS process for a treatment already covered (Doc.120-6, 93:13-21); (4) bypassing the employees typically tasked with conducting GAPMS processes (Doc.120-9, 85:16-19); and (5) closely coordinating with and having the process originate from other agencies like FDOH and the Governor's Office, (Doc.120-6, at 89:18-19, 90:25-91:1, 92:2-4; Opp. Ex. D (Weida), 15:2-18:3; Ex.302).
- *The contemporary statements and actions of key legislators:* Plaintiffs have pointed to some of these demeaning and offensive statements. (Doc.1, ¶126(g).)

- *The foreseeability of the disparate impact and knowledge of that impact:* The impact on transgender Medicaid beneficiaries was both foreseeable and communicated to Defendants during the notice-and-comment process. (Ex. 323, at 6; Ex. 324, at 2; Ex. 325, at 3-4).
- *The availability of less discriminatory alternatives*: "There is no evidence [Defendants] considered less discriminatory alternatives." *Lange II*, 608 F.Supp.3d at 1356.

When it comes to whether Defendants engaged in purposeful discrimination, "the facts are hotly disputed," at least. *Lange II*, 608 F.Supp.3d at 1356.

IV. CONCLUSION

For the foregoing reasons, the Court should deny Defendants' Motion.

Respectfully submitted this 28th day of April 2023.

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CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Motion contains 7,999 words.

CERTIFICATE OF SERVICE

I hereby certify that on this 28th day of April 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ Omar Gonzalez-Pagan
Counsel for Plaintiffs

TAB 200-1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
Tallahassee Division

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

DECLARATION OF OMAR GONZALEZ-PAGAN

Pursuant to 28 U.S.C.§ 1746, I, Omar Gonzalez-Pagan, do hereby declare as follows:

1. I am over 18 years of age.

2. I am Counsel at Lambda Legal Defense and Education Fund, Inc. and serve as counsel of record for the plaintiffs in the above-captioned matter.

3. I have personal knowledge of the stated herein, except those stated on information and belief, and if called upon, could and would testify competently to them.

4. I submit this declaration in support of Plaintiffs' Memorandum of Law in Opposition to Defendants' Motion for Summary Judgment.

5. Attached as **Exhibit A** is a true and accurate copy of an email with the subject line "A Message from your WPATH President, Dr. Marci Bowers" sent to WPATH members on April 21, 2023, as publicly posted on https://listloop.com/wpath/mail.cgi/archive/adhoc/20230421130649/.

6. Attached as **Exhibit B** is a true and correct copy of article "Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand," published in the peer-reviewed academic Journal of New Zealand Medical Journal in December 2018.

7. Attached as **Exhibit C** is a true and correct copy of the publication "Primary Care Gender Affirming Hormone Therapy Initiation Guidelines: Aotearoa New Zealand guidelines for commencing GAHT for adults in primary care," published in March 2023.

8. Attached as **Exhibit D** is a true and correct copy of excerpts of the transcript of the deposition of Jason Weida on April 24, 2023 taken in relation to the above-captioned matter.

9. Enclosed as **Exhibit E** is a true and correct copy of the press release issued by Equality Florida on April 11, 2023 announcing their "TRAVEL ADVISORY: FLORIDA MAY NOT BE A SAFE PLACE TO MOVE OR VISIT."

I declare under the penalty of perjury that the foregoing is true and correct.

Dated this 28th day of April 2023.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan

TAB 200-2

ListLoop (https://listloop.com/wpath/mail.cgi)

A Message from your WPATH President, Dr. Marci Bowers

From: "WPATH" <wpath@PROTECTED>
Subject: A Message from your WPATH President, Dr. Marci Bowers
Date: April 21st 2023

WPATH
WORLD PROFESSIONAL ASSOCIATION FOR TRANSGENDER HEALTH

April 21, 2023

Dear Colleagues,

In the United States, 2023 has been a difficult year thus far for trans rights, to say the least. Although anti-trans sentiment has simmered for years, the exponential rise in TGD identification among adolescents has triggered unprecedented attacks against all things trans. More than 400 anti-transgender bills, particularly in conservative states, see anti-transmessaging as a winning political posture for some. Eleven (11) states alone have already banned or restricted gender affirming care for gender diverse adolescents. Last week, Missouri became the first state to attempt gender enforcement on *adult* populations when attorney general, Andrew Bailey, issued an 'emergency declaration' that added draconian new hurdles for adult trans care to its adolescent ban. It is already probable that gender affirming care will be a wedge issue in the 2024 US election cycle.

Globally, many of the arguments used here in the US to ban transgender care have been cherry-picked or use narrowly excerpted language for restrictions that have been implemented in gender

services policies in Sweden and the UK---'lack of evidence', 'experimental' and 'focus on mental health'. They also ignore European countries where access to trans care has recently expanded (Spain, Portugal, and France). And unlike Swedish and British restrictions---which do not end treatment but rather, make research participation compulsory in order to answer remaining questions---conservative US policy makers have no interest in research on TGD medical therapy; they only care about shutting it down. Rather than safeguard young people by outlawing automatic weapons and high-capacity munitions, conservatives feel that banning trans care and removing LGBTQ-themed books will better protect society.

Caught in the middle are TGD individuals, providers, and families, who are now in anguish here in US-affected states. WPATH membership continues to receive stories of growing despair, clinics closing, families moving or seeking healthcare out of state [see link]. (https://www.vice.com/en/article/wxj5pw/florida-lgbtq-clinics-anti-trans-laws) Suicidality and desperation are again, needlessly in play.

Telemedicine and the emergence of sanctuary US states (California, Minnesota, and Colorado) that have chosen to defend access to trans care, provide some hope. But real progress on the road back will be difficult until the flow of anti-trans legislation slows and then stops. If there is one reductionist word that WPATH does not deserve, it is advocacy--all scientific organizations participate in some form of advocacy.

That said, the scientific and biological arguments can all be won and should continue to be argued. In a recent interview, Dr. Eli Coleman responded "*WPATH followed a rigorous, multi-year process and was based on the best available scientific evidence and weighing all risks and benefits to arrive at the recommendations in our Standards of Care 8 guidelines. Our multi-step methodology is clearly set forth in the guidelines themselves. When you compare the process we followed, the SOC8 has by far the more robust methodology than any other trans health related guidelines. We had 119 experts from around the world involved, developed PICO questions which formed the basis of systematic reviews, used a consensus-based approach (Delphi) involving all committee members to arrive at our conclusions and then graded the strength of our recommendations. We had an extensive period of public comment on a draft of the SOC8 and this input was checked against the available evidence resulting in the final version of the SOC8. The rationale for our recommendations is clearly explicated in the SOC8 referencing the extant research. WPATH stands behind our process and conclusions.*"

The recent New York Times opinion piece, "*What Decades of Providing Trans Care Have Taught Me*", was my take on the situation and can be read here (https://wpath.org/media/cms/Documents/NYT%20OpEd%20M%20Bowers%20Apr%201%202023.pdf).

The **first step** on the road back, in my opinion, will be to allow the public to hear the anguish and the stories of those in pain as a direct result of anti-trans legislation, difficult as this will be to watch---and to pin this pain upon those legislators and policy makers who have inflicted the agony. In my interview

with CBS Evening News to be aired any day, I called it 'legislative cruelty'. The moment we are in reminds me of San Francisco's Harvey Milk and his plea to gay persons to come out. We need to be heard—trans persons, allies, parents, families, politicians, clergy---those who have been hurt and those who know us.

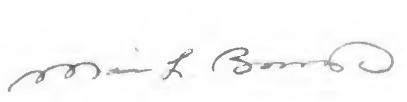
The **second step** on the road back will be to unite disparate causes in our fight against a common foe. An attack on trans care is an attack on women. It is an attack on black people, brown people, and Asian people. It is an attack on Jewish, Muslim, Hindi, Sikh, and true Christian communities. It is an attack on diversity and all of the ideals that diversity holds. It is an attack on us all. A majority of Americans favor access to adolescent trans care see link to NPR-Marist poll (https://maristpoll.marist.edu/polls/npr-pbs-newshour-marist-poll-transgender-rights-april-2021/) but the support is regional and it is thin. We need to better explain what adolescent TGD care looks like, why it is effective and indicated and who these patients really are. Anti-trans legislation needs to be fought with every voice, every thought, every inclination by all who know it. We need to make anti-trans legislation a *losing political issue*.

Already lost in this debate is the deplorable state of health and sex education throughout the Southern US. Furthering this ignorance, books are now banned, especially and specifically those with LGBTQI themes. It is of little surprise to many that persistent rates of new HIV infection, incest, and STDs remain highest where sex education is lowest, most in states where anti-trans legislation has been proposed.

And finally, '*What is a Woman?*', the title to a trite and condescending 2022 American movie produced by conservative Matt Walsh, whose edits left out any answer to the question, as though the answer was obvious. What was cut from the piece was reality; that nature lacks a definitive answer to the question. Because there is no biological measure----not chromosomes, not hormones, not anatomy nor any of the six other biological markers of sex---a woman is what society sees based upon the gender identity the individual projects. No measure in biology gets it right every time. For every rule, there is an exception. Sex and gender are complicated and diverse---but let us explain the phenomena, not allow the issues to be put back in the societal closet. Ultimately, what terrifies conservatives most is that gender diversity is a force of nature that can no longer be contained by religious conscription or enforcement of a gender binary.

Killarney, Ireland and EPATH will again surely exceed expectations as we meet April 26-28, 2023.

Until we all dance once more….



Marci L Bowers, MD

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TAB 200-3

Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand

Jeannie Oliphant, Jaimie Veale, Joe Macdonald, Richard Carroll, Rachel Johnson, Mo Harte, Cathy Stephenson, Jemima Bullock, David Cole, Patrick Manning

ABSTRACT

Internationally and within Aotearoa, New Zealand, there has been a substantial increase in the demand for gender affirming healthcare over the past decade. It is likely that this level of referrals to health services will continue in the foreseeable future. The Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand were developed following the recognition that the previous good practice guide required updating to be in step with current practice and international standards. This article presents a summary of the guideline focusing on puberty blockers, hormonal therapies, access to surgery and other gender affirming healthcare. We hope these guidelines will support the development and provision of services providing gender affirming healthcare around the country and provide helpful guidance to all health professionals involved in the care of trans people.

Internationally and within Aotearoa, New Zealand, there has been a substantial increase in the demand for gender affirming healthcare over the past decade. The Youth'12 survey estimated that approximately 1.2% of adolescents in Aotearoa, New Zealand identify as transgender.[1] As societal acceptance for trans people grows, it is likely that this level of referrals to health services will continue in the foreseeable future.[1,2]

Transgender healthcare is rapidly evolving. Table 1 includes some of the terminology healthcare professionals may encounter. The World Professional Association of Transgender Health (WPATH) is the international body responsible for producing standards of care (SOC) for transgender health based on international clinical consensus.[3] These are currently being revised and version 8 will inform practice internationally and in Aotearoa, New Zealand.

The Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand[4] were developed following the recognition that the previous good practice guide required updating to be in step with current practice and international standards. This guideline is not intended to replace the WPATH SOC but to present additional guidance for the provision of gender affirming healthcare in Aotearoa, New Zealand. This article presents a summary of gender affirming healthcare discussed in the larger document.

Methods

This guideline was produced in collaboration with trans community members and after consultation with many services and health professionals throughout Aotearoa, New Zealand, who work professionally

Table 1: Terminology.

Gender identity
A person's concept of their self as male, female, a blend of both or neither. Gender identity can be the same as, or different to, the sex assigned at birth.
Gender expression
The external presentation of one's gender. This can be expressed through one's name, clothing, behaviour, hairstyle, voice or any other way. A person's gender expression may or may not conform to socially defined behaviours and characteristics typically associated with being either solely masculine or feminine.
Gender diverse
A term to describe people who do not conform to their society or culture's expectations for males and females. Being transgender can be one way of being gender diverse, but not all gender diverse people identify as being transgender and vice versa. Gender creative or gender expansive are other similar terms that are used when referring to children.
Assigned male at birth
A person who was thought to be male when born and initially raised as a boy.
Assigned female at birth
A person who was thought to be female when born and initially raised as a girl.
Trans or transgender
A term for someone whose gender identity does not align with their sex assigned at birth. This term is often used as an umbrella term, recognising that people may describe themselves in many ways including the use of indigenous terms such as; whakawāhine, tangata ira tāne, tāhine (Māori), mahu (Hawai'i and Tahiti), vakasalewalewa (Fiji), palo- pa (Papua New Guinea), fa'afafine (Samoa), akava'ine (Rarotonga), fakaleiti or leiti (Tonga), fakafifine (Niue).
Cis or cisgender
A term for someone whose gender identity aligns with their sex assigned at birth.
Trans boy/male/man
A term to describe someone, assigned female at birth, who identifies as a boy/male/man.
Trans girl/female/woman
A term to describe someone, assigned male at birth, who identifies as a girl/female/woman.
Non-binary
A term to describe someone who doesn't identify exclusively as a man or a woman. There are many different ways that people may be non-binary male or female.
Gender dysphoria
A term that describes the distress experienced by a person due to the incongruence between their gender identity and their sex assigned at birth.
Social transition
The process by which a person changes their gender expression in social situations to better align with their gender identity.
Gender affirming healthcare
Healthcare that is respectful and affirming of a person's unique sense of gender and provides support to identify and facilitate gender healthcare goals. These goals may include supporting exploration of gender expression, support around social transition, hormone and/or surgical interventions. This may also involve providing support to whānau, caregivers or other significant supporting people.
Pronoun
A word used in place of a noun (or name). Pronouns include: he/him, she/her or they/them. Other gender neutral pronouns in use include ze and hir.

to advance healthcare for trans people. While regional differences in practice exist, the document describes principles and approaches that encompass this diversity. The gender affirming hormonal therapy guidelines in this document draw significantly on those published by the Endocrine Society.[5]

Principles of gender affirming healthcare

These guidelines are based on the principle of Te Mana Whakahaere; trans people's autonomy of their own bodies, represented by healthcare provision based on informed consent.[6] The informed consent process involves several conversations between the trans person and clinician(s) before starting treatments that have an irreversible component to increase certainty that they are adequately prepared and are making a fully informed decision.[7]

The use of Sir Mason Durie's Te Whare Tapa Whā as a framework highlights the equal importance of spiritual, family, mental and physical health.[8] Health providers have a duty to approach care holistically and in partnership.[4] Involving practitioners with expertise in mental health is important for two reasons. Firstly, mental health professionals with the appropriate skills can assist with the informed consent process. Secondly, it is increasingly recognised that discrimination and marginalisation experienced by trans people contributes to high rates of anxiety and depression.[9–11] The Youth'12 survey highlighted the mental health disparities experienced by trans young people compared to their cisgender peers with 41% vs 12% experiencing significant depressive symptoms and 20% vs 4% reporting an attempted suicide, respectively, in the past 12 months.[1] While there is no New Zealand data for older trans people it is likely that they also experience elevated rates of anxiety and depression as overseas studies have found.[9] Because of this, health services that have good links with peer support groups and mental health professionals will be more responsive to the needs of trans people accessing gender affirming healthcare.

Each person presenting to a health service has their own unique clinical presentation and needs. While many trans people will benefit from hormone therapies and surgical interventions, some may require only one or neither of these options.[12] Clinicians should not assume that everyone wants to conform to binary (male or female) gender norms and be open to gender affirming healthcare that aligns with non-binary identities.[3] When outer gender expression is congruent with an inner sense of self, most trans people will find increased comfort, confidence and improved function in everyday life.[13] Avoiding harm is a fundamental ethical consideration for health professionals when considering healthcare. Withholding or delaying gender affirming treatment is not considered a neutral option, as this may cause harm by exacerbating any gender dysphoria or mental health problems. This is no different from harm that can be caused by withholding or delaying other medically necessary care.

Gender affirming healthcare

Gender affirming healthcare may include provision of puberty blockers in children and adolescents, and hormone therapy in older adolescents and adults. The criteria for access to gender affirming hormones are persistent well-documented gender dysphoria, the capacity to make a fully informed decision and to consent for treatment, 16 years of age or older, and significant medical or mental health concerns must be reasonably well controlled. However, it is increasingly recognised that there may be compelling reasons, such as final predicted height, to initiate hormones prior to the age of 16 years for some individuals, although there is as yet little published evidence to support this.[5] There is no upper age limit to starting gender affirming hormone therapy. These criteria reflect the WPATH SOC which emphasise that having medical or mental health concerns does not mean gender affirming care cannot be commenced, rather that these need to be managed as part of an informed consent process.[3] This readiness can be assessed by a prescribing provider or mental health professional who is experienced and competent at working with trans people.

The informed consent process for readiness for puberty blockers, gender affirming hormones or surgery are detailed in the WPATH SOC.[3] The main components include assessing gender dysphoria, discussing social transition, gender expression and physical transition options, and providing a space to consider the implications of these options, with regard to safety, expectations

and impact on social, emotional, academic/occupational functioning. For all trans, particularly children and young people, consideration of psychosocial supports, especially family/whānau support is essential. Provide support to families and additional guidance if this support is absent. If this aspect of the assessment is not completed by a medical professional, then communication between the mental health professional and the prescriber/surgeon should occur to ensure a holistic approach to assessment.

Fertility preservation should be discussed prior to starting puberty blockers, gender affirming hormone therapy or gonadectomy.[5] Refer to local fertility services for access to funded cryopreservation of gametes. For those starting feminising hormones, who have reached at least Tanner stage 3, it is recommended that cyropreservation of sperm be considered.[5] For those in early adolescence (Tanner stage 2–3), collection of mature sperm will not usually be possible as mature sperm are produced from mid puberty (Tanner stage 3–4).[7] For those starting masculinising hormones, the option of egg or ovarian tissue storage should be discussed, recognising however, that this involves invasive procedures that are not currently funded where reproductive organs remain. There is no current evidence to suggest that testosterone exposure affects the likelihood of future healthy egg harvesting, and there are many reports of trans men who have ceased testosterone, for the purposes of achieving conception, having successful pregnancy outcomes.[14] However, it is unknown what effect the duration of testosterone therapy has on ovarian function.

Testosterone therapy does not provide a guarantee of adequate contraception and is contraindicated in pregnancy because of potential harm to the fetus from the androgenising effects of treatment.[15] Provide contraceptive advice prior to starting testosterone. Progesterone based Long Acting Reversible Contraception (LARCs) such as (Depo provera®, Jadelle®) or Intrauterine Devices (IUDs) such as Mirena®/ IUCDs are suitable options. Note that IUD insertion may be technically more challenging in those with a degree of cervical atrophy from testosterone therapy.

Puberty suppression using gonadotropin releasing hormone (GnRH) agonists

Puberty blockers can be prescribed from Tanner stage 2 to suppress the development of secondary sex characteristics and may be still beneficial when prescribed later in puberty to prevent ongoing masculinisation/feminisation.[5] Puberty blockers are considered to be fully reversible and allow the adolescent time prior to making a decision on starting hormonal therapies. Monitoring of height is recommended as adult height may potentially be increased if prolonged puberty suppression delays epiphyseal fusing.[5] A bone age may be helpful to assess whether epiphyseal closure has occurred when considering what rate of hormonal induction to use. Concern has been raised regarding the long-term impact of puberty suppression on bone mineral density.[5] It is therefore advisable to encourage young people on puberty blockers to have an adequate calcium intake, provide vitamin D supplementation where needed and encourage weight bearing exercise.[7] Bone density measurements (DEXA) can be considered in those requiring a prolonged period on puberty blockers or have significant additional risks for reduced bone density.

Puberty blockers halt the continuing development of secondary sexual characteristics, such as breast growth or voice deepening, and relieve distress associated with these bodily changes for trans young people.[16,17] For trans men and others assigned female at birth, the puberty blockers will induce amenorrhoea, reducing distress associated with menstruation.

Currently goserelin (Zoladex®) implants have sole subsidy status, although leuprorelin (Lucrin®) injections are fully funded for children and adolescents who are unable to tolerate administration of goserelin.[18] Table 2 presents clinical recommendations for puberty blockers, and standard dosing schedules. Puberty blockers should be continued until further treatments such as initiating other anti-androgens, accessing orchiectomy or other surgical interventions are decided on.

Table 2: Clinical recommendations and dosing schedules for puberty blockade.

Medical examination and investigations during suppression of puberty	
Examination	Every 3–6 months: height, weight, consider sitting height, BP, Tanner stage to ensure complete suppression
Blood tests	Every 6–12 months: LH, oestradiol or testosterone. LH should be suppressed <2.0 units/L along with clinical features of puberty arrest.
X-rays	Bone age on left hand if clinically indicated
If major risk factors for osteoporotic # or prolonged time on puberty blockers	Consider DEXA imaging and Vitamin D treatment.
Leuprorelin (Lucrin®)	11.25mg IM every 12 weeks*
Goserelin (Zoladex®)	10.8mg SC implant insertion into lower abdomen every 12 weeks*

*Frequency can be reduced to 10 weeks if incomplete LH suppression, puberty progression, or ongoing menses.

Gender affirming hormonal therapy

Adults should undergo a medical examination and investigations prior to starting hormones (Table 3). It is important to evaluate and address any medical conditions that could be exacerbated by treatment.[5] As with the use of oestrogen or testosterone in any context, clinicians should consider whether patients are; smokers, have a history of heart failure, cerebrovascular disease, coronary artery disease, atrial fibrillation, or personal risk factors for cardiovascular disease, history or family history of venous thromboembolism (VTE), migraine, history of sleep apnoea or hormone-sensitive cancers (eg, breast, prostate, uterine or testicular). Prescribers are advised to not consider any of the above conditions as absolute contraindications, but to consider and discuss any risks presented as part of the informed consent process.

Feminising hormonal therapy (Table 4)

Oestradiol valerate can be started in conjunction with an anti-androgen agent or added to a GnRH agonist (leuprorelin/goserelin). Goserelin (Zoladex®) is an option where oral anti-androgen agents are not tolerated. Anti-androgens are no longer required following orchiectomy or genital gender reassignment surgery. Start a low dose of oestradiol valerate (Progynova®/Estradot®) and increase the dose every 6–12 months depending on the clinical effect.

Table 3: Medical examination and investigations prior to commencing gender affirming hormonal therapy.

Physical examination	**Investigations**
Blood pressure	Electrolytes if starting spironolactone
Height	HbA1c if risk factors suggest indicated
Weight	Lipids if risk factors suggest indicated
BMI	Prolactin if starting oestrogen
Tanner stage (in adolescents)	LH
	Testosterone level
	Oestradiol level
	Urine/serum HCG if commencing testosterone

Table 4: Feminising gender affirming hormonal therapy dosing regimen and expected effects.[5]

Medication	**Dose (adults and older adolescents)**		
Anti-androgen agent options (not required post gonadectomy)			
Cyproterone	Starting dose: 25–50mg po daily Usual maintenance dose: 25–50mg po daily, although smaller doses (12.5mg) may be effective		
Spironolactone	Starting dose: 50–100mg po daily Usual maintenance dose: 100–200mg po daily		
Oestrogen options			
Oestradiol valerate (Progynova®)	Starting dose: 1mg po daily* Usual maintenance dose: 2–4mg, maximum 6mg po daily		
Oestradiol patch (Estradot®)	Starting dose: 25mcg patch twice weekly Usual maintenance dose: 100–200mcg patch twice weekly		
Effect of oestrogen	**Expected onset**	**Expected maximum effect**	**Reversibility**
Redistribution of body fat	3–6 months	2–3 years	Likely
Decrease in muscle mass and strength	3–6 months	1–2 years	Likely
Softening of skin/decreased oiliness	3–6 months	unknown	Likely
Decreased sexual desire	1–3 months	3–6 months	Likely
Decreased spontaneous erections	1–3 months	3–6 months	Likely
Breast growth	3–6 months	2–3 years	Not possible
Decreased testicular volume	3–6 months	2–3 years	Unknown
Decreased sperm production	unknown	>3 years	Unknown
Thinning and slowed growth of body and facial hair[a]	6–12 months	>3 years	Possible
Male pattern baldness	Variable	b	
Voice changes	None	c	

a - Complete removal of hair requires laser treatment;
b - Familial scalp hair loss may occur if estrogens are stopped;
c - Treatment by speech-language therapists for voice training is most effective.

Potential complications for feminising oestrogen therapy include VTE particularly if aged >40 years and within the first two years of treatment.[5] Transdermal oestrogen has lower risks for thromboembolism than oral oestrogen and should be considered particularly if increased risks are present. It is unclear whether oestrogen therapy may adversely affect the lipid profile and blood pressure, but any effect is likely to be modest.[19,20] Liver dysfunction and gallstones are occasionally seen, although a clinically significant rise in the prolactin level is an uncommon occurrence.[21] There may be alterations in mood and libido.

Table 5: Masculinising gender affirming hormonal therapy dosing regimen and expected effects.[5]

Medication	**Dose (adults and older adolescents)**		
Androderm® patches	7.5mg daily (local irritation common)		
Sustanon® (testosterone esters)	250mg/ml IM every 3 weeks[a]		
Depo T (testosterone cypionate)	100–200mg IM every two weeks or, 100mg SC weekly–200 mg SC every 2 weeks		
Reandron® (testosterone undecylate)	1,000mg IM every 10–12 weeks (second dose at six weeks to achieve steady state)		
Effect of testosterone	**Expected onset**	**Expected maximum effect**	**Reversibility**
Skin oiliness/acne	1–6 months	1–2 years	Likely
Facial body/hair growth	6–12 months	4–5 years	Unlikely
Scalp hair loss	6–12 months[b]	variable	Unlikely
Increased muscle mass/strength	6–12 months	2–5 years	Likely
Redistribution of body fat	1–6 months	2–5 years	Likely
Cessation of periods	1–6 months		Likely
Clitoral enlargement	1–6 months	1–2 years	Unlikely
Vaginal atrophy	1–6 months	1–2 years	Unlikely
Deepening of voice	6–12 months	1–2 years	Not possible
Increased sexual desire	variable	variable	Likely

a - Sustanon contains peanut oil (arachis oil) and should be potentially avoided in those with peanut allergies.
b - Highly dependent on age and inheritance; may be minimal.

Masculinising hormonal therapy (Table 5)

Testosterone can be added to a GnRH agonist or started on its own. Start a low dose of testosterone and increase gradually. Potential complications include polycythemia, which if severe, increases the risk of a thrombotic event. Periods will usually cease within the first 3–6 months of therapy. For those moving from GnRH agonists to testosterone, continue the blocker until the person is on the full testosterone dose and well virilised to avoid any undesired bleeding. For those not started on a GnRH agonist and not ready to start testosterone other interventions to achieve bleeding cessation include:

- Primolut® (norethisterone) po 5mg bd to 10mg tds. Note: Norethisterone is partially metabolised to ethinylestradiol, which at these high doses is equivalent to levels in the combined oral contraceptive.
- Provera® (medroxyprogesterone) po 10mg tds or 20mg nocte
- Combined Oral Contraception—continuous active pill taking to avoid menstruation
- Depo-provera® (medroxyprogesterone acetate) 150mg IM every 12 weeks
- Mirena® (levonorgestrel)—intra-uterine device

The additional consideration of need for adequate contraception may affect the choice made.

Trans people receiving maintenance hormonal therapy should have ongoing medical assessments and investigations as illustrated in Table 6.

Table 6: Maintenance surveillance for gender affirming hormone therapy.[5]

	Investigation	Frequency
All persons	HbA1c—if risk factors suggest indicated	Annual
	Lipids—if risk factors suggest indicated	Annual
	Consider DEXA imaging if major risk factors for osteoporosis	
Feminising gender affirming hormone therapy	Electrolytes if on spironolactone and after a change in dose	Annual
	Liver function tests	Annual
	Testosterone—aim for <2nmol/L	3 monthly during first year, then annually
	Oestradiol – avoid supraphysiological levels (target <500pmol/L)	3 monthly during first year, then annually
	Prolactin	2 yearly
Masculinising gender affirming hormonal therapy	Testosterone – aim for male reference range[a]	3 monthly during first year, then annually
	Full blood count[b]	Every 3 months for first year, then 1–2 yearly
	Liver function tests	3 monthly during first year, then annually

a – testosterone should be measured midway between Depo T and Sustanon injections, immediately prior to a Reandron injection, and at least two hours after application of a testosterone patch.
b-consider testosterone dose reduction if Hct >0.54.

Gender affirming surgery

While many trans people are comfortable without, for others surgery is essential to alleviate their body dysphoria and live fully and authentically in their gender. Availability and funding are significant issues within Aotearoa, New Zealand. District health boards (DHBs) have expertise around provision of chest surgery (chest reconstruction to masculinise/breast augmentation to feminise where there has been no response to oestrogen), hysterectomy, oophorectomy and orchiectomy. Some DHBs have expertise in plastic surgical techniques such as laryngeal shaves and facial feminisation. Clinicians should be aware of local services and referral pathways. Currently access to genital reconstruction surgery (metoidioplasty or phalloplasty (masculinising) and vaginoplasty (feminising)) is via the Ministry of Health high-cost treatment pool (see website[23]).

Table 7 presents the surgical criteria recommended in the Aotearoa, New Zealand guidelines. These are the same as the current WPATH SOC.[3]

Other gender affirming care

Laser hair removal is important, particularly as feminising therapies will not completely halt facial hair growth that is already established. Be aware of local providers and support access where possible. Wearing a chest binder to achieve a more masculine chest appearance may be important; discuss safe use to prevent health risks associated with prolonged use.[24] Speech and communication are fundamental to people's genders. The goal of speech-language therapy is to help trans people develop voice and communication that reflects their gender.

General healthcare

All New Zealanders have the right to healthcare that is respectful and non-discriminatory. Ensuring healthcare services

Table 7: Aotearoa, New Zealand Guidelines and WPATH SOC v7 criteria for access to gender affirming surgery.[3]

- Criteria for access to chest reconstruction surgery:
  - Persistent, well-documented gender dysphoria.
  - Capacity to make a fully informed decision and to consent for treatment.
  - Age of majority.
  - If significant medical or mental health concerns are present, they must be reasonably well controlled.

Hormonal therapy is not a prerequisite for masculinising chest surgery but is recommended for a minimum of 12 months prior to consideration of feminising chest surgery.

- Criteria for access to hysterectomy, salpingo-oophorectomy and orchidectomy:
  - Persistent, well documented gender dysphoria.
  - Capacity to make a fully informed decision and to consent for treatment;
  - Age of majority.
  - If significant medical or mental health concerns are present, they must be well controlled.
  - 12 continuous months of hormone therapy as appropriate to the patient's transition goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).
- Criteria for access to metoidioplasty or phalloplasty (masculinising) and for vaginoplasty (feminising):
  - Persistent, well documented gender dysphoria.
  - Capacity to make a fully informed decision and to consent for treatment.
  - Age of majority.
  - If significant medical or mental health concerns are present, they must be well controlled.
  - 12 continuous months of hormone therapy as appropriate to the patient's gender goals (unless the patient has a medical contraindication or is otherwise unable or unwilling to take hormones).
  - 12 continuous months of living in a gender role that is congruent with their gender identity (note that this can include gender identities other than male and female).

In New Zealand, current practice is that the person must be 18 years or older to access publicly funded surgeries as above and in addition to the referral letter from the prescribing clinician, a letter of support from a mental health professional should be provided. The role of the mental health professional is to ensure that the person is psychologically prepared for the surgery (for example, has made a fully informed decision with clear and realistic expectations and is practically prepared for the event).

are inclusive of gender diversity is fundamental to good health care for trans people. Apart from gender affirming healthcare, trans people experience the same health needs as others. Those who have not undergone surgical removal of their breasts, cervix, uterus, ovaries, prostate or testicles remain at risk of cancer in these organs and should undergo screening as recommended. Manage sensitively, as many trans people find cancer screening extremely challenging, both physically and emotionally. Refer trans women for mammograms as per the National Breast Screening programme. Use of internal oestrogen cream prior to cervical smears in trans men may reduce discomfort and reduce the risk of inadequate smear tests.

General recommendations

Based on the guidelines outlined above, to best support the needs of transgender people in Aotearoa, New Zealand, we recommend that:

1. All health services provide equitable and accessible gender affirming healthcare services that align with international standards, evidence-based literature and community feedback.

2. DHBs enable flexible and responsive pathways on the basis of informed consent and self-determination.
3. Health services enable the involvement of trans people, including Māori trans people, in decisions that affect them regarding the development and provision of services.
4. Health services must support the development of culturally appropriate practice within clinical settings that acknowledges kaupapa Māori health frameworks.
5. DHBs provide clear information about pathways to access gender affirming healthcare services. This is inclusive of health services delivered by DHBs and primary healthcare.

Conclusion

The Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand have been developed in acknowledgement of the substantial increase in demand and significant evolution that has occurred in the period since the publication of currently used documents. The above summary provides an overview of gender affirming healthcare, while the full guideline details the role of the healthcare workforce in the provision of holistic healthcare for transgender people. We hope these guidelines will support the development of health services around the country, and provide helpful guidance to all health professionals involved in the care of transgender people.

Competing interests:
Nil.

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TAB 200-4

Primary Care Gender Affirming Hormone Therapy Initiation Guidelines

Aotearoa New Zealand guidelines for commencing GAHT for adults in primary care.

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Contents

Glossary of terms

In the field of transgender health, language continues to change and evolve. When in doubt about what language to use with patients, clarify the patient's preferred terminology and use their preferred language.

Transgender (or trans)

People whose genders differ from societal expectations based on their sex assigned at birth; in this document we use this term to include transgender men, transgender women, non-binary people (who do not solely identify as a man or a woman), tangata ira tāne, whakawāhine, irawhiti, and some takatāpui and MVPFAFF+[a] people.[1]

Cisgender (or cis)

A term for someone whose gender identity aligns with their sex assigned at birth.

Gender dysphoria

The distress or discomfort some trans people experience when their gender and body do not feel connected or congruent. Not all trans people experience gender dysphoria.

Gender euphoria

Feeling comfortable in your body. Some people experience this as joy and happiness.

Gender incongruence

A marked and persistent incongruence between an individual's presumed and experienced gender. Often referred to as a diagnostic code from the ICD-11 as outlined in Appendix A.

Gender affirming hormone therapy (GAHT)

The hormone therapy taken by some transgender people to embody and affirm their gender, often leading to improved psychological wellbeing and quality of life.

E-GAHT is used to abbreviate oestrogen-based gender affirming hormone therapy, and T-GAHT to mean testosterone-based gender affirming hormone therapy.

[a] MVPFAFF+ is an acronym to describe Pasifika gender identities: Mahu (Hawai'i and Tahiti), Vaka sa lewa lewa (Fiji), Palopa (Papua New Guinea), Fa'afafine (Samoa), Akava'ine (Rarotonga), Fakaleiti (Tonga) and Fakafifine (Niue).

Purpose and scope

This guideline aims to facilitate a primary care-based approach and to give general practitioners (GPs) and nurse practitioners (NPs) tools and information to safely initiate gender affirming hormone therapy (GAHT) in collaboration with their patients. They remove a standard requirement for a mandatory mental health assessment, instead encouraging an individualised approach which utilises psychological support and input only when needed.

Referral to secondary care is only initiated when needed and the primary care prescriber remains the primary or sole treating clinician for the majority of people. This aims to reduce unnecessary barriers and improve access to GAHT, in turn improving health outcomes for transgender adults in Aotearoa New Zealand (NZ).

All transgender people have a right to self-determination, autonomy and dignity when accessing healthcare, including gender affirming healthcare. This guideline aims to outline an open and transparent, person-centred approach to commencing GAHT which views the patient as a competent adult who has the capacity to make their own decisions about their body and health.

By working in partnership with the patient, this approach aims to empower patients by helping them to understand the benefits and risks of GAHT, enabling them to make an informed decision about starting GAHT.

Many transgender people will be well informed about their healthcare and patients will arrive with a wide range of levels of knowledge about GAHT. The prescriber's role is to ensure safety by following prescribing and dosing guidelines, assessing medical risk, providing education about expected outcomes, and monitoring treatment, in collaboration with their patient.

This document describes an approach to care for adults. Whilst the principles of self-determination, autonomy and informed consent remain the same in adolescents, there are added considerations and complexities in working with a younger population which were felt to be beyond the scope of this guideline. These considerations include the importance of youth development, family support, safety and the potential differences in both medications used and dosing. We recommend healthcare providers refer to the latest Standards of Care version 8 (SOC-8), released by the World Professional Association for Transgender Health (WPATH), for guidance for working with transgender children and adolescents.[2]

It is intended that these guidelines are used in conjunction with the *Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa New Zealand* [3] and local health pathways. They sit within the context of these national guidelines, which have a broader scope of all types of gender affirming care for people of all ages. These national guidelines were informed by Tā Mason Durie's models of health: Te Pae Māhutonga, using guiding principles of te mana whakahaere (autonomy) and ngā manukura (community leadership),[4] and Te Whare Tapa Whā, considering physical health, spiritual health, whānau health, and mental health.[5]

Importantly, GAHT is only one aspect of the wider process of gender affirmation, which may include medical, legal and social steps. Every transgender person is unique, and so may want to undertake some, none, or all of these steps to affirm their gender. Similarly, they may place different weight upon each of these and so pursue these in different orders. How to affirm one's own gender is a very individual decision, and there is no right or wrong way to do so.

Introduction

GAHT refers to the hormone therapy taken by some transgender people to embody and affirm their gender, often leading to improved psychological wellbeing and quality of life.[6] As outlined in the national guidelines,[3] gender affirming care, including GAHT, is a key part of transgender people's lives, and should be considered holistically in the context of their social and whānau relationships and spiritual wellbeing.[5]

Historically, the provision of GAHT has been limited to specialised secondary care services, which has contributed to restricted access to gender affirming care. Transgender people continue to face many barriers to accessing appropriate care in a timely manner, including cost, travel (particularly for patients in rural areas) and waiting times, partly due to increasing numbers of people accessing this type of care.[7] The increase in numbers of people seeking GAHT is thought to be due to greater awareness and reduced societal stigma when compared with previous decades. In the 2018 Counting Ourselves transgender health survey, 19% of participants reported an unmet need for GAHT.[8] The most commonly reported barriers were not knowing where to go (40%), cost (28%) and fear (26%). An informed consent model of care (further explained below), distributed among primary care providers, is the best model of care to reduce the current unmet need for GAHT.

In NZ, GAHT is currently initiated by a variety of health professionals in different clinical settings. This can include GPs, NPs, endocrinologists, sexual health physicians, adolescent health physicians and paediatricians. At the time of writing, pathways to access GAHT vary depending on locality. However, initiation of GAHT is increasingly being provided in primary care settings due to increasing demand and greater recognition of the barriers that transgender people, particularly those living outside of main cities, face when accessing secondary care services. Patients have a right to access GAHT in a timely manner within their local communities. To work towards this, these guidelines have been developed to assist all primary care providers by providing the information they need to initiate and provide repeat prescriptions of GAHT, with the aim of supporting their patients' gender affirmation and removing barriers for transgender adults accessing hormones. These guidelines are informed by the *Aotearoa Guidelines for Gender Affirming Health Care*[3] and overseas guidelines which have been adapted for local use.[9-13]

This document is a partnership between transgender and cisgender professionals; its authors include general practitioners, a primary care nurse, endocrinologists, a sexual health physician, an adolescent health physician, psychologists, academics and peer supporters. Whilst we appreciate that not all GPs and NPs will choose to initiate GAHT, this guideline has been written for those who do want this guidance.[b]

Many of the current pathways to access GAHT in NZ include the requirement of a psychosocial assessment by a mental health professional. These are often performed by psychologists and psychiatrists, resulting in long wait times for clients or a high cost barrier if more timely care is sought in the private system (which is not available or affordable to many people). Many transgender people experience this approach as pathologising, and may worry they have to prove they are 'transgender enough' or say the right thing in order to access the treatment they know they need to affirm their gender.[14] It is not the role of a health professional to make a judgement on whether a patient's gender (e.g. a non-binary gender) is valid or whether a patient is male or female enough. In some parts of NZ, it can be challenging to find a mental health professional to conduct this assessment at all.

[b] We recognise that not all primary care prescribers will want to initiate GAHT, and that challenges such as funding, appointment length and availability, increasing workloads and burnout all exist in NZ at this time. However, we feel it is important that those who wish to provide this care have access to practical guidance as provided in this document and are supported to prescribe GAHT for their patients. Supporting transgender patients to access GAHT in a timely manner which recognises their autonomy is very rewarding work, and we encourage primary care to get involved.

These guidelines outline an approach where the primary care team works in collaboration with patients to meet their gender goals, provides education about GAHT and general health, and helps to support patients' understanding of the risks and benefits of GAHT to make well-informed decisions about their health. This is often referred to as an 'informed consent model' and is the approach used in this document (see 'Informed consent' below for more detail).

Being transgender is not a mental illness.[15] Societal stigma and prejudice can lead to transgender people experiencing disproportionately high levels of discrimination, harassment, homelessness, unemployment, abuse and violence. The resulting gender minority stress can lead to the inequitable rates of poor mental health experienced by transgender people as a population.[16-18]

As a result, some transgender people will present with mental health conditions which require input from secondary care. As with any patient seen in primary care, psychologists, psychiatrists or secondary mental health services only need to be involved for those who are experiencing moderate to severe mental illness. Everyone else can, in theory, be managed in the community with their regular primary care team, which could include support from counsellors, health improvement practitioners or other mental health providers as needed.

For those who request it, counselling or psychotherapy can be of benefit, not as an assessment tool or mandatory part of accessing GAHT, but instead to provide psychological support during a time of change which can be stressful due to both personal and societal factors. For example, people may find it helpful to have support with exploring their gender or sexuality (particularly adolescents), the 'coming out' (or disclosure) process (especially to family or their workplace), and navigating experiences and concerns around transphobia, social stigma and other aspects of adjusting to this time of change. Ideally this support would be provided by mental health professionals such as counsellors or psychologists (or peer supporters where appropriate) who have high levels of transgender cultural safety.

Primary care is the ideal place for meeting most of the healthcare needs of transgender people, including hormone initiation, as primary care teams are part of patients' local communities, and are experts in whole life experience, including normal life events which may require their input. GPs and NPs take a holistic approach which considers a patient's physical health, mental health, culture, social supports, environment and lifestyle factors, which is well suited to providing gender affirming healthcare.

Primary care practitioners are able to work together with each transgender person to understand their gender embodiment goals, discussing options and together finding the most appropriate care for the individual. A patient with more complex mental health issues can still be referred to a psychologist or mental health team as needed, but there is no good reason for this to be the default approach. Likewise, a patient with more complex physical health issues can still be referred to an endocrinologist or sexual health physician. The Counting Ourselves survey[8] found that 48% of respondents felt that their doctor did not know enough about transgender healthcare, so health provider education is an important aspect of ensuring health needs can be adequately met.

The authors recognise that this is a rapidly evolving field of medicine. The guidelines were written in February 2023 and will require review in three years' time. We welcome and encourage research to evaluate the impact and outcomes of these guidelines, as well as the experiences of patients and providers.

Informed consent

The informed consent model of care views treatment as collaborative between the patient and healthcare provider. It is a term commonly used in medical practice to describe the interactive process of a health practitioner providing a patient with information and the patient using this to make an informed decision about their healthcare. In gender affirming healthcare, the term acknowledges that transgender people are the experts on their own gender, and the experiences, goals and needs that are related to their gender, while also acknowledging that healthcare providers have the expertise to provide this care in a way that maximises safety and efficacy.[19]

Informed consent is a process that respects patient autonomy and dignity and assumes capacity. As such it does not require a routine referral to secondary services or the private equivalent for a psychosocial assessment prior to initiating GAHT. We acknowledge the varied interpretations of the term 'informed consent' within transgender healthcare, and so have described here what is meant by informed consent in this guideline.

The use of 'informed consent' in this guideline reflects that used by the Medical Council of New Zealand (MCNZ)[20] to describe the process of providing information, including risks and benefits about a treatment, in a way that the patient can understand, as part of a trusting clinician–patient relationship, so that the patient can make a fully informed decision about care. In the case of a patient-centred approach to GAHT, the patients bring their own individualised gender embodiment goals and are active participants in the process.

Informed consent is an important component of the biomedical ethics principle of respect for patients' autonomy; this respect for autonomy should be balanced against the principles of beneficence and nonmaleficence.[21] This is reflected in *Cole's Medical Practice in New Zealand*, which states that the principle of informed consent serves to protect patient autonomy and a patient's right to determine what they want to do with their body, but that patients do not have a right to be provided treatment that is not clinically indicated.[22]

Primary care is the ideal place to create a safe and affirming space for gender affirming care. Primary care clinicians work as collaborative partners to establish lifelong relationships with the patient as the primary decision-maker. This partnership supports patient understanding of the risks and benefits of GAHT, including the impact on other areas of life such as work or education, relationships, sexual function and fertility, and works to promote general health and wellbeing. These guidelines serve as a starting point for patients and clinicians to develop a care plan appropriate to each individual's needs. Peer supporters, primary care nurses, primary mental health services, counsellors, psychologists and social workers may be involved in the delivery of hormones and GAHT health education. A multi-disciplinary approach is useful, although we recognise this is not always possible.

Like other medical interventions with similar risks, an external mental health assessment is not mandatory before accessing GAHT for adult patients. Providers should be aware that GAHT is often associated with improvements in a patient's mental health.[23] A patient who has severe mental health difficulties will likely still be able to provide informed consent, but may require support and treatment from a mental health professional alongside starting GAHT. For adults with a complex presentation or those who are requesting less common treatments or treatments with limited research evidence, further advice or assessment from different health professionals is likely to be required.[2] Remember that gender affirming healthcare may reduce mental distress, and that withholding or delaying care unnecessarily is unethical and could worsen a person's mental health. See FAQ 2 for more details.

The starting point when assessing capacity is always to presume that an adult has capacity to make the decision.[22] A patient has capacity to make a decision if they understand the nature and effects of the treatment; can weigh up options; balance risks and benefits; foresee consequences of consenting (or not consenting); demonstrate consistency in their decision-making; have no undue influence from a third party and can communicate their decision. In most cases for patients with diminished capacity to consent, external support may be required to assess capacity.

Examples of situations where capacity to consent may be diminished include cognitive impairment, intellectual disability, dementia, psychosis, or mania of a degree that it may be impacting on their ability to adequately understand and balance necessary information. In these cases only, a formal capacity assessment is an essential part of the informed consent process, ideally conducted by a health professional who knows the patient well.[24] A mental health professional may be able to assist with a capacity assessment. Providers should be aware that patients with diminished capacity still have a right to timely access to care, and this may involve the use of a supported decision-making process; see the section on diminished capacity in the Frequently Asked Questions section (FAQ 4) for more details.

We encourage prescribers to take a harm reduction approach to the initiation of GAHT, particularly when a patient is self-sourcing GAHT. If a patient is taking GAHT formulations which are unavailable in NZ or outside of recommended dose ranges, a plan to transfer onto NZ medications and doses in line with these guidelines should be negotiated in partnership with your patient.

WPATH Standards of Care Version 8

These guidelines align with the GAHT recommendations from the WPATH Standards of Care version 8.[2] Full details of the SOC-8 criteria for GAHT can be found in Appendix A, and these have been incorporated throughout this guideline. The SOC-8 recommendations refer to the International Classification of Diseases and Related Health Problems (ICD-11)[25] coding for Gender Incongruence, the details of which can also be found in Appendix A.

Stages of gender affirming hormone therapy initiation

These guidelines are based on providing individualised care in a staged format with a new patient. There is no set number of appointments that a patient must be seen for prior to starting GAHT, and this will vary depending on complexity, practitioner experience and appointment length. In some situations, several stages could be completed in one longer appointment, whilst in other situations it might take multiple appointments to work through one stage. Similarly, each person's body and gender embodiment goals are different, and it may take more appointments, working with your patient, for you both to understand what works best for them. This may require trialling different dosages and types of hormones and making changes where needed.

When patients consent to treatment it is good practice to allow reasonable time for the patient to make their decision. The MCNZ states that a key principle of informed consent is that it is an interactive process and not a one-off event.[20] For this reason, prescribers may wish to separate stages 3 and 4 into separate appointments, to allow patients time to consider the information provided, and to provide an opportunity to ask further questions.

The stages outlined below help to ensure that GAHT is prescribed as safely as possible, and help to ensure the best outcome for the patient's overall wellbeing. Stages 1 to 3 should be completed prior to prescribing hormones. These can be undertaken by a GP, NP, primary care nurse, or a combination of these colleagues working together in one practice.

Terminology used in this guideline

E-GAHT is used to abbreviate o*estrogen-based GAHT* (previously known as feminising GAHT).

T-GAHT is used to abbreviate *testosterone-based GAHT* (previously known as masculinising GAHT).

Stages in starting GAHT	
Stage 1	Introduction, relationship building, information gathering
Stage 2	Medical review (including fertility discussion)
Stage 3	Hormone information and education
Stage 4	Hormone initiation (first prescription)
Stage 5	Maintenance prescribing and long-term follow-up

Stage 1:

Introduction, relationship building, information gathering

Stage 1

Introduction, relationship building, information gathering

- General introduction to the service and how the process of getting started on GAHT will work.
- Check patient's name, gender and pronouns and ensure they are recorded accurately on the Practice Management System (PMS). Check which name your patient would like you to use when calling them from the waiting room. Adding this information as an alert or a 'post-it note' on the PMS may be helpful.
- Explore gender embodiment goals for gender affirming care.
  - You could ask: Think about your body as it is now, what would you like to stay the same? What would you like to change?
  - See Tables 1 and 2 for physical effects of GAHT. Sometimes people's goals may not require or be achievable with GAHT, so it is important to explore this with your patient.
  - People's goals are individual and may change over time. Work together with your patient over time, adjusting medication as needed in response to their needs and goals.
- Current and recent past gender experiences (see example questions in Appendix B).
- Give information about other supports. These may be available on your health pathways. Some examples can be found here:

  Gender diversity support services – Health Navigator

  Rainbow organisations – Te Ngākau Kahukura
- Give hormone information sheet (Appendix E) if appropriate at this stage (this will be explained to patient fully at Stage 3, but this gives the patient an opportunity to take it home and read it).
- HEeADSSS[26] or similar psychosocial assessment, including asking about patient supports.

Stage 2:

Medical review (includes fertility discussion)

Stage 2

Medical review (includes fertility discussion)

- Past medical and surgical history – for E-GAHT ask specifically about breast cancer, venous thromboembolism (VTE), cardiovascular disease (CVD), migraines, liver disease.
- Review mental health including current supports and strengths (consider PHQ-9 and GAD-7 if relevant) – arrange any extra support or referrals if indicated.
- Social history – including alcohol, drugs, and smoking/vaping. Discuss risk reduction, e.g. smoking cessation.
- Family history – ask specifically about VTE, CVD, breast cancer and liver disease.
- Medications and allergies – you may wish to check if the patient is 'self-medicating' with hormones (e.g. self-sourcing hormones online).
- Sexual health review (including discussion about the need for any STI testing, contraception and/or HIV PrEP where relevant).
- Any increased risks from hormonal therapy to manage – there are very few, if any, medical contraindications.
  - For E-GAHT consider discussion with secondary care if there is migraine with aura, CVD, VTE history or significant liver disease. (See E-GAHT section and FAQ 5 for more detail.)
  - Pregnancy is an absolute contraindication for T-GAHT (consider checking a Beta hCG level). Relative contraindications include severe hypertension, sleep apnoea and polycythaemia since these conditions can be exacerbated by testosterone.[2]
- Recommend cervical screening for patients who are over 25 years old and have a cervix.
- Update or establish baseline observations – blood pressure and weight.
- Offer trans culturally safe counselling or peer support – this can be very useful alongside GAHT.
- For those starting E-GAHT offer speech and language therapy referral for voice therapy (in some regions this may be available for those starting T-GAHT, but as T-GAHT lowers the voice this is less often required).

Note: There is no need for a routine genital or breast examination.

Stage 2

Medical review (includes fertility discussion)

Baseline bloods

- E-GAHT – LFT, lipids, FSH, LH, oestrogen, testosterone. Electrolytes if starting spironolactone. HbA1c if indicated by risk factors.
  - If referring for fertility preservation include HIV, syphilis, hepatitis B&C.
- T-GAHT – LFT, lipids, FSH, LH, oestrogen, testosterone FBC and Beta hCG. HbA1c if indicated by risk factors.
- Prolactin measurement is not usually required, see FAQ 6.

Fertility (reproductive options)

You will need to assess your patient's capacity to understand the effect of GAHT on reproduction and explore reproductive options with the individual prior to the initiation of gender affirming treatment. This is discussed in more detail at Stage 3 (hormone information) but is also included here so that relevant blood tests can be included in the baseline bloods if required for those starting E-GAHT.

A pamphlet about fertility preservation for transgender people can be found here:
Transgender fertility: Preservation and treatment (PDF, 813KB)

- E-GAHT (assigned male at birth): E-GAHT may result in permanent loss of fertility.[27] There is funding available for fertility preservation (check with your local service for current eligibility criteria).

  Fertility preservation is not a requirement for GAHT, but it is essential to discuss this with your patient. If referral for fertility preservation is desired, include HIV, Syphilis and Hepatitis B & C on baseline bloods.
- T-GAHT (assigned female at birth): T-GAHT usually causes ovarian suppression. This may be reversible on stopping testosterone (which may result in a return of spontaneous fertility) but may also be irreversible.[28-30] Patients should be aware that if they wish to become pregnant in the future, they will need to stop testosterone (as it is a teratogen) and that they may require fertility assistance in the form of egg harvesting. Egg harvesting can usually be undertaken at the time of desired pregnancy (and egg quality is unaffected by testosterone), so is not necessarily required prior to starting GAHT.[30] For this reason, egg harvesting is currently only funded for those having a surgical removal of reproductive organs. A funded assessment with a fertility specialist to discuss options prior to starting T-GAHT may be available if your patient wishes to discuss this in more detail.

Menstrual cessation

Many transgender and non-binary people assigned female at birth experience dysphoria with menstruation. This can be significant, and for some may contribute to poor mental health or even suicidality. It is important to discuss this and to offer menstrual cessation options if this is desired. Although testosterone usually results in amenorrhoea, starting menstrual cessation sooner is often welcomed and desired by patients.

When considering which option to use it is important to take into account whether contraception is required. Table 1 outlines options for menstrual cessation. Medication used for menstrual cessation can usually be stopped (if not needed for contraception) once the patient is established on testosterone and menstruation has ceased. Menstruation may persist despite adequate testosterone levels in 5–10% of people,[31] in which case progesterone therapy could be continued.

Table 1: **Menstrual cessation options**

Contraceptive	Depo-provera Mirena Combined contraceptive pill	Usual contraception dose	Oestrogen containing medication may not be desired by trans masculine people.
Not contraceptive	Norethisterone (Primolut)	5mg BD	Can increase to 10mg BD for 1 week if breakthrough bleeding then reduce slowly. Occasionally need to stay at higher doses.
	Medroxyprogesterone (Provera)	10–20mg once daily – up to 10mg TDS	
	Utrogestan	100–200mg daily	

Note: Testosterone is NOT a contraceptive.

Stage 3:

Hormone information and education

Stage 3

Hormone information and education

Check blood results and discuss these with the patient as necessary.

Address any remaining concerns or questions.

Ensure referrals are completed and that the patient is linked to appropriate supports.

Prior to starting E-GAHT: check that fertility preservation has been organised (if desired).

Go through hormone information and education (detailed in the following pages), including gender embodiment goals, side effects, risks, permanent effects, and time frame for changes. Some people may decide not to continue with GAHT in the future, so it is important to discuss the permanent and non-permanent changes. (See also FAQ 1.)

Highlight that changes will be gradual, occurring over years. Explain the need for regular review and monitoring in the first year and ongoing need for bloods and clinical review thereafter.

Provide written information and a copy of the consent form.[c] These forms can be found in Appendices E and F.

Document whether the patient has capacity to provide informed consent to commence GAHT, whether they meet the SOC-8 criteria for hormone treatment (see Appendix A) and that you have discussed fertility (see PMS shortcuts in Appendix C).

The checklist in Appendix D can be used to ensure all steps have been completed prior to prescribing.

[c] A consent form can be a useful addition and may act as a guide to the clinician to check all of the relevant points have been discussed, but is not a requirement. We have included it here as an option. By far the most important aspect of informed consent is the conversations between the patient and clinician outlined here. If these are well documented and the patient has had time to consider the information and ask questions, this is more important than a written consent form. See the MCNZ statement on informed consent for more detail.

Stage 3

Hormone information and education

T-GAHT — Information to cover in the consent process

We recommend using the patient information sheet in Appendix E to make it easier to cover this information with the patient. This will provide a handy reminder and prompt of what you need to cover when providing information about GAHT.

- Explain which preparations of testosterone are available (and check patient preferences for which to use), frequency of administration and the option of self-injecting (full medication details can be found below in 'GAHT initiation protocol').
- Recommended monitoring for T-GAHT:
  - Bloods and blood pressure (BP) 3–6-monthly in the first year, thereafter annually or as clinically indicated. Note the timing of the blood test when measuring testosterone levels (see below).

Discuss the changes expected with T-GAHT

Changes occur gradually over months to years (see Table 2). Physical examinations are not necessary. Often reassurance is required, especially in the first 6 months.

The following infographic can be helpful: Effects and expected time course of a regimen consisting of testosterone

Note – your patient may prefer the use of non-gendered language when describing their genitals, so we recommend asking them what words they prefer and then using those. Commonly used terms (at the time of writing) include 'front hole' or 'internal genitals'.

- Permanent effects:
  - Deepening of the voice,
  - Increased body hair growth including facial hair,
  - Androgenetic alopecia,
  - Genital changes: clitoral enlargement (may be up to 1–3cm) and this can feel uncomfortable and even painful initially. Vaginal dryness can be relieved with oestrogen cream or an over-the-counter product for vaginal dryness and ensuring use of extra lubrication for vaginal sex.
- Sex – vaginal dryness increases the risk of STIs including HIV, so it is advisable to use condoms if having sex using this part of the body. Lubrication can help with any associated discomfort. Testosterone is not a contraceptive.
- Effects which are likely reversible: acne/oily skin, increased muscle mass/ strength, redistribution of body fat, increased libido. Irritability and frustration may be variably present.
- Menstruation stops in most people (around 90%) after 1–6 months.[31] *(Many patients prefer the term 'monthly bleeding'.)*
- Fertility – You may have already discussed this in Stage 2, but it is repeated here to ensure it isn't missed. T-GAHT usually causes ovarian suppression. This may be reversible on stopping testosterone (which may result in a return of spontaneous fertility) but may also be irreversible.[28-30] Patients need to understand that if a future pregnancy is desired it will mean stopping testosterone (as it is a teratogen) and may require fertility assistance in the form of egg

harvesting. Egg harvesting is more effective at the time of desired pregnancy (and egg quality is unaffected by testosterone), so is not required prior to starting GAHT.[28]

It is possible to become pregnant while taking testosterone even if menstruation has stopped, so **contraception is essential if there is any sexual contact that would put someone at risk of pregnancy**. Testosterone is likely to be harmful to a developing fetus and should not be used during pregnancy.

- Risks – Polycythaemia, liver dysfunction, pelvic pain, raised cholesterol and raised blood pressure.[32-34] Studies in cisgender men indicate a slight increased VTE risk in the first 6 months on testosterone therapy.[35]
- Cancer screening
  - Discuss the importance of cervical screening for anyone with a cervix.
  - Breast screening is recommended from age 45 years for anyone who has breasts. Those who have had 'top surgery' (this commonly used term refers to chest reconstruction surgery or bilateral mastectomy) should follow the advice of their surgeon, as this may depend on the extent of the surgery performed. Some people may be advised to have clinical examinations and possibly ultrasound screening.
  - Ensure recalls are not removed if gender is changed on the PMS.
- Gender affirming surgery – provide information on local pathways for surgery. Your patient may be especially interested in accessing top surgery. Availability varies between localities; check your local health pathways. A stocktake of availability as of 2021 can be found here: An update for the provision of gender affirming healthcare across the district health boards of Aotearoa New Zealand – PATHA. Gender affirming genital surgery referral forms can be found here: The Gender Affirming (Genital) Surgery Service – Ministry of Health.

Table 2: **Effects of testosterone-based hormones (T-GAHT)**

Effect of testosterone	Expected onset	Expected maximum effect	Reversibility
Skin oiliness/acne	1–6 months	1–2 years	Likely
Facial body/hair growth	6–12 months	4–5 years	Unlikely
Scalp hair loss	6–12 months[a]	Variable	Unlikely
Increased muscle mass/strength	6–12 months	2–5 years	Likely
Redistribution of body fat	1–6 months	2–5 years	Likely
Cessation of periods	1–6 months		Likely
Clitoral enlargement	1–6 months	1–2 years	Unlikely
Vaginal atrophy	1–6 months	1–2 years	Unlikely
Deepening of the voice	6–12 months	1–2 years	Not possible
Increased sexual desire	Variable	Variable	Likely

[a] Highly dependent on age and inheritance; may be minimal.

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Stage 3

Hormone information and education

E-GAHT — Information to cover in the consent process

We recommend using the patient information sheet in Appendix E to make it easier to cover this information with the patient. This will provide a handy reminder and prompt of what you need to cover when providing information about GAHT.

- Explain that E-GAHT involves using two medications – an oestrogen and a testosterone blocker:
  - — Oestrogen:

    Explain which preparations of oestrogen are available (tablets or patches). Explain that there is no good evidence yet that one form of oestrogen is better than another in terms of effects, but that oestrogen patches are likely to carry a lower risk of VTE and LFT dysfunction than tablets.[36, 37]
  - — Testosterone blocker:

    Discuss options for androgen blockade (spironolactone or cyproterone). There are no studies yet that compare efficacy in E-GAHT, therefore patients can select their preferred approach, in discussion with their prescriber and taking into account potential side effects and risks, and any relevant health conditions or medications.
    - o Spironolactone is a blood pressure tablet at low doses but works as a weak anti-androgen at higher doses. It will not suppress testosterone levels but will block the effects of testosterone in the body, promoting breast growth and slowing down body hair. Common side effects include dizziness and urinary frequency.
    - o Cyproterone in very small doses (12.5mg daily or less) will suppress testosterone to < 2 nmol/L but does not suit everyone. Side effects can include fatigue and low mood. Shortness of breath is an uncommon side effect but should be counselled for. Larger doses have been associated with liver function abnormalities and there is a dose-dependent and cumulative risk of meningioma thought to be related to doses of 25mg daily or greater.[38-40] Evidence in other areas of healthcare shows the risk of VTE is increased with cyproterone use.[41]
- Recommended monitoring for E-GAHT
  - — Bloods and blood pressure 3–6-monthly in first year, thereafter annually or as clinically indicated.

Discuss the changes expected with E-GAHT

- Changes occur gradually over months to years (see Table 3). Physical examinations are not necessary. Often reassurance is required, especially in the first 6 months. The following infographic can be helpful: Effects and expected time course of a regimen consisting of an anti-androgen and estrogen.
- Permanent effects:
  - — Fertility is thought to be permanently affected by E-GAHT.[27, 42] Fertility preservation is recommended in young people and is usually funded. It is essential to have and document this discussion prior to prescribing E-GAHT.

  - Breast development is gradual over 2–years.[32] It can be helpful to manage expectations as many people develop an A cup or smaller after 1 year on E-GAHT.[43] This can be a common source of dissatisfaction.[44]
- Effects which are likely reversible: softer skin, decreased muscle mass, thinning of body hair, fat redistribution to buttocks, hips and thighs.
- Libido usually reduces when taking androgen blockers. Erections usually reduce in frequency and may be less firm and shorter lasting (Sildenafil can be helpful for some people). Testicles can shrink to less than half their original size.
- E-GAHT does NOT change:
  - Voice pitch (voice therapy may be available via a speech and language therapist depending on local pathways)
  - Facial bone structure
  - Prominence of the tracheal cartilage (Adam's apple)
  - Growth of facial and body hair, which slows but does not stop completely (laser hair removal if desired can be funded by a WINZ disability allowance if the patient has a community service card or is on a low income.
- Side effects – breast tenderness and weight gain. In the first few days to weeks there may be nausea and headaches which usually settle.
- Risks – VTE (risk can be lowered, see FAQ 5), raised cholesterol, gallstones, raised BP, possible increase in breast cancer risk.[32] We recommend explaining the symptoms of deep vein thrombosis and pulmonary embolism and advising patients to seek urgent medical help if these occur.
- Cancer screening – Breast screening is recommended from age 45 years for anyone who has breasts.
- Gender affirming surgery – provide information on local pathways for surgery. Availability varies between localities; check your local health pathways. A stocktake of availability as of 2021 can be found here: An update for the provision of gender affirming healthcare across the district health boards of Aotearoa New Zealand – PATHA. Gender affirming genital surgery referral forms can be found here: The Gender Affirming (Genital) Surgery Service – Ministry of Health.

Table 3: **Effects of oestrogen-based hormones (E-GAHT)**

Effect of testosterone	Expected onset	Expected maximum effect	Reversibility
Redistribution of body fat	3–6 months	2–3 years	Likely
Decrease in muscle mass and strength	3–6 months	1–2 years	Likely
Softening of skin/decreased oiliness	3–6 months	Unknown	Likely
Decreased sexual desire	1–3 months	3–6 months	Likely
Decreased spontaneous erections	1–3 months	3–6 months	Likely
Breast growth	3–6 months	2–3 years	Not possible
Decreased testicular volume	3–6 months	2–3 years	Unknown
Decreased sperm production	Unknown	>3 years	Unknown
Thinning and slowed growth of body and facial hair	6–12 months	>3 years[a]	Possible
Male pattern baldness	Variable	[b]	
Voice changes	None	[c]	

[a] Complete removal of hair requires laser treatment. [b] Familial scalp hair loss may occur if oestrogens are stopped.
[c] Treatment by speech-language therapists for voice training is most effective.

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Stage 4:

Hormone Initiation

Stage 4

Hormone Initiation

- Ensure Stages 1–3 are complete and that patient is happy to start GAHT (see checklist in Appendix D). If using the consent form, ensure this has been signed by the patient.
- Document patient's capacity to provide informed consent, whether they meet the SOC-8 criteria for GAHT (see Appendix A) and that you have discussed fertility (see Appendix C for PMS shortcut suggestions).
- Inform the patient that using these medications for gender affirmation is an unapproved use of an approved medication.[45] These medications are widely used around the world for this purpose and there is a recognised clinical justification for their use. This is also known as 'off-label' use.

  As a prescriber you must explain what is being prescribed, and why, and obtain informed consent from your patient. It is acknowledged, however, that when off-label use of a medicine is so common that it is regarded as usual practice, obtaining separate consent (for off-label use) may not be considered necessary, and this is at the clinician's discretion.[46]
- Give GAHT prescription as per GAHT initiation protocol below. Arrange to follow up in 3 months.
- T-GAHT: arrange a nurse appointment for ongoing injections.

Stage 5:

Maintenance prescribing and long term follow up

Stage 5

Maintenance prescribing and long term follow up

In the first year, follow up every 3 months, or more often if needed; thereafter as needed depending on individual needs. Generally, an annual review is recommended, but for patients who have been stable on GAHT for a significant time it may be appropriate to extend this.

- Review effects of medications and check the patient is happy to continue taking GAHT.
- Adjust doses as per hormone protocol.
- Monitor BP and bloods 3–6-monthly in the first year (or more often if necessary) then annually or as clinically indicated. Monitoring is primarily with dose changes, which is likely to be every 3 months, but flexibility may be needed. Monitor weight as appropriate.
- Monitor mental and physical health. Encourage lifestyle/health behaviours which reduce the risks associated with GAHT, e.g. smoking cessation, cholesterol reduction, moderate alcohol use.
- If needed, connect to mental health and peer support.
- Make referrals for other gender affirming care as desired by your patient.
  - Gender affirming genital surgery referrals are via the Ministry of Health. For further detail see 'Gender affirming (genital) surgery service forms' here: The Gender Affirming (Genital) Surgery Service – Ministry of Health
  - For other gender affirming surgeries refer to your locality health pathways.

GAHT Initiation Protocol

GAHT Initiation Protocol

This protocol relates only to the initiation of gender affirming hormone therapy in adults and is to be used by prescribers after following GAHT Stages 1–3 described above.

The starting protocols below are for adults who have NOT been on gonadotropin releasing hormone (GnRH) agonists (also known as puberty blockers) from a young age (Tanner stage 2–3). For those who have been on puberty blockers from Tanner stage 2–3, GAHT initiation should progress more gradually.[32]

This section outlines the medications used in GAHT, dosage guidance, recommended monitoring, and a protocol for initiating GAHT.

Oestrogen-based Gender Affirming Hormones (E-GAHT)

Table 4: **Overview of E-GAHT**

Oestrogen formulation	Starting dose	Maximum (usual maintenance dose)	Notes
Oestradiol valerate (Progynova)	1–2mg daily	4–6mg daily	Increasing by 1–2mg every 3–6 months is generally recommended.
Oestradiol patch (Estradot)	25–50mcg patch twice weekly	100-200mcg patch twice weekly	Increasing by 25–50mcg every 3–6 months is generally recommended. Lower VTE risk than oral oestrogen. Recommended if liver or lipid dysfunction or >45 years old.
Androgen blocker*	**Starting dose**	**Maximum (usual maintenance dose)**	**Notes**
Spironolactone	50–100mg daily	200mg daily	Unable to use serum testosterone for clinical guidance as spironolactone blocks the effect of testosterone on the tissues rather than its production. Monitor potassium level.
Cyproterone	12.5mg daily (or 12.5-25mg on alternate days)	12.5mg once daily (or 12.5-25mg on alternate days)	Use lowest effective dose. Use of higher doses long-term has been linked to meningioma. Consider review and discussion every 5 years if remaining on this long term. Contra-indicated in history of thromboembolic disorders as increases VTE risk. Monitor liver function.
Goserelin	10.8mg SC implant insertion into lower abdomen every 12 weeks		Not first line in adults due to high cost and good availability of alternative options.

***The androgen blocker is no longer required if the patient has had an orchiectomy.**

For guidance on E-GAHT in individuals with increased cardiovascular or VTE risk, see FAQ 5. For a comment on Progesterone use See FAQ 8.

Table 5: **E-GAHT recommended monitoring**

Investigation	Comment
Electrolytes	If patient is on spironolactone.
Liver function tests	If abnormal, use transdermal oestrogen as first choice. Monitor if on cyproterone.
Lipids	
Oestrogen	Only checked to ensure levels are not supraphysiological. Some guidelines would recommend an upper limit of 700–750 pmol/L[32] but there is insufficient evidence to definitively recommend any target range. Experience suggests that oestrogen levels or dose do not correlate well with physical effects or self-reported satisfaction with E-GAHT, and exogenous oestrogen is not well measured in the serum.
Testosterone	On cyproterone – levels would typically be <2nmol/L (or higher if wanting to maintain erectile function). On spironolactone – no need to measure as it doesn't usually suppress (see above); instead, be guided by clinical response.

E-GAHT
Starting Protocol

Prior to first prescription	Complete Stages 1–3 in the primary care protocol for starting GAHT. This includes a psychosocial assessment, medical review, baseline blood tests, blood pressure, weight, fertility preservation (if desired), and informed consent outlining effects (including permanent changes) and risks of GAHT by a knowledgeable healthcare provider. Provide the patient with information sheet and document consent.
Commence GAHT – first prescription	**Oestrogen** – *one of*: Estradiol (Progynova) 1–2mg OD *or* Estradot patches 25–50mcg twice weekly ***AND*** **Testosterone blocker** – *one of*: Spironolactone 50–100mg OD *or* Cyproterone 12.5mg OD (or 12.5–25mg on alternate days)
3 months after commencing hormones	If no concerns, adjust androgen blocker to maintenance dose and commence gradual increase in oestrogen dose: • Oestrogen can be increased: — Progynova by 1–2mg every 3–6 months up to maximum of 6mg — Estradot by 25–50mcg every 3–6 months up to maximum of 100–200mcg twice weekly. • Spironolactone – consider increasing to 200mg OD (if potassium level is normal). • Cyproterone – continue 12.5mg OD (or 12.5–25mg on alternate days). • Bloods for potassium (if taking spironolactone), liver function, lipids. • Check blood pressure.
3-monthly appointments in first year, can be 12-monthly thereafter if stable	At each follow-up visit: • Review progress and discuss any issues or questions. • Check on physical and mental health and social supports. • If your patient has an orchiectomy the androgen blocker can be stopped. • Ensure monitoring is up to date: — Check blood pressure 3–6-monthly in the first year, thereafter 12-monthly. — Monitor blood tests 3–6-monthly in the first year, thereafter 12-monthly or as clinically indicated (see Table 5 for details).

Testosterone-based Gender Affirming Hormones (T-GAHT)

Table 6: **Overview of T-GAHT**

Testosterone formulation	Standard starting dose	Maximum (usual maintenance) dose	Notes
Depo-testosterone (testosterone cypionate)	100mg IM/SC* every 2 weeks or 50mg SC weekly	200mg IM/SC* every 2 weeks or 100mg SC weekly	Testosterone level should be measured mid-way between injections. Patient can be taught to self-inject.
Sustanon (testosterone esters)	125mg (0.5ml) IM* every 3 weeks	250mg (1ml) IM* every 3 weeks	Testosterone level should be measured mid-way between injections. Patient can be taught to self-inject.
Reandron (testosterone undecylate)	Less commonly used as a starting testosterone, but can be started at 500mg IM The second dose can be given after 6 weeks to achieve steady state and thereafter continue 12-weekly	750–1000mg IM every 10–14 weeks	Testosterone level should be checked immediately prior to injection. Injection must be given by a health professional (due to risk of oil embolism).
Androderm patches	5mg daily	5–10mg daily	Testosterone level should be measured in the morning. Skin irritation is common.

* Depo-testosterone is licensed for IM use. It is not licensed for subcutaneous administration in NZ but can be administered this way if preferred, with weekly dosing appearing to be most commonly used.[47]

Low dose testosterone is discussed in FAQ 7.

Table 7: **T-GAHT recommended monitoring**

Investigation	Comment
Full blood count	If the haematocrit > 0.52 reduce the dose of testosterone and/or discuss with an endocrinologist or haematologist.
Liver function tests	
Lipids	
Testosterone	• Aim for usual male reference range for standard doses. • Check 6–12-monthly once patient has been on testosterone for around 6–9 months (it takes time for levels to stabilise initially). • Timing of blood test is dependent on testosterone formulation – see Table 6 above. • If raised, reduce testosterone dose and repeat level in 3 months.

T-GAHT
Starting Protocol

Prior to first prescription	Complete Stages 1–3 in the primary care protocol for starting GAHT. This includes a psychosocial assessment, medical review, baseline blood tests, blood pressure, weight, and informed consent, outlining effects (including permanent changes) and risks of hormones by a knowledgeable healthcare provider. Provide the patient with an information sheet and document consent.
Commence GAHT – first prescription	Depo-testosterone 100mg IM/SC fortnightly (or 50mg SC weekly) *or* Sustanon 125mg (0.5ml) IM every 3 weeks *or* Reandron 500mg IM with 750–1000mg IM at 6 weeks (thereafter 3-monthly) *or* Testosterone patch 5mg daily
3 months after commencing hormones	• Review progress and discuss any issues. • Bloods for complete blood count (monitor haematocrit), liver function, lipids. • Blood pressure. • If no concerns, increase hormones to maintenance therapy. If patient wishes to switch testosterone preparation, the preferred testosterone can be administered at the time the next dose of the previously used testosterone is due. • Plan for testosterone level measurement at the appropriate time (after at least 6 months on GAHT. See Table 6 for timing of blood test).
3-monthly appointments in first year, can be 12-monthly thereafter if stable	At each follow-up visit: • Review progress and discuss any issues or questions. • Check on physical and mental health and social support. • Ensure monitoring is up to date: — Blood pressure 3–6-monthly in first year, thereafter 12-monthly. — Bloods 3–6-monthly in first year, thereafter 12-monthly or as clinically indicated (see Table 7 for details, including timing of testosterone measurements). • Provide education about self-injection if appropriate.

Frequently Asked Questions

(FAQs)

1. What if my patient stops taking hormones?

Affirming one's gender is not necessarily a linear process and may take place over a lifetime. Some people experience their gender more fluidly than others and it is common for someone's understanding of, and comfort with, their gender identity and gender expression to evolve throughout their lives. Someone's decision to start GAHT and a later decision to stop GAHT can both be the right decision for them at that stage of their lives. This is not – and should not – be viewed as a mistake or a failure. Similarly, some patients may shift from identifying with a binary gender to non-binary gender (or vice versa), and their goals from their transition may change accordingly. Stories of this nature are common, and often referred to as 'non-linear transitions'. They are simply reflective of the variety of human experience.

Some providers may feel anxious about 'getting it wrong' or worry that their patient may later regret their decision. The informed consent process outlined in this document respects the autonomy of the patient as a competent adult who has the capacity to make their own decisions about their body and health once they have been given the necessary information. Patients accessing GAHT have an equal right to receive support from health professionals and from family/friends/whānau where needed. By working in partnership, this approach seeks to enhance a given patient's understanding of the potential benefits and risks of GAHT. The provider's role is to provide support and information, and to ensure safety by following prescribing and dosing guidelines, monitoring treatment and monitoring for potential risk. As part of a patient-centred approach, the patient should be an active partner in decisions about GAHT based on their own gender embodiment goals, and information provided to them about likely changes to them (both reversible and irreversible) and risks.

We are beginning to understand more about non-linear transitions (sometimes discussed in the context of 'retransition' or 'detransition') and the reasons people's goals, gender identities, gender expressions, or engagement with treatment change. Frequently, people who have stopped affirming their gender (whether temporarily or permanently) do so due to external factors, including pressure from family, discrimination and social stigma.[48] Detransition is not the same as regret. Social connections and support can be a preventative factor by allowing people to be themselves despite external pressures. Trying to ensure that patients have relational support for their decision-making –for example, from family, friends, whānau and health professionals – where this is requested or needed is important. It is essential that healthcare providers are available to support patients with non-linear transitions, and it can be useful to make this support clear when initiating GAHT. If hormones are stopped, it is important to ensure restoration of physiological sex hormone levels to remove risks of longer-term hypogonadism.

2. Can I still prescribe GAHT where there are significant mental health concerns?

Many (but not all) transgender people experience mental health conditions, often due to gender minority stress.[49] This is caused by negative social attitudes, discrimination, prejudice and violence. Discomfort between a person's intrinsic sense of identity, their body and how they are perceived by others also contribute to distress, as can difficulty in accessing gender affirming services (including GAHT) in a timely manner.[50] Symptoms of anxiety, low confidence, depression, anxiety, disordered eating and trauma are common.

Where a patient has severe mental health concerns that meet the criteria for secondary mental health services, then refer them to these services. However, if a patient's mental health concerns *do not* affect their capacity to provide informed consent for GAHT, then you can concurrently commence GAHT. If you are concerned about your patient's capacity to give consent to GAHT due to their mental health, then this may need to be addressed first and onward referral may be recommended (refer to FAQ 4 on diminished capacity below for more detail). If you are unsure, you can seek consultation from secondary services to see if an onward referral would be recommended. If secondary mental health input is not required,

give your patient advice, support, and treatment for mental health as with any other patients.

Gender affirming healthcare may reduce mental distress, so withholding or delaying care unnecessarily is unethical and could worsen a person's mental health. It is important to weigh up the risks and benefits of these decisions, noting that onward referral may at times come with barriers for patients such as long wait times, transport issues or cost. Doing nothing is not a neutral option and can result in harm to your patient. There should always be the option to refer more complex situations to secondary care for input if a GP or NP feels it is outside of their scope or experience.

3. My patient is autistic. Does this impact on their capacity to give informed consent to start GAHT?

It has been consistently shown that transgender or non-binary people are more likely to be autistic than cisgender people, although there is no consensus as to why.[51] Autism is a neurodevelopmental phenomenon that manifests in a wide variety of ways dependent on the individual. Autistic people may have different cognitive, sensory or social processing, and as a result they may see the world and interact with others differently.

Being neurodivergent does not routinely impact on an individual's capacity to give informed consent. However, some autistic people may need more time to provide information about themselves or may need questions to be asked in a different way, so they are able to communicate their gender identity, embodiment goals for GAHT, and/or demonstrate their understanding of the risks and benefits. It is important to recognise these differences and to create an environment where autistic patients are supported to communicate and engage in a way which feels more comfortable to them, to share the cognitive load, increase their overall comfort, and reduce their feelings of stress. Where a patient is not able to provide you with the information you need, or demonstrate understanding, then it is hard for them to show capacity. It is the job of providers to reduce barriers in any way we can to maximise their ability to demonstrate this.

For patients whose social communication difficulties impair their ability to demonstrate their understanding, in a way required to give informed consent, additional support may be required. This could include referral to communication, mental health or Autism support services (if timely access to these services is available locally).

4. When does a patient have diminished capacity to provide consent?

In Aotearoa New Zealand, adult patients have the right to be presumed to have capacity to give informed consent, unless there are reasonable grounds to believe otherwise.[52] Reasons for diminished capacity might include intellectual disability, brain injury or cognitive impairment, e.g. dementia, psychosis and mania. Some people may have capacity but have difficulty in communication and may need support to aid this process.

If a patient can retain information that they need about GAHT (i.e. risks and benefits), demonstrate understanding of how this will affect their lives (e.g. changes to their body, including permanent changes), weigh the information to come to a decision and clearly communicate a decision based on this understanding and reasoning, then they have capacity to give informed consent to GAHT.

Patients without full capacity still have a right to access care in a timely manner and to have a supported role in decision-making for their care, as indicated under Right 7(4) HDC Code of Rights:[52] The usual procedure for this is for the GAHT prescriber to come to a decision that is in the patient's best interest based on:

(1) the patient's views, level of capacity, wishes and assent.

(2) the views of a suitable person suitable person who is interested in the welfare of the patient, such as a caregiver or family member who knows the person well, or a wider circle of people that includes friends and whānau. This may include an enduring power of attorney or a welfare guardian if one is appointed.

(3) the prescriber's and other

health professionals' expertise of the risks and benefits to the patient.[53]

Prescribers should take care to ensure to provide information to patients in a way that is accessible and appropriate to their level of understanding. Referral to a colleague or appropriate secondary service may aid the decision-making process for patients with diminished capacity.

5. What if my patient starting E-GAHT has a heightened risk of thrombosis or cardiovascular disease?

Patients need to be informed that oestrogen increases the risk of thrombosis and cardiovascular disease. Smoking cessation should be strongly supported. However, it would be unethical to withhold E-GAHT on these grounds. Instead, clinicians should discuss both benefits and risks of E-GAHT with their patients and mitigate any increased risk as much as possible.

In someone with risk factors for thrombosis and/or increased cardiovascular risk (e.g. smoking, ischaemic heart disease, migraine with aura, older age) it is recommended:

- To use transdermal rather than oral oestrogen, as evidence suggests the risk of VTE with transdermal use is similar to population risk.[36, 37] It is sensible to use the lowest effective dose.
- Cyproterone at higher or contraceptive doses (Ginet) increases the risk of VTE[41] and is contraindicated in those with a history of thromboembolic disorders.[54] There are insufficient data to be certain as to whether these risks are removed through the use of lower doses (12.5mg daily). Clinicians should consider alternative androgen blockade options (spironolactone or Gosarelin) in those with an increased VTE risk.

6. Do I need to measure prolactin?

Several guidelines recommend measuring prolactin at baseline and during follow-up in those on E-GAHT, but at present there is no compelling evidence to suggest that E-GAHT increases the risk of pathological hyperprolactinaemia outside of cyproterone use at higher than contemporary recommended doses.[55] There is no such recommendation for cisgender women using contraceptive doses of oestrogen, oestrogen for menopausal therapy, or during pregnancy when oestrogen levels would be expected to be similar or higher to those achieved with E-GAHT. Indeed, oestrogen therapy is frequently used in women with known prolactinomas who are intolerant of dopamine agonist therapy. Furthermore, mildly elevated prolactin measurements that are unlikely to be significant are very common, and the routine measurement of prolactin therefore raises the risk of unnecessary further investigations. We suggest clinicians use clinical judgement when determining if prolactin measurements are required.

7. My patient is requesting low-dose testosterone.

Some people, often those who are non-binary, choose to start on lower doses of testosterone (sometimes referred to by patients as 'micro-dosing'). There is a lack of any evidence to guide low-dose hormone regimens. Patients may choose to remain on a low dose long term, or more slowly increase up to standard maintenance doses over time. A more gradual increase may give some control over the speed of onset of the experienced effects, although this is not guaranteed. When obtaining consent, it is essential to inform the patient about all the same effects, including the permanent changes, as standard testosterone dosing, as all of these occur at lower doses.

There is a lack of evidence to support an optimum testosterone level in this context. Testosterone supplementation is indicated in hypogonadal cisgender men to reduce an increased cardiovascular and bone health risk that is otherwise seen. However, there is currently no literature to indicate an absolute testosterone level below established local reference ranges at which this increased risk becomes apparent. Acknowledging this, and the lack of data in the context of T-GAHT, it is not yet possible to define a minimum testosterone

level when using T-GAHT and patients should be aware of this. In practice, many clinicians would recommend a minimum testosterone level of 6–8 nmol/L.

8. My patient is requesting a medication that is either not in these guidelines or not licensed in New Zealand.

In these guidelines, we recommend the use of medications that either have an established evidence base in the use of GAHT, have a long history of use in GAHT, or are widely used in other populations and risk profiles are therefore well understood. These guidelines align with and support many other guidelines in this area. However, overseas practice may differ, and patients may ask about the use of medications not included in these guidelines. The following are frequently encountered enquiries:

T-GAHT

Oral testosterone

Andriol capsules are not licensed in Aotearoa New Zealand for GAHT, and at the time of writing are not funded. Oral testosterone is not used as a first-line option in T-GAHT due to the fluctuation in testosterone levels throughout the day and the need for frequent dosing, as well as being less effective at stopping menstruation.[12] They can be used on a case-by-case basis, particularly in someone who is needle-phobic and is unable to tolerate transdermal testosterone. They should be avoided if liver disease is present[54] and LFTs should be monitored as with other testosterone regimes. If this option is used, Andriol can be started at 40mg daily and be increased up to 120mg daily in 2 divided doses. When measured, testosterone levels should be checked prior to the morning dose.

E-GAHT

Progesterone

Progesterone is occasionally prescribed as part of gender affirming care. Anecdotally, some people who take E-GAHT have reported benefits of using progesterone on breast development, sleep, mood, and other physical changes. Micronised progesterone (utrogestan) is prescribed for menopausal hormone therapy in many cisgender women and is now funded in Aotearoa New Zealand.

However, there are no current high-quality data to indicate any effect of progesterone for gender affirmation,[56, 57] and no data on safety. It is therefore not included in the majority of international guidelines for gender affirming hormone therapy.[2, 3, 10, 32] Authors of the WPATH SOC-8 attempted to complete a systematic review on this issue but failed to identify enough data to make any recommendations for or against the use of any progesterone in this context, and noted 'existing data suggest harm is associated with extended progestin exposure'.[2] Progesterone treatment in other contexts is associated with weight gain, mood disturbance, fatigue, an increased risk of breast cancer, and venous thromboembolism (VTE).[2, 58] It is not clear how generalisable the data from cisgender women is to transgender populations, who tend to be younger and less likely to use equine oestrogen.[2, 59] Utrogestan is likely to have a lower risk of side effects than older progesterones,[60, 61] and emerging evidence suggests a lower associated risk of breast cancer. Further studies in cisgender and transgender people are required however to confirm this.

This guideline is therefore unable to make a recommendation for or against progesterone use in GAHT at this stage, and we await the outcome of research trials designed to address these questions with interest.

Clinicians may be asked to prescribe progesterone as part of E-GAHT. This should prompt a discussion about expectations and outcomes, potential risk, and current evidence. This discussion may reveal other ways in which doses of existing medications can be adjusted to support your patient's gender embodiment goals. Prescribing decisions ultimately rest with the clinician, but patient autonomy, gender embodiment goals and self-determination for patient choice should be considered and respected.

Anti-androgens

There are no high-quality data to indicate that the use of any particular anti-androgen is superior to any other. We support the use

of spironolactone or cyproterone as both have been used widely in E-GAHT for several decades, and experience with both medications is now extensive in both transgender and other populations. Both are funded for use in GAHT. Cyproterone is associated with an increased risk of liver dysfunction, VTE[41] and meningioma,[38, 39] however, and the lowest effective dose (12.5mg daily or on alternate days) should be used if this is chosen. GnRH agonists (Goserelin) are licensed for use in GAHT and are an option if oral options are not tolerated, with the available evidence suggesting a comparable effect.[62]

Flutamide is recommended by some overseas guidelines on E-GAHT, but is associated with hepatotoxicity, and its use is recommended against by many guidelines on the management of hirsutism in cisgender women for this reason.[63] 5α-inhibitors (often termed dihydrotestosterone blockers) are less effective than other anti-androgens but are occasionally used to reduce androgenic hair loss. Bicalutamide is a potent anti-androgen but is associated with hepatotoxicity and reported cases of fulminant hepatitis.[64] While there remains a lack of any evidence to indicate superiority of Flutamide, 5α-inhibitors or Bicalutamide as anti-androgens in E-GAHT, we recommend against their use because of likely increased treatment risks.[62]

Oestrogen

The goal of GAHT is to provide physiological hormone levels. To achieve this with E-GAHT, oestrogen must be administered, and testosterone must be blocked or lowered, and neither approach is effective in isolation. Unfortunately, many of the physical effects of having progressed through a testosterone-based puberty are not reversed through hormonal therapy alone, and the effect of E-GAHT commenced beyond this age may therefore be less than optimal.

— Higher doses of oestrogen

There is currently no evidence to suggest that a dose of oestrogen higher than 200mcg/24 hours via patch or 6mg daily orally is helpful, and, indeed, poor evidence to suggest any strong correlation between oestrogen doses at recommended levels and outcomes at all.[65] The recommended upper limits of oestrogen dosing in these guidelines align with SOC-8 and the Endocrine Society.[2, 32] While some guidelines recommend a target oestrogen level, there are few available data to definitively specify any target range, and those guidelines that do incorporate such a target generally acknowledge this.

— Oestrogen use without anti-androgen therapy

Some patients advocate for the use of oestrogen therapy alone at higher doses to suppress testosterone production in lieu of additional anti-androgen therapy. By definition, however, this requires the use of oestrogen at supraphysiological levels, with high circulating levels of oestrogen required to suppress pituitary gonadotrophin output and therefore lower testosterone levels to the desired target. There is no evidence to suggest this approach results in improved physical outcomes, and, while there is little evidence specifically on this approach, the use of oestrogen at higher than physiological levels is likely to increase the risks associated with oestrogen use.[65] Aligning with most guidelines on this subject,[32] we therefore recommend against this approach.

— Intramuscular oestrogen

Some international guidelines include IM oestrogen alongside oral and transdermal options,[10, 32] but it is neither licensed nor funded in Aotearoa New Zealand. There is no evidence to suggest that IM oestrogen is any more effective than transdermal oestrogen, and both are likely to be associated with a lower risk of liver dysfunction than oral oestrogen. It is unclear whether the VTE risk may also be lower than seen with oral oestrogen. However, in contrast to transdermal oestrogen, significant variation in oestrogen levels is noted with IM oestrogen, with levels far in excess of those recommended by most guidelines often seen shortly after administration in particular.[32] There are no high-quality data to advise on whether this may increase oestrogen-related risks. There is little guidance on monitoring levels in patients on intramuscular oestrogen as part of GAHT but dosing guidance can be found in the Endocrine Society guidelines.[32]

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Appendix A:

WPATH SOC-8 hormone criteria and ICD-11 gender incongruence

The statements below outline a summary of the SOC-8 criteria for GAHT. However, there are a lot of nuances around each point, which are discussed in more depth in the full SOC-8 document, which can be found here: Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

SOC-8 Summary Criteria for hormonal treatment for adults and adolescents[2]

- Gender incongruence is marked and sustained;
- Meets diagnostic criteria for gender incongruence prior to gender-affirming hormone treatment in regions where a diagnosis is necessary to access health care;
- Demonstrates capacity to consent for the specific gender-affirming hormone treatment;
- Other possible causes of apparent gender incongruence have been identified and excluded;
- Mental health and physical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed;
- Understands the effect of gender-affirming hormone treatment on reproduction and they have explored reproductive options.

ICD-11 description of Gender Incongruence[25]

Gender Incongruence of Adolescence and Adulthood is characterised by a marked and persistent incongruence between an individual´s experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual´s body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behaviour and preferences alone are not a basis for assigning the diagnosis.

Appendix B:

Sample questions for gender history and embodiment goals

- How would you describe your gender?
- How did you come to learn your gender as it is now?
- What steps have you taken to feel more comfortable in your gender? For example, changed your name or pronouns, dressing differently? How does that feel for you?
- Are you hoping to take any other steps in your transition? What are your current goals? How would you like to embody your gender?
  - *Thank you for sharing that with me. I'm going to make a note of your goals – please let me know if these goals ever change so I can continue to recommend the best care for you.*
- Have you thought about how you will manage a change in appearance at school/work/study/home?
- Who is/are your support/s with this process?
- Have you talked to anyone about your gender identity and your plans to affirm your gender through medical treatment?

  (Of course, there is no requirement for a person to discuss this with others, but this question can help to identify support – or lack of it – and thereby facilitate conversations around this. For example, if a younger person hasn't got parental support, it might be worth having a conversation about how they plan to approach this when there are noticeable physical changes. Family support is important and if not available then other supports should be identified.)
- When did you start thinking about taking hormone therapy?
- What do you think will be the main benefits of hormone therapy? What are you looking forward to?
- Think about your body as it is right now:
  - What would you like to stay the same?
  - What would you like to change?
- How do you imagine your life will change if you start hormone treatment?
- Are there any changes that you are not sure about?
- Do you foresee any concerns or challenges?
- Are you aware of the impacts of hormones on your fertility/ability to have children in the future? Would you consider a referral to a fertility service to store gametes?
  - *Lots of people find it quite difficult to think about how our fertility might affect us in the future, so I'd really encourage you to take your time when you're thinking about this. You don't have to answer now but we should talk about this again before you start hormones.*
- Some people find it useful to have the support of a peer support worker or talk therapist to help with decisions or support. Would you like a referral to a talk therapist with experience around this?
- Some people change their minds about taking hormones, often because of family or society pressures. Have you thought about this at all? (You can emphasise that this does not worry you and encourage them to talk to you, let them know that you are available for support whatever decisions they make in the future.)

Appendix C:

Examples of Practice Management System shortcuts

These can be added to your practice management system (PMS) to use as personal shortcuts to save time when writing your notes.

Capacity

Patient has the capacity to provide informed consent to start gender affirming hormone therapy.

WPATHSOC-8

Patient meets the criteria for hormonal treatment from the WPATH Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (SOC-8).

T-GAHT

We have discussed the information on the consent form and patient information sheet, and I have provided copies of both. Discussed effects of hormones, time taken to see changes, which changes are permanent, risks, side effects, medication options and monitoring, cervical screening, and importance of not getting pregnant on testosterone and need for contraception even if periods have stopped. Discussed potential impact on future fertility including that testosterone needs to be stopped if wishing to conceive and that egg harvesting may be required to achieve a pregnancy.

E-GAHT

We have discussed the information on the consent form and patient information sheet, and I have provided copies of both. Discussed effects of hormones, time taken to see changes, which changes are permanent, risks, side effects, medication options and monitoring. I have explained that GAHT does not change voice, bone structure or Adam's apple. Discussed permanent effect on loss of fertility and fertility preservation has been offered.

Appendix D:

Checklists which can be used prior to first GAHT prescription

T-GAHT Checklist

- ☐ Discussed gender embodiment goals and expectations of GAHT
- ☐ PMH, DH, FH, SH, HEeADSSS
- ☐ MH review – offer support options as needed
- ☐ Check on family/community support
- ☐ Fertility/reproductive options discussed
- ☐ Information on consent form and info sheet explained and copy provided to patient
- ☐ Offered menstrual cessation options
- ☐ Discussed contraception
- ☐ Discussed cervical screening and set recall
- ☐ Baseline bloods (FBC, LFT, LH, FSH, oestrogen, testosterone, lipids and consider HbA1c & Beta hCG)
- ☐ Baseline BP & Wt
- ☐ Document capacity to provide informed consent and whether they meet the SOC-8 criteria for hormone treatment
- ☐ Consent form signed (if using)
- ☐ Arrange for nurse appointment for injection, GP appointment for follow-up in 3 months and set recall for 3–6-monthly bloods and plan to measure testosterone after 6–9 months

E-GAHT Checklist

- ☐ Discussed gender embodiment goals and expectations of GAHT
- ☐ PMH, DH, FH, SH, HEeADSSS
- ☐ MH review – offer support options as needed
- ☐ Check on family/community support
- ☐ Discuss likely infertility and offer fertility preservation
- ☐ Information on consent form and info sheet explained and copy provided to patient
- ☐ Discussed – voice therapy, other supports
- ☐ Baseline bloods (LFT, lipids, electrolytes, LH, FSH, testosterone, oestrogen, consider HbA1c & HIV, syphilis, hep B & C if preserving fertility)
- ☐ Baseline BP & Wt
- ☐ Document capacity to provide informed consent and whether they meet the SOC-8 criteria for hormone treatment
- ☐ Consent form signed (if using)
- ☐ Arrange for follow-up in 3 months and set recall for 3–6-monthly bloods

Appendix E:

Patient information sheets

Oestrogen-based gender affirming hormone therapy

The person prescribing your hormones should go through and discuss all of this information with you. If you have any questions or anything is unclear, please discuss this with your health provider.

Which medications are used?

Two medications are used as part of oestrogen-based hormone therapy:

- Oestrogen to provide the hormone oestrogen.
- Testosterone blockers (or anti-androgens) are given alongside this to block the hormone testosterone. If you have an orchiectomy (removal of external gonads or testicles) this medication is no longer needed.

Oestrogen comes in tablets or patches. There is no evidence of a difference in feminising outcomes or effects between these, so you can choose which you prefer, in discussion with your prescriber and taking into account your medical history. Patches are likely to carry a lower risk of blood clots. Taking high doses does not cause changes to happen more quickly and can put your health at risk. There is no evidence to support higher doses or regimes outside of standard guidelines.

Oestrogen tablets are taken every day. Oestrogen patches are applied to the lower abdomen and changed twice a week.

Testosterone blocker options are spironolactone or cyproterone. Both are a tablet taken every day or every other day. There is no evidence of a difference in feminising effects between these.

Spironolactone is a blood pressure tablet at low doses but works as an anti-androgen at higher doses. It will not suppress testosterone levels but will block the effects of testosterone in the body, promoting breast growth and slowing down body hair. Side effects can be low blood pressure, dizziness and passing urine more often.

Cyproterone in very small doses (12.5mg daily or less) will suppress testosterone but it does not suit everyone. Side effects can include fatigue/tiredness and low mood. Shortness of breath is an uncommon side effect but is possible. Larger does have been associated with liver function abnormalities and with a benign brain tumour called a meningioma, but this is thought to be related to long-term use of doses greater than 25mg daily. Evidence in other areas of healthcare shows the risk of blood clots is increased with cyproterone use.

These hormones are fully funded by PHARMAC, which means they cost the same as other routine prescriptions.

What blood tests do I need?

A baseline blood test is often performed before starting hormone therapy, then ongoing monitoring blood tests are usually 3–6-monthly for the first year and 6–12-monthly thereafter (or as agreed with your healthcare provider). You will usually also need to have your blood pressure and weight checked every year.

The blood test will check your liver function and cholesterol levels, as well as monitoring hormone levels. If you are taking spironolactone your potassium level will be monitored.

When taking spironolactone, the testosterone level measured in your blood test may remain raised, as spironolactone mostly acts to blocks testosterone's effect on the tissues in the body, rather than reducing the release of testosterone. For this reason, there is no need to check testosterone levels on a blood test if you are taking spironolactone.

Oestrogen levels are only checked to ensure levels are not too high as this can lead to health risks. Oestrogen levels do not correlate well with physical effects or reported satisfaction, and there isn't enough evidence to suggest a target range. Instead your oestrogen dose will be adjusted in line with standard dose ranges and your experiences of the effects.

Expected effects

Effects are gradual and timing varies, but it can take years for the full effects to be seen. The effects are largely dependent on genetics and the age you start hormones, rather than the dose or type of medication you take. It is important to have realistic expectations about the effects of hormones. The table below outlines the expected timing of the effects, and this link shows the expected effects in a picture: Effects and expected time course of hormone therapy consisting of an anti-androgen and oestrogen

The following changes are permanent (these will not reverse if you stop taking hormones):

- Breast growth – breast growth is gradual over 2–3 years. Most people starting oestrogen-based hormone therapy after puberty can expect to develop an A cup or smaller. As with all people who develop breasts, these vary in size and shape.
- Loss of fertility – your external gonads (testicles) may shrink and eventually stop producing sperm. This may lead to a permanent loss of fertility. Fertility preservation is usually available free of charge. Your GP or nurse practitioner can refer you for this before you start hormones.

The following changes are not permanent (these may reverse if you stop hormones):

- Softer skin
- Decreased muscle mass and strength
- Less body hair – decreases in thickness and grows more slowly but it doesn't go away completely. Some people choose electrolysis or laser treatment for a more permanent solution.
- Redistribution of fat (more on hips, bum, thighs)

Things that don't change:

- Facial hair growth slows down but doesn't stop completely.
- Voice stays the same (voice therapy may be available in your region).
- Bone structure of your face and Adam's apple doesn't change.

Effect of oestrogen	Expected onset	Expected maximum effect	Reversibility
Redistribution of body fat	3–6 months	2–3 years	Likely
Decrease in muscle mass and strength	3–6 months	1–2 years	Likely
Softening of skin/decreased oiliness	3–6 months	Unknown	Likely
Decreased sexual desire	1–3 months	3–6 months	Likely
Decreased spontaneous erections	1–3 months	3–6 months	Likely
Breast growth	3–6 months	2–3 years	Not possible
Decreased testicular volume	3–6 months	2–3 years	Unknown
Decreased sperm production	Unknown	>3 years	Unknown
Thinning and slowed growth of body and facial hair	6–12 months	>3 years[a]	Possible
Male pattern baldness	Variable	[b]	
Voice changes	None	[c]	

[a] Complete removal of hair requires laser treatment.
[b] Depending on your family history, balding may occur if oestrogens are stopped.
[c] Treatment by speech-language therapists for voice training is most effective.

(Reproduced with permission from the *Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand*)

Sex

A baseline blood test is often performed Your sex drive is likely to be lower. You will soon notice that you get hardening or stiffening of your erectile tissue (erections) less often and when this does occur, it may be more difficult to sustain. If this is causing issues with sex, you can ask your GP for medication to help this. Lowering the dose of your testosterone blocker may also help. Your external gonads (testicles) will usually shrink to less than half of their original size. Although your sperm count is likely to be lowered (see below), it isn't always, and so if you have sex with someone who is able to become pregnant, you should use contraception.

Fertility

The impact on fertility is unclear but it is safest to assume that within a few months of starting oestrogen-based hormone therapy you could permanently and irreversibly lose the ability to create sperm. Fertility preservation is usually fully funded and your GP or nurse practitioner can refer you for this.

Side effects and risks

- Common side effects include breast tenderness and weight gain. Nausea and headaches can occur when starting oestrogen and usually settle in the first few days or weeks.
- Please tell your healthcare provider if you develop migraine headaches.
- Full medical effects and long-term safety are not known. For most people, benefits outweigh risks, but it depends on other risk factors you may have (such as family history, body size, smoking and blood pressure level).
- There is a small increased risk of liver problems and raised cholesterol (these are both monitored on the blood tests).
- There is an increased risk of blood clots. Using oestrogen patches instead of tablets reduces this risk.
- Risk of health problems are higher if you smoke or are overweight or are over the age of 45 years.
- There may be a slight increased risk of breast cancer compared with cisgender men.

Emotional health

You may feel more emotional. It is not known exactly how hormones will impact your mental health and this varies between individuals. It is a bit like going through a second puberty, so you may experience a rollercoaster of emotions, or you may notice no change. Some people experience mood swings or a worsening of anxiety or depression. You may prefer to start the hormones when you have an upcoming period without big life stressors. We know that gender affirmation can also be a stressful time and many people benefit from extra support through this. Please discuss this with your health provider who can give you options for counselling or peer support. Many people find it very helpful to talk to someone who understands gender affirmation, and it can be helpful to explore concerns around coming out (disclosure), stress with family, social and internalised transphobia, anxiety, uncertainty, acceptance etc. You can find details about support options here:

Gender diversity support services – Health Navigator

Rainbow organisations – Te Ngākau Kahukura

Cancer screening

Breasts – breast screening (mammograms) from the age of 45 years as per national screening guidelines is recommended for anyone with breasts. This is a free service. You can find out more about breast screening and mammograms here: Breast screening – Time to Screen

Prostate – the prostate is a small gland which surrounds the opening of the bladder. If you have a prostate gland it is possible to develop cancer in this. Prostate cancer is most common over the age of 50 years. If you develop trouble with peeing, such as poor flow, dribbling, trouble starting or stopping peeing, peeing more often or blood in your pee, you should speak to your health provider.

Appendix E:

Patient information sheets

Testosterone-based gender affirming hormone therapy

The person prescribing your hormones should go through and discuss all of this information with you. If you have any questions or anything is unclear, please discuss this with your health provider.

Testosterone

Testosterone comes in injections and patches. The most common form is injectable testosterone, as patches commonly cause skin irritation. These hormones are fully funded by PHARMAC, which means they cost the same as other routine prescriptions. There is no evidence of any difference in outcomes or effects between the different forms of testosterone.

There are three forms of injectable testosterone:

- Depo-testosterone is given every 2 weeks.
- Sustanon is given every 3 weeks.
- Reandron is given approximately every 3 months.

Depo-testosterone and Sustanon can be self-injected at home if you wish to do so (but can also be given in clinic by a nurse). The nurse can teach you how to safely self-inject if this is your preferred option. You can also find useful information about this here: Transgender health injection guide

Reandron must be given by a health professional, and you will be seen in clinic for these injections.

Monitoring

Monitoring blood tests are usually needed before starting hormone therapy, then usually 3–6-monthly for the first year and 6–12-monthly thereafter (or as agreed with your healthcare provider). You will usually need to have your blood pressure and weight checked every year. The blood test will check your liver function and cholesterol levels, as well as monitoring hormone levels.

While most monitoring is started at baseline and then 3-monthly, the exception to this is your testosterone level. It takes time for this to stabilise, so it is not usually measured until 9–12 months after starting testosterone. When having a blood test for testosterone, the timing of your blood test is important and depends on which formulation of testosterone you are on:

- Depo-testosterone and Sustanon – check testosterone level mid-way between injections.
- Reandron – check testosterone level just before next injection.

Expected effects

Everyone is different in how quickly they respond to testosterone, but you will start to notice changes in your body gradually over the first few months (see table below). It takes years for the full effects to be seen. This link shows this in a picture: Effects and expected time course of testosterone hormone therapy

The following changes are permanent (these will not reverse if you decide to stop taking testosterone):

- Deeper voice (this can start with a scratchy feeling in the throat)
- Increased hair growth on your body (chest, back, arms)
- Facial hair (the amount varies from person to person)
- Hair loss at temples, possibly becoming bald with time depending on your age and family history.
- Genital changes: Erectile tissue (clitoris) growth around 1–3cm. This can feel uncomfortable or even painful initially.

The following changes are not permanent (these may reverse if you stop testosterone):

- Skin oiliness and acne (acne is usually worst in the first year then gradually improves. You can discuss acne medications with your health provider if needed.)
- Redistribution of body fat (less fat on hips, bum and thighs)
- Increased muscle mass and upper body strength
- Increased sex drive
- Monthly bleeding (periods) usually stops after 1–6 months (for most people but not all. Your prescriber can give you medication to stop monthly bleeding in the meantime if you need this.) Please let us know if you experience any bleeding after your monthly bleeding has stopped.

Effect of testosterone	Expected onset	Expected maximum effect	Reversibility
Skin oiliness/acne	1–6 months	1–2 years	Likely
Facial body/hair growth	6–12 months	4–5 years	Unlikely
Scalp hair loss	6–12 months[a]	Variable	Unlikely
Increased muscle mass/strength	6–12 months	2–5 years	Likely
Redistribution of body fat	1–6 months	2–5 years	Likely
Cessation of periods	1–6 months		Likely
Clitoral enlargement	1–6 months	1–2 years	Unlikely
Vaginal atrophy	1–6 months	1–2 years	Unlikely
Deepening of the voice	6–12 months	Variable	Not possible
Increased sexual desire	Variable	Variable	Likely

[a] Highly dependent on age and inheritance; may be minimal.

(Reproduced with permission from the *Guidelines for Gender Affirming Healthcare for Gender Diverse and Transgender Children, Young People and Adults in Aotearoa, New Zealand*)

Fertility and contraception

Long-term effects on fertility are not clear. Testosterone stops the ovaries from working and it is not known whether this is reversible or not. If you wish to carry a pregnancy in the future, you will need to stop testosterone as it is harmful to a developing fetus (the exact length of time it needs to be stopped before getting pregnant is not known, so make sure you discuss this with your doctor).

After stopping testosterone your fertility could return allowing you to become pregnant without assistance. However, it may not return, and you may not be able to become pregnant without fertility assistance. This assistance usually involves egg harvesting which is an invasive procedure where eggs are removed using a needle. Testosterone does not usually affect the quality of the eggs, so if it is desired this procedure can be carried out at the time it is needed and is not usually recommended before starting hormone therapy.

If you have surgery which involves removing your reproductive organs, you may be able to access funded egg storage and can discuss this with your health provider. If you would like to discuss fertility options in more detail you can request a referral to a fertility specialist.

Testosterone is NOT a form of contraception. If you are having sex which could result in pregnancy (front hole (vaginal) sex with someone whose body produces sperm), you should use contraception even if your periods have stopped.

Sex

Your libido (sex drive) may increase and your genitals, especially your erectile tissue (clitoris), will grow. This can lead to sex and orgasms feeling different. Testosterone can cause the internal genitals (vagina) to become dry, which can cause sex to feel uncomfortable. This can be eased by using additional lubrication (lube). If you have ongoing problems with discomfort in this area, an oestrogen cream can make the internal genital area feel much more comfortable. Your GP or nurse practitioner can prescribe oestrogen cream, or you can try an over-the-counter cream for dryness such as the Vagisil range.

Side effects and risks

- Increased red blood cells (this can thicken the blood increasing risk of stroke or heart attacks. Red blood cells are monitored on your blood tests.)
- Possible risk of liver problems or raised cholesterol (these are monitored on your blood tests).
- There may be an increased risk of blood clots.
- Risk of health problems are higher if you smoke or are overweight.
- Full medical effects and risks are not known.
- Potential risk of testosterone injections include pain at the site and infection. Steps are taken to reduce this risk. Reandron can rarely cause an oil embolism which is when a tiny amount of oil gets into the blood stream. This is why Reandron should be given by a health professional.

Emotional health

It is not known exactly how it will impact on your mental health and this varies between individuals. It is a bit like going through a second puberty, so you may experience a rollercoaster of emotions, or you may notice no change. You may prefer to start the hormones when you have an upcoming period without big life stressors. You may find your mental health improves, but we know that gender affirmation can also be a stressful time and many people benefit from extra support through this. Please discuss this with your health provider who can give you options for counselling or peer support. Many people find it very helpful to talk to someone who understands gender affirmation, and it can be helpful to explore concerns around coming out, stress with family, social and internalised transphobia, anxiety, uncertainty, acceptance, etc. You can find details about support options here:

Gender diversity support services – Health Navigator

Rainbow organisations – Te Ngākau Kahukura

Cancer screening

Cervical screening – this is recommended for anyone aged 25–69 years old who has a cervix. From July 2023 this can be done using a simple swab (which you can choose to do yourself in private). More details here: Cervical screening – Time to Screen

It is possible that changing your gender marker on your primary care practice computer system could result in you not getting a reminder when you are due for this test, so please discuss with your GP or nurse if you think this could be the case. The HPV vaccine greatly reduces your risk of cervical cancer. If you have not had this vaccine, please discuss this with a nurse or GP.

Breast screening – if you have breasts, screening mammograms are recommended from age 45 years. If you've had top surgery, you will need to follow the advice of your surgeon, which may be to perform regular self-exams and ask your GP about annual chest wall examinations with possible ultrasound scans. More information here: Breast screening – Time to Screen

Appendix F:
Consent forms

Consent form for starting oestrogen-based hormone therapy

This consent form outlines important information you might want to talk to your health team about before starting hormones to feminise the body.

Progynova (oestradiol valerate) tablets or **Estradot** (oestradiol hemihydrate) patches provide the feminising hormone oestrogen. Testosterone blockers are needed as well unless orchiectomy surgery has occurred.

Oestrogen tablets/patches will gradually feminise the body.

Permanent body changes (even if you stop taking the tablets):

- Gradual increase in breast size over 2–3 years.
- Your oestrogen dose is increased slowly for best breast development.
- It is not known if taking oestrogen increases the risk of breast cancer. Take care of your breasts – it is recommended to follow the normal breast screening guidelines for women.

Non-permanent body changes (that may reverse if you stop the oestrogen):

- Softer skin
- Decreased muscle mass
- Less body hair
- More fat on buttocks, hips and thighs

Things that don't change much:

- Facial hair slows down but doesn't stop completely
- Voice stays the same
- Bone structure of your face and Adam's apple doesn't change

If you stop taking your hormones some body changes stay but you may find that your body will slowly masculinise.

Fertility

Taking the hormones stops your testicles producing testosterone. Your testicles may shrink by up to 50% and may eventually stop sperm production. If it is important for you to preserve your fertility you might want to freeze your sperm before you start treatment. Your health team will talk to you about this.

Sex

Taking the blocker tablets may lower your sex drive so that you are not as interested in having sex any more. You may find that you get erections less often and that your penis doesn't get as hard any more. If you want to be able to use your penis for sexual pleasure talk to your health team and they will review your medications.

Mental health

Some people may feel more emotional taking oestrogen. Some people find their mental health improves – the effects of hormones on the brain are not fully understood. Transitioning can be a stressful time and many people need some help adjusting to the physical and emotional changes. It is really important that you let your health team know if you are having problems so that they can help you access the support you need.

Common side effects

- Nausea
- Headaches
- Tender breasts
- Weight gain

Most side effects should settle within a few days to weeks of starting the medications. Please tell your health team if you have any side effects, especially headaches or migraines.

Potential risks of oestrogen

The full medical effects and safety of taking hormones are not fully known. The potential risks of taking oestrogen must be weighed against the benefits that hormones can have on your health and quality of life.

Likely increased risk

- Blood clots – deep vein thrombosis (DVT), pulmonary embolism (blood clot in the lung), stroke, heart attack
- Changes to cholesterol (may increase risk of pancreatitis and heart disease)
- Gallstones

Possible increased risk

- Increased blood pressure
- Liver problems
- Increased prolactin and possibility of benign pituitary tumours

Possible increased risk if you have extra risk factors

- Heart disease
- Diabetes

No increased risk or unknown

- Breast cancer

Some of these risks are reduced by using oestrogen patches instead of tablets.

Go to the emergency department or seek medical help urgently if you have:

- A swollen painful leg
- Chest pain or difficulty breathing
- Vision or speech problems.

These symptoms might mean you have a serious problem like a blood clot.

The risk of having a blood clot is much higher if you smoke or are overweight.

Blood clots are more common as you get older. Stopping oestrogen before and after surgery can help reduce the risks of blood clots around this time.

Keeping in touch with your health team for regular check-ups and blood tests is an important part of your care and will reduce the risks of taking hormonal therapy.

Are there any other questions you want to ask?

It is your health team's responsibility to best support you to make the decisions that are right for you and to keep ourselves up to date so that we can best inform you.

For many different reasons people question whether or not they want to continue to take hormones. This can be a normal part of your journey. Please feel free to discuss this with your prescriber before you stop your medication. Come and talk – your health team is always ready to listen.

I wish to start feminising hormone therapy:

Name .....

Date .....

Prescribed by:

Name .....

Date .....

Appendix F:
Consent forms

Consent form for starting testosterone-based hormone therapy

This consent form outlines important information you might want to talk to your health team about before starting hormones to masculinise the body.

There are different types of testosterone that are taken to masculinise the body. Everyone is different in how quickly they respond to testosterone but you will start to notice changes in your body gradually over the first few months. It may take several years before the full effect is felt. While there are different ways of getting testosterone into the body most people are on injections.

Permanent body changes (even if you stop taking testosterone):

- Deeper voice
- Increased growth of hair – with thicker hairs on arms, legs, chest, back and abdomen
- Gradual growth of moustache/beard hair
- Hair loss at the temples – possibly becoming bald with time
- Genital changes – clitoral growth (typically 1–3 cm) and vaginal dryness.

Non-permanent body changes (that may reverse if you stop the testosterone):

- Skin changes – increased oil and acne
- Change in body shape – less fat on buttocks, hips and thighs
- Increased muscle mass and upper body strength
- Increased sex drive
- Periods usually stop after 1–6 months

Things that don't change much:

- Breast tissue looks a bit smaller due to fat loss
- Possible weight gain or loss

Fertility

While it is not known what the long-term effects are of taking testosterone some trans men find that if they stop their testosterone they will become fertile again and can get pregnant. There are no guarantees for anyone and it is probably harder to get pregnant the older you are and the longer you have been on testosterone.

Testosterone is dangerous for the developing fetus – you must not get pregnant while you are on testosterone. Even after your periods stop you might still be at risk of getting pregnant. If you are having any sexual contact that puts you at risk of pregnancy you must talk to your health team about contraception options.

Sex

Taking testosterone causes your vagina to become dryer and more fragile. This increases the risk of sexually transmitted infections (STIs), including HIV if you are having any sexual contact with this part of the body. Condoms provide good protection against STIs and lubricant helps to prevent any discomfort.

Mental health

Some people find that testosterone can cause emotional changes such as increased irritation, frustration and anger. Some people find their mental health improves – the effects of hormones on the brain are not fully understood.

Transitioning can be a stressful time and many people need some help adjusting to the physical and emotional changes. It is really important that you let your health team know if you are having problems so that they can help you access the support you need.

Potential risks of testosterone

The full medical effects and safety of taking hormones are not fully known. The potential risks of taking testosterone must be weighed against the benefits that hormones can have on your health and quality of life.

Likely increased risk

- Increased red blood cells (polycythemia) – might thicken the blood and increase the risk of a stroke or heart attack
- Sleep apnoea (sleep disorder)

Possible increased risk

- Increased blood pressure
- Liver problems
- Increased prolactin and possibility of benign pituitary tumours

Possible increased risk if you have extra risk factors

- Diabetes
- Increased blood pressure

No increased risk or unknown

- Breast cancer
- Cervical, ovarian, uterine cancer
- Blood clots – deep vein thrombosis (DVT)

The risk of health problems is higher if you are a smoker or overweight.

Keeping in touch with your health team for regular check-ups and blood tests is an important part of your care and will reduce the risks of taking hormonal therapy.

Are there any other questions you want to ask?

It is your health team's responsibility to best support you to make the decisions that are right for you and to keep ourselves up to date so that we can best inform you.

For many different reasons people question whether or not they want to continue to take hormones. This can be a normal part of your journey. Please feel free to discuss this with your prescriber before you stop your medication. Come and talk – your health team is always ready to listen.

I wish to start masculinising hormone therapy:

Name .....

Date .....

Prescribed by:

Name .....

Date .....

Appendix G:

Testosterone administration

Practical tips for health professionals

Visual overview of available formulations of injectable testosterone

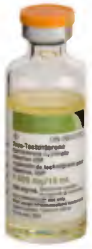
NB: this is not patient information. Useful resources for patients wishing to self-administer Sustanon or Depo-testosterone can be found here: Transgender health injection guide

Reandron
(testosterone undecanoate)

Comes in a vial. Usually given 12-weekly. Single use vial, dose up to 4ml.

Sustanon
(testosterone esters)

Comes in a glass ampoule. Single use, usually given 3-weekly. Can be self-administered.



Depo-testosterone
(testosterone cypionate)

Comes in a vial, each vial contains 5-10 doses. Usually given fortnightly. Can be self-administered.

General advice for all formulations:

- The first injection can be very significant for people – they may have waited a long time to start. Important not to rush; ensure privacy.
- Obtain and document consent, ensure person is aware of potential side effects.
- All formulations should be administered slowly.
- 20-minute wait after the first injection is recommended in case of allergy.

Storage

- All formulations need to be stored below 30°C (e.g. in a cool cupboard away from direct sunlight). Do not refrigerate or freeze.
- Sustanon should be used immediately once the ampoule is open as it cannot be resealed.

Preparation

- As with all medicines, check expiry date first, and '5 rights of medication administration' (the right person, drug, dose, route, time).
- Slightly warming the formulation beforehand in one's hands it easier to prepare and administer.
- Injecting the same volume of air as the dose required into the vial for Reandron and Depo-T can break the vacuum and make it easier to draw up the liquid, but this is not essential. This will not be possible with Sustanon.
- Always check for air bubbles in the syringe and remove prior to administration.

Administration

- As with any deep intramuscular injection the ***ventrogluteal*** site is the best administration site for all formulations: reported to be less painful, less risk of injury to underlying nerve structures, less risk of oil embolism as no major blood vessels, and usually less adipose tissue and more muscle. However, it can be given in the ***dorsogluteal*** site. The same site should not be used every time, so rotate between left and right side each injection.
- Can be given standing or supine per personal preference (supine recommended for Reandron). People self-administering their testosterone usually use the vastus lateralis or rectus femoris sites as better access.
- All formulations are given as a deep intramuscular injection so best use a 38mm (1.5") 22 G needle to administer. Important to inject into deep muscle as testosterone can cause necrosis or abscess formation if given too superficially/into adipose tissue.
- Depo T can also be given subcutaneously but there is not yet enough evidence around the safety and efficacy of giving Sustanon via this route. Note that the dose and regime for subcutaneous administration of Depo T is not the same as for the intramuscular route.
- As with all intramuscular injections, Z-track technique is recommended to prevent tracking of the medication into the subcutaneous tissue.
- Always aspirate first before injecting solution to ensure the needle is not in a blood vessel.
- All formulations should be administered ***slowly*** and at a steady, controlled pace.

Disposal

- Some people like to keep their ampoules/ vials so check first before disposal.
- Dispose of all syringes per usual protocol, e.g. via a sharps bin.
- Local needle exchanges often have facilities for safe sharp disposal for self-administration.

Reandron

- Ideally given over 4 minutes, very thick solution so takes time, be patient!
- Doses should not be split (i.e. needs to be given as 4ml dose not 2 x 2ml).
- Use an 18G needle to draw up medication then change to 38mm 22G or 21G needle to administer.
- For dose of 3ml or less, use a 3ml syringe as resistance will be less. For a dose of 4ml use a 5ml syringe.

Sustanon

- Contains arachis oil – check no peanut allergies first.
- When breaking the top, have the 'small blue dot' facing away from you. This indicates the weakest point of the vial. You can then break the vial by snapping the top off towards you. Use a gauze or tissue to do this to protect your fingers from the glass – can be sharp.
- Use a blunt filter needle in case of glass fragments to withdraw solution into the syringe.
- Change to 38mm 22G needle when ready to administer.
- Use a 1ml tuberculin syringe or 3ml syringe, depending on dosage. For a dose of 1ml, a 3ml syringe is usually easier to prepare.

Depo-testosterone

- Use within 28 days.
- Use alcohol swab to clean the rubber bung each time before drawing up (allow time to dry).
- Replace lid and secure until next visit.
- Can use 18G needle to draw up medication then change to 38mm 22G needle to administer.
- Can use 1ml tuberculin syringe or 3ml syringe, depending on dose.

RULE FOUNDATION
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TAB 200-5

United States District Court
Northern District of Florida

Case Number: 4:22-cv-00325-RH-MAF

August Dekker, et al.
Plaintiffs,
vs.
Jason Weida, et al.
Defendants:
_____/

VIDEOCONFERENCE DEPOSITION OF
JASON WEIDA

DATE: April 24, 2023
TIME: 3:00 p.m. - 6:31 p.m.
LOCATION: 119 South Monroe Street, Suite 500
Tallahassee, Florida 32301
REPORTED BY: John Bilich, Notary Public
JOB NO.: 5884626

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Southern Legal Counsel
BY: Chelsea Dunn, Esquire
BY: Simone Chriss, Esquire
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Also Present:
Thomas Thomas, Videographer
Anna Gonzalez, Paralegal (By Video Conference)
Pillsubry Winthrop Shaw Pittman, LLP

A No.
Q Do you recall being in attendance at a meeting with officials from the governor's office and people from the Florida Department of Health, as well as people from AHCA prior to April 20th of 2022?
A Not -- may I ask you a clarifying question?
Q Yes, of course.
A Okay. Regarding gender-related issues?
Q Correct. Well, gender dysphoria and transgender issues in particular, not gender issues generally.
A Right, I just want to make sure, because we have a lot of meetings and I have met with the Department of Health in the past on a range of topics. But with respect to the topics at issue in this lawsuit, I do not recall being at a meeting with all of those individuals.
Q Do you recall being in a meeting with some subset of those individuals?
A Yes, I do.
Q Okay. When was that?
A I don't have an exact date, but I believe it would have been early April.

Q Who was present in the meeting?
A So in addition to myself -- well, I want to be -- I just want to be clear here. So I remember two such meetings, and I don't remember exactly who was at one meeting versus the other, but I can tell you who I remember being at both of those meetings cuz I know that there was at least one person and possibly more who was at one, but not both, and I just don't remember which ones those were. But I can just tick through the whole list if that's okay with you?
Q Fair enough. Before you do that, was the other meeting -- you mentioned that one meeting was early April. Was the other meeting in March, or was the other meeting after the meeting in early April?
A I believe it was after the meeting in early April.
Q So, as you recall today, you had a meeting in early April and then a meeting after that meeting, correct?
A That's correct.
Q All right. So let's start with, tell me everyone that you can remember that was in those meetings collectively, since you can't remember who was in which one.

A Right. So, collectively, obviously without representing that they were all there for both, the people that I remember being at one or the other, or possibly both of those meetings, were secretary Marstiller, who was the secretary of the Agency for Healthcare Administration at the time. Cody Farrill, who was the chief of staff at the Agency for Healthcare Administration at the time, Josie Tamayo, who was the General Counsel for the Agency for Healthcare Administration at the time. Andrew Sheeran, who at the time was the chief litigation counsel. He worked for Josie Tamayo. He's our current General Counsel, but at the time he was the chief litigation counsel. I recall Ryan Newman being present. Ryan is and was at the time the governor's General Counsel. And at one or both of those meetings, Katie Strickland, who is the deputy chief of staff for the governor, one of the deputy chiefs of staff. And I also recall Maureen Furino, although I don't remember if she was present or just called in. I think she might have called into the meeting. So I don't think she was technically present.

Q And who is she?

A She is a deputy General Counsel. She

worked for Mr. Newman.

Q Okay. Anyone else you recall being there?

A Not that I can recall.

Q Who called the meeting?

A I don't know who --

Q -- organized -- (Talking simultaneously.) [Inaudible].

A I don't know.

Q How did you find out you were going to be there, or needed in the meeting?

A I believe I was invited by somebody from the agency management team at the Agency for Healthcare Administration. I just don't remember who that would've been.

Q What were you told the meeting was going to be about?

A I was told the meeting was going to be about recent guidance that had been issued by the United States Department of Health and Human Services regarding treatments for gender dysphoria.

Q And do you recall who told you that?

A No, I don't.

Q Do you recall, did you get a calendar invitation for the meeting?

A I don't recall. It was about a year ago,

Q Yes.

A So, I don't have the full list in front of me, but my understanding is that there are, I don't know exactly how many, but several coverage policies in the Bureau of Medicaid policy that provide for various mental health and behavioral health services for the treatment of gender dysphoria.

Q What analysis was done to determine whether or not there's any evidence that psychotherapy or behavioral health therapy on its own is an appropriate treatment for gender dysphoria?

A Well, the GAPMS report focused on the procedures that are described in the current rule. The GAPMS report did not focus on, directly at least behavioral health services. So that was not part of the GAPMS process or the review.

Q Has any analysis been done to determine whether or not psychotherapy or behavioral health therapy alone is an appropriate treatment for gender dysphoria?

A I don't know the answer to that question.

Q Shouldn't you know the answer to that question? Is if that's the only thing that's covered for gender dysphoria, shouldn't you know, as

TAB 200-6

Posted on 04/11/2023 by **brandon (/user/730)**

Equality Florida Issues Advisory Warning For Travel

ST. PETERSBURG, FL -- Today, Equality Florida took the extraordinary step of issuing a travel advisory, warning of the risks posed to the health, safety, and freedom of those considering short or long term travel, or relocation to the state. The move comes in response to a wave of safety inquiries Equality Florida has received following the passage of laws that are hostile to the LGBTQ community, restrict access to reproductive health care, repeal gun safety laws, foment racial prejudice, and attack public education by banning books and censoring curriculum.

“As an organization that has spent decades working to improve Florida’s reputation as a welcoming and inclusive place to live work and visit, it is with great sadness that we must respond to those asking if it is safe to travel to Florida or remain in the state as the laws strip away basic rights and freedoms,” said **Nadine Smith, Equality Florida Executive Director**. “While losing conferences, and top students who have written off Florida threatens lasting damage to our state, it is most heartbreaking to hear from parents who are selling their homes and moving because school censorship, book bans and health care restrictions have made their home state less safe for their children. We understand everyone must weigh the risks and decide what is best for their safety, but whether you stay away, leave or remain we ask that you join us in countering these relentless attacks. Help reimagine and build a Florida that is truly safe for and open to all, and where freedom is a reality, not a hollow campaign slogan.”

Governor Ron DeSantis, who has made the extremist policies the centerpiece of his presidential campaign strategy, has weaponized state agencies to silence critics and impose sanctions on large and small companies that dissent with his culture war agenda or disagree with his attacks on diversity, equity, and inclusion.

Already, the adopted and proposed policies detailed in the travel advisory have led Florida parents to consider relocating (https://19thnews.org/2023/02/queer-florida-parents-leaving-state-dont-say-gay/), prospective students to cross Florida colleges and universities off their lists (https://www.forbes.com/sites/petergreene/2023/03/31/survey-1-in-8-florida-incoming-freshmen-plan-to-flee-desantiss-education-policies/?sh=c2cc6f42dfda), events and conferences to cancel future gatherings (https://www.lgbtqnation.com/2022/09/large-gaming-event-set-florida-canceled-dont-say-gay-law/), and the United States military to offer redeployment for service members whose families are now unsafe in the state. Businesses have spoken out against the governor’s abuse of state power to punish dissent, with Disney CEO Bob Iger calling DeSantis “anti-business and anti-Florida (https://www.theguardian.com/us-news/2023/apr/04/disney-bob-iger-ron-desantis-florida).” The worsening attacks, especially those targeting transgender youth, have also led to the proposal of policies around the country (https://thehill.com/homenews/3861492-amid-tidal-wave-of-anti-trans-legislation-democratic-states-race-to-become-refuges-for-gender-affirming-care/) to provide refuge for those fleeing states like Florida.

The Florida Immigrant Coalition, a statewide immigrant rights coalition of 65 member organizations and over 100 allies, also issued a travel advisory today (https://floridatraveladvisory.com/), urging reconsideration of travel to Florida and providing critical information about where immigrant travelers can learn more about their constitutional rights. And just weeks ago, Florida chapters of the NAACP voted unanimously (https://naacp.org/articles/naacp-florida-state-conference-recommends-travel-advisory-state-response-african-american) to request similar warnings to the Black community about the risk of traveling or relocating to the state.

Equality Florida's full travel advisory follows.

MEMORANDUM

To: Interested Parties

From: Equality Florida

Subj.: TRAVEL ADVISORY: FLORIDA MAY NOT BE A SAFE PLACE TO MOVE OR VISIT

Date: April 12, 2023

Today, Equality Florida took the unprecedented step of issuing a travel advisory to individuals, families, entrepreneurs, and students warning that Florida may not be a safe place to visit or take up residence. The advisory comes after passage of laws that are hostile to the LGBTQ+ community, restrict access to reproductive health care, repeal gun safety laws and allow untrained, unpermitted carry, and foment racial prejudice. The Governor has also weaponized state agencies to impose sanctions against businesses large and small that disagree with his attacks on diversity, equity, and inclusion.

Florida has recently adopted a slate of hateful laws, and is fast-tracking additional measures that directly target the rights of LGBTQ+ individuals and basic freedoms broadly. Already, those policies have led Florida parents to consider relocating (https://19thnews.org/2023/02/queer-florida-parents-leaving-state-dont-say-gay/), prospective students to cross Florida colleges and universities off their lists (https://www.forbes.com/sites/petergreene/2023/03/31/survey-1-in-8-florida-incoming-freshmen-plan-to-flee-desantiss-education-policies/?sh=c2cc6f42dfdahttps://www.forbes.com/sites/petergreene/2023/03/31/survey-1-in-8-florida-incoming-freshmen-plan-to-flee-desantiss-education-policies/?sh=c2cc6f42dfda), events and conferences to cancel future gatherings (https://www.lgbtqnation.com/2022/09/large-gaming-event-set-florida-canceled-dont-say-gay-law/), and the United States military to offer redeployment for service members whose families are now unsafe in the state. These laws and policies are detailed below.

Assaults on Medical Freedom

- Florida's Boards of Medicine and Osteopathy have adopted policies banning access to lifesaving medical care for transgender youth and the Agency For Health Care Administration has eliminated Medicaid coverage for transgender adults accessing that care
- Florida is poised to pass laws creating criminal penalties for medical providers who provide medically necessary care for transgender youth, weaponizing the courts to shred existing child custody agreements and reassign transgender youth to an unsupportive parent, and severely restricting access to prescribed medical care for transgender adults
- Florida has passed or is poised to pass bills that restrict access to reproductive health care, including a near-total abortion ban, which threatens to force people to travel out of state or seek unsafe, illegal abortions.

These policies disproportionately harm marginalized communities, including the direct impacts on the transgender community and communities of color, and could lead to serious health consequences. Transgender people in Florida are facing the immediate threat of loss of lifesaving, medically necessary care and families risk interference in child custody arrangements at the hands of an unsupportive parent and a weaponized state court system. These attacks pose an imminent threat to the health and safety of all in Florida and potential travelers should be aware of the risks.

Assaults on Academic Freedom

- The Florida legislature has sought to strip Diversity, Equity, and Inclusion (DEI) programs from colleges and universities, that help LGBTQ and minority students thrive
- The Governor has initiated a hostile, right-wing takeover of higher education, and installed partisan allies to implement a conservative overhaul of public universities
- His administration has taken aim at AP African American studies, threatening to sever ties with the College Board over the inclusion of queer history and intersectionality in the course, and college majors, including gender studies

These actions by the Governor pose a serious threat to academic freedom, free speech, and the pursuit of knowledge. DEI departments play a crucial role in promoting diversity and inclusion on campus, and their removal undermines the ability of students and faculty to engage in critical discussions about issues of race, gender, and identity.

Furthermore, the replacement of university presidents with political appointees threatens the independence of higher education institutions, and undermines the ability of these institutions to make decisions that are in the best interest of their students, faculty, and staff. These attacks on public education are deeply concerning, and further reinforce the message that Florida is not a welcoming state for people from all backgrounds. We urge individuals, families, entrepreneurs, and students to consider the implications of traveling to or residing in Florida, and to support efforts to defend public education and academic freedom in the state.

Censorship and Erasure of the LGBTQ Community

- Florida has passed a prohibition on classroom instruction on sexual orientation and gender identity in public schools
- This law has already precipitated a raft of damaging impacts in school districts across the state, including
    - Hundreds of book challenges and bans targeting titles written by LGBTQ authors and/or including LGBTQ characters
    - The refusal of districts like Miami-Dade to recognize LGBTQ History Month
    - The removal of rainbow Safe Space stickers
    - The censorship of graduation speech content to remove references to LGBTQ identities
    - Warnings to educators and administrators to hide family photos
- Lawmakers are currently considering a bill to extend that prohibition through 8th grade, while the Department of Education is set to decide on a policy proposal that would expand it to all grades and revoke teacher licenses over violations
- Florida is poised to pass a bill that would ban transgender people from updating their birth certificates to reflect their gender identity

The infamous Don't Say LGBTQ law has made Florida synonymous with the anti-LGBTQ movement to empower government censorship and book banning across the nation. That law, along with additional proposals being considered, has turned the state's classrooms into political battlefields and is telegraphing to LGBTQ families and students that they are not welcome in Florida.

Assaults on Arts, Entertainment, and Sports Participation

- Florida has passed a ban on transgender women and girls from participating in school sports consistent with their gender identity
- Lawmakers are poised to pass restrictions on certain live drag performances, stage shows, and local pride celebrations, limiting parents' ability to determine what content may be suitable for their families

The far-right's obsession with drag queens has put LGBTQ people in physical danger across the country, but especially in Florida. In 2022 alone, the LGBTQ media organization GLAAD found 141 incidents of anti-LGBTQ protests and threats targeting drag events. Right-wing media like Fox News and Libs Of TikTok have misrepresented what occurs at drag events and taken examples out of context to create fear and misunderstanding. This has had real world consequences, with protests and threats of violence against venues hosting drag shows.

In Florida, Orlando organizers were forced to cancel Drag Queen story hour due to threats from Neo-Nazis (https://www.orlandoweekly.com/news/orlando-area-drag-queen-story-hour-canceled-due-to-neo-nazi-threats-32762594). This last December in Lakeland (https://www.fox13news.com/news/demonstrators-wearing-nazi-gear-show-up-outside-lakeland-charity-event-that-included-drag-performers), masked individuals in Nazi gear, waving Nazi flags ambushed a charity event hosted by drag queens while projecting hateful messages onto local buildings.

Assaults on Business

- DeSantis has recently signed a bill that restricts businesses from providing diversity and inclusion training to their employees, a blatant attempt to dictate to businesses what they can and cannot do, and to prevent them from training their employees to be better prepared for a diverse workforce and customer base
- The Florida legislature is expected to pass SB 1438, which weaponizes state agencies with more power to politically target LGBTQ-friendly businesses who open their doors to live drag performances, with threats of fines, license revocation, and jail time. Individuals that admit minors with an accompanying parent would be charged with first degree misdemeanor crimes.
- The governor has weaponized the state legislature against businesses that stand with their LGBTQ employees and clients and against his agenda, most notably wielding two special sessions of the legislature to punish Disney, the state's largest single-site employer

The Miami Herald recently reported (https://www.miamiherald.com/news/politics-government/state-politics/article273247175.html) that DeSantis-controlled agencies sought to punish and revoke the liquor license of an Orlando establishment that hosted a live drag performance even after the state's own investigators reported that they saw nothing "lewd". The discriminatory targeting of LGBTQ-friendly businesses by the state will have a broader chilling effect over drag performances, an intended consequence of this type of censorship.

Disney has also recently denounced the governor's actions against them, with CEO Bob Iger calling the state's policies "anti-business and anti-Florida (https://www.theguardian.com/us-news/2023/apr/04/disney-bob-iger-ron-desantis-florida)."

These laws and actions are harmful to businesses and their employees, as they undermine efforts to create inclusive workplaces and hinder the ability to effectively engage with diverse customers and clients. It also sends a message that Florida is not a welcoming state for people from all backgrounds and that discrimination is acceptable.

Efforts to Foment Racial Prejudice

- Florida has passed a bill that would limit the honest teaching of history and systemic racism in schools
- The state passed another that restricts voting access for people of color and is currently considering additional voting restrictions
- DeSantis' new elections police have abused their power to aggressively target and prosecute returning citizens, mostly Black Floridians, for voting after official government entities told them they were eligible to vote (https://www.politico.com/news/2022/08/26/desantis-voter-fraud-defendants-florida-00053788)

These laws create an unsafe and unwelcoming environment for LGBTQ+ individuals, women, people of color, and other marginalized communities. They send a message that discrimination and prejudice are acceptable in Florida, and we cannot in good conscience encourage people to visit or move to a state that is openly hostile to their basic human rights.

As a result of these dangerous and discriminatory laws, we urge individuals, families, entrepreneurs, and students to reconsider travel plans to Florida and to consider the impact that their travel and economic choices can have on promoting equality and justice for all.

Repealing of Gun Safety Laws

The passage of deadly permitless carry makes Floridians less safe (https://everytownresearch.org/solution/strong-standards-for-carrying-concealed-guns-in-public) and signals the reversal of the progress made after Pulse and Parkland. Coupled with the state's infamous Stand Your Ground law, Permitless Carry threatens to exacerbate Florida's violent crime rate at a time when the state's homicide rate ranks 20th in the nation, exceeding both California and New York.

LGBTQ Floridians know all too well that the gun lobby's obsession with easy access to deadly weapons can make hatred and bigotry lethal (https://www.hsph.harvard.edu/news/hsph-in-the-news/do-guns-make-us-safer-science-suggests-no/). Gun violence is not abstract or hypothetical -- it is stealing our loved ones. Those considering travel to Florida should weigh the potentially deadly consequences of the DeSantis Administration's decision to eliminate basic training and permitting requirements in order to concealed carry a firearm.

Attacks on Immigrant Communities

Florida has passed and is poised to pass legislation targeting immigrant communities, with consequences that could include arrest for operating a vehicle, no matter the state you are from, reduced access to health care services, and compromised safety. A bill currently being considered by the Florida legislature could impose criminal penalties on any who shelter, support, or provide transportation to undocumented immigrants. And these moves come just months after Governor DeSantis trafficked migrants from Texas to Massachusetts in a cruel scheme to use their suffering as campaign marketing material.

The threats posed to immigrants in Florida led the Florida Immigrant Coalition to issue its own advisory urging reconsideration of any travel to the state. That advisory can be found here (https://floridatraveladvisory.com/).

Conclusion

Taken in their totality, Florida's slate of laws and policies targeting basic freedoms and rights pose a serious risk to the health and safety of those traveling to the state. We regret that these attacks have already led many to flee the state and are driving others to consider relocation. And, in a state whose economy is fueled by visitors from around the world, it is with great sadness that Equality Florida has had to take the extraordinary step of responding to inquiries by issuing an official advisory warning about the risks of travel to the state.

Equality Florida will continue providing information and resources to those impacted by these laws and policies. Visit our Open Doors Florida directory (https://opendoorsflorida.com/) to find businesses with nondiscrimination policies and procedures. And if you experience discrimination, report it to our team here (https://eqfl.org/lgbtq-protections) or call our Main Office at 813-870-3735.

It is our hope that those Floridians who can, will stay and engage more deeply in the fight against the state's all-out assaults on democracy and freedom. This moment calls for a grassroots movement in defense of justice and equality for all -- so that we can turn back the tide of right wing authoritarianism, recommit to building a state that is safe and open to all, and once again celebrate Florida as a free state.

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Privacy Policy (/privacy)

TAB 210

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, *et al.*, *Plaintiffs*, v. JASON WEIDA, *et al.*, *Defendants*.	Case No. 4:22-cv-00325-RH-MAF

PLAINTIFFS' MOTION REQUESTING JUDICIAL NOTICE AND INCORPORATED MEMORANDUM OF LAW AS TO GOVERNMENTAL ACTIONS, POLICIES, AND REPORTS

Pursuant to Federal Rule of Evidence 201, Plaintiffs respectfully request that this Court take judicial notice of the governmental actions, policies, reports, statements, and proposed legislation detailed below, which document the history of discrimination against transgender people and governmental positions relating to gender-affirming care and the treatment of gender dysphoria:

(1) Florida Agency for Healthcare Administration, *Prior Authorization Criteria, Testosterone (non-injectable formulations)* (revised March 13, 2023), filed as **Pl. Trial Ex. 27** (ECF 175-27).

(2) U.S. Department of Health and Human Services, *EPSDT – A Guide for States: Coverage in the Medicaid Benefit for Children and Adolescents* (2014), filed as **Pl. Trial Ex. 62** (176-22).

(3) Centers for Medicare & Medicaid Services, *CMCS Informational Bulletin 2* (July 21, 2022), filed as **Pl. Trial Ex. 63** (ECF 176-23).

(4) Centers for Medicare & Medicaid Services, *Decision Memo for Gender Dysphoria and Gender Reassignment Surgery* (Aug. 30, 2016), filed as **Pl. Trial Ex. 64** (ECF 176-24).

(5) U.S. Commission on Civil Rights, *The U.S. Commission on Civil Rights Statement Condemning Recent State Laws and Pending Proposals Targeting the Lesbian, Gay, Bisexual, and Transgender Community* (April 18, 2016), (statement by the U.S. Commission on Civil Rights "strongly condemn[ing] recent state laws passed, and proposals being considered, under the guise of so-called 'religious liberty' which target members of the lesbian, gay, bisexual, and transgender ('LGBT') community for discrimination"), filed as **Pl. Trial Ex. 69** (ECF 176-29).

(6) U.S. Commission on Civil Rights, *The U.S. Commission on Civil Rights Condemns the Announced Military Ban on Transgender Individuals* (August 18, 2017) (statement by the U.S. Commission on Civil Rights

condemning the announced policy to "not accept or allow transgender individuals to serve in any capacity in the U.S. Military" and "strongly urg[ing]" its reconsideration), filed as **Pl. Trial. Ex. 70** (ECF 176-30).

(7) U.S. Department of Health and Human Services, Departmental Appeals Bd., Appellate Div., Decision No. 2576 (May 30, 2014), filed as **Pl. Trial Ex. 71** (ECF 176-31).

(8) U.S. Department of Health and Human Services, Office of the Assistant Secretary for Health, *Gender Affirming Care and Young People*, filed as **Pl. Trial Ex. 72** (ECF 176-33).

(9) Substance Abuse and Mental Health Services Administration, *Ending Conversion Therapy* (Oct. 2015), filed as **Pl. Trial Ex. 73** (ECF 176-33).

(10) Substance Abuse and Mental Health Services Administration, *Moving Beyond Change Efforts* (2023), filed as **Pl. Trial. Ex. 74** (ECF 176-34).

(11) National Child Traumatic Stress Network, *Gender-Affirming Care is Trauma-Informed Care*, filed as **Pl. Trial Ex. 75** (ECF 176-35).

(12) U.S. Presidential Proclamation, Transgender Day of Visibility, 2022, filed as **Pl. Trial Ex. 76** (ECF 176-36).

(13) U.S. Presidential Proclamation, Transgender Day of Visibility, 2023, filed as **Pl. Trial Ex. 77** (ECF 176-37).

(14) Executive Order, Preventing and Combating Discrimination on the Basis of Gender Identity or Sexual Orientation (Jan. 20, 2021), filed as **Pl. Trial Ex. 78** (ECF 176-38).

(15) U.S. Commission on Civil Rights, *Working for Inclusion: Time for Congress to Enact Federal Legislation to Address Workplace Discrimination against Lesbian, Gay, Bisexual, and Transgender Americans* (Nov. 29, 2017), filed as **Pl. Trial Ex. 131** (ECF 178-11).

(16) National Academies of Sciences, Engineering, and Medicine, *Understanding the Well-Being of LGBTQI+ Populations* (2020), filed as **Pl. Trial Ex. 142** (ECF 178-22).

(17) National Academies of Sciences, Engineering, and Medicine, *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding* (2011), filed as **Pl. Trial Ex. 143** (ECF 178-23).

(18) U.S. Department of Justice, Dear State Attorneys General Letter re Transgender Youth (March 31, 2022), filed as **Pl. Trial Ex. 356** (ECF 184-21).

(19) Office of the Press Secretary, *Presidential Memorandum for the Secretary of Defense and the Secretary of Homeland Security* (August 25, 2017), 82 Fed. Reg. 167, https://trumpwhitehouse.archives.gov/presidential-actions/presidential-memorandum-secretary-defense-secretary-homeland-security/ (Presidential directive excluding transgender people from open service or accession in the United States armed forces) (last visited May 2, 2023).

(20) Fla. SB 254/H.B. 1421 (2023) (criminalizing doctors for providing gender-affirming care to minors and prohibiting gender marker amendments on Florida birth certificates), https://www.flsenate.gov/Session/Bill/2023/254 (last visited May 2, 2023).

(21) Fla. H.B. 1223/S.B. 1320 (2023) (redefining "sex" to exclude the existence of transgender people, mandating the use of pronouns corresponding to sex assigned at birth, and banning classroom instruction relating to sexual orientation and gender identity in schools through the 8th grade),

https://www.flsenate.gov/Session/Bill/2023/1223 (last visited May 2, 2023).

(22) Fla. S.B. 1674/H.B. 1521 (2023) (prohibiting gender-inclusive restrooms and changing facilities in schools, private businesses, public shelters, and healthcare facilities), https://www.flsenate.gov/Session/Bill/2023/1674 (last visited May 2, 2023).

(23) Fla. S.B. 952/H.B.1265 (officially titled the "Reverse Woke Act," if passed the law would punish companies for providing affirming health insurance policies by holding employers liable in perpetuity for any future "detransition" treatment an employee may ever seek if they provide health insurance coverage for gender-affirming healthcare), https://www.flsenate.gov/Session/Bill/2023/952 (last visited May 2, 2023).

MEMORANDUM OF LAW

Federal Rule of Evidence 201 allows this Court to take judicial notice of adjudicative facts that cannot reasonably be disputed and are subject to ready proof. Specifically, "[t]he court may judicially notice a fact that is not subject to reasonable dispute because it: (1) is generally known within the trial court's territorial jurisdiction; or (2) can be accurately and readily determined from sources whose

accuracy cannot reasonably be questioned." Fed. R. Evid. 201(b). The Court is required to take judicial notice upon Plaintiffs' request where, as here, the Court "is supplied with the necessary information." Fed. R. Evid. 201(c). All of these requirements are met here.

The facts proposed for judicial notice are relevant to this proceeding. Plaintiffs have asserted that Florida Administrative Code 59G-1.050(7) (the "Challenged Exclusion") discriminates against them based upon their transgender status and sex, which includes, but is not limited to, their gender identities. The adjudicative facts contained within the governmental actions, policies, reports, statements, and proposed legislation referenced above are relevant to show and summarize the unfortunate history of discrimination, harassment, and violence transgender people have faced because of their gender identity, and to detail policies regarding Medicaid coverage for gender-affirming healthcare and treatments both at the federal level and in Florida. That the above-listed actions, policies, reports, statements, and proposed legislation document the history of discrimination against transgender people, or describe federal and state policies pertaining to coverage for gender-affirming care, are admissible facts and, as publicly available records, can be readily authenticated by this Court. *See* Fed. R. Evid. 902(6).

A court may take judicial notice of various governmental actions, including matters of political history, the enactment of statutes, agency reports, and public

records. *See*, *e.g.*, *Mincey v. Head*, 206 F.3d 1106, 1130 n.58 (11th Cir. 2000) (taking judicial notice of the enactment of federal legislation); *Bryant v. Avado Brands, Inc.*, 187 F.3d 1271, 1278 (11th Cir. 1999) (holding that a court "may take judicial notice (for the purpose of determining what statements the documents contain and not to prove the truth of the documents' contents) of relevant public documents"); *Shahar v. Bowers*, 120 F.3d 211, 214 (11th Cir.1997) (en banc) (stating by way of explanation that judicial notice may be taken of "matters of political history: for instance, who was president in 1958"); *Terrebonne v. Blackburn*, 646 F.2d 997, 1000 n. 4 (5th Cir. 1981) ("Absent some reason for mistrust, courts have not hesitated to take judicial notice of agency records and reports"); *Wilder v. Aramark Svcs., Inc.*, No. 3:17cv239/RV/EMT, 2018 WL 5274257 (N.D. Fla. 2018) (taking judicial notice of a contract that was a matter of public record, noting that court may take judicial notice of "public records[.]"); *Capece v. The Depository Tr. & Clearing Corp.*, No. 05-80498 CIV RYSKAMP, 2005 WL 4050118, at *5 (S.D. Fla. Oct. 11, 2005) ("The excerpts from the Federal Register, as well as the SEC release and website information are records or reports of a governmental agency, which satisfy the second prong of Rule 201(b)."); *Brooks v. United States*, 273 F. Supp. 619, 624 (D.S.C. 1967) (taking judicial notice of adjudicative facts "taken from official governmental reports").

Facts and documents found on government websites are also proper subjects for judicial notice. *See Sec. of Labor v. American Bronze Foundry, Inc.*, 2013 WL 5720146, *3, fn. 4 (M.D. Fla. Oct. 21, 2013); *Setai, Hotel Acquisition, LLC v. Miami Beach Luxury Rentals, Inc.*, 2017 WL 3503371, *7 (S.D. Fla. Aug. 15, 2017); *Turbyfill v. Scottsdale Indemnity Co.*, 2016 WL 741657, *2 (N.D. Fla. Feb. 24, 2016); *Paralyzed Veterans of America v. McPherson*, 2008 WL 4183981, *5 (N.D. Cal. Sept. 9, 2008).

CONCLUSION

Wherefore, based on the foregoing, Plaintiffs respectfully request that this Court take judicial notice of the above adjudicative facts pursuant to Federal Rule of Evidence 201(b), as they are not subject to reasonable dispute.

Dated: May 3, 2023

Respectfully Submitted,

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CERTIFICATE OF WORD COUNT

As required by Local Rule 7.1(F), I certify that this Motion and Incorporated Memorandum of Law contains 1,461 words.

/s/ William C. Miller
Attorney for Plaintiffs

CERTIFICATE OF SATISFACTION OF ATTORNEY-CONFERENCE REQUIREMENT

Pursuant to Local Rule 7.1(B), counsel for Plaintiffs and counsel for Defendants conferred via email regarding the instant motion on May 3, 2023. Defendants indicated they oppose the relief requested herein.

CERTIFICATE OF SERVICE

I hereby certify that on this 3rd day of May, 2023, a true copy of the foregoing has been filed with the Court utilizing its CM/ECF system, which will transmit a notice of electronic filing to counsel of record for all parties in this matter registered with the Court for this purpose.

/s/ William C. Miller
Attorney for Plaintiffs

TAB 230-4

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA

TALLAHASSEE DIVISION

CASE NO.: 4:22-cv-00325-RH-MAF

AUGUST DEKKER, et al.,

Plaintiffs,

vs.

JASON WEIDA,

Defendant.

_____/

DEPOSITION OF: ANN DALTON

DATE: TUESDAY, JANUARY 24, 2023

TIME: 10:04 A.M. - 6:05 P.M.

PLACE: AGENCY FOR HEALTH CARE ADMINISTRATION
2727 MAHAN DRIVE
TALLAHASSEE, FLORIDA 32308

STENOGRAPHICALLY REPORTED BY: GREG T. SMITH

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I N D E X

INDEX OF EXHIBITS

PLAINTIFF'S EXHIBITS

S T I P U L A T I O N S

It is hereby stipulated and agreed by and between the counsel for the respective parties and the deponent that the reading and signing of the deposition transcript be reserved.

P R O C E E D I N G S

THE COURT REPORTER: Do you swear or affirm that the testimony you are about to give will be the truth, the whole truth, and nothing but the truth?

THE WITNESS: Yes.

ANN DALTON,

having first been duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MS. DEBRIERE:

Q. Ms. Dalton, have you ever had your deposition taken before?

A. Yes.

Q. Okay. So I'm just going to walk through some preliminary issues and go over some basic instructions that you've probably heard a million times, and then I'll get started with the questioning.

A. Okay.

MS. DUNN: Sorry. Before we start, can we introduce everybody who is on the phone.

MS. DEBRIERE: Absolutely. Thank you, Chelsea. Before we start, we want to introduces folks on the phone.

MS. DUNN: I think there's one person who is currently muted. Someone just joined.

Shani, are you there?

MS. RIVAUX: Good morning. This is Shani Rivaux.

MS. DEBRIERE: Anyone else, Chelsea?

MS. DUNN: There is one person. I just don't know who it is.

MS. DEBRIERE: Is anybody else there?

MS. DUNN: It's a 305 number. So it's Miami.

MS. CHRISS: That's Jennifer.

MS. DEBRIERE: Okay. Jennifer Altman is the other person.

MS. DUNN: If folks on the line could mute their phones just so we don't have any background noise, that would be helpful. Thanks.

MS. DEBRIERE: So we're just going to mark exhibits as they're discussed. I'll be showing you papers to read off, and we'll just mark them as we move through. As I mark those exhibits, I'm going to read something called a Bates number; that just helps us track what pages we're on when we discuss things. If there's a Bates number, it's probably going to start with "DEF," then underscore, then the Bates number.

I'd like to go ahead and mark the notice of deposition as Exhibit 1. There's no Bates number on

that one.

MS. DUNN: And Catherine McKee just joined the line as well.

MS. DEBRIERE: It's just the notice that brings you here today.

(Plaintiff's Exhibit No. 1 was marked for identification.)

BY MS. DEBRIERE:

Q. So I'm going to be using the acronym GAPMS quite a bit. Do you know what that stands for?

A. Yes.

MS. DEBRIERE: And, Court Reporter, it's G-A-P-M-S.

BY MS. DEBRIERE:

Q. And it stands for generally accepted professional medical standards; which is set forth in 59G-1.035. You probably don't have that memorized. That's okay.

I will use the term "gender dysphoria," which is defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth and the associated gender role and/or primary and secondary sex characteristics. When I use that term, can we just agree that's the definition I'm using?

A. Okay.

Q. I'm also going to be using the phrase "categorical exclusion of gender affirming care." And that's just the exclusion set out in 59G-1.050, Subpart 7. That's why we're here for today, for that exclusion of gender affirming care. Do you understand what I mean when I say that?

MR. PERKO: I'm going to object to the form. You can answer.

THE WITNESS: Yes.

BY MS. DEBRIERE:

Q. Well, I do want to make sure you understand what I'm talking about. Would you like to see a copy of the rule before we can agree on use of that phrase? Because as I use it, I do want to make sure we're talking the same thing.

A. Yeah.

MS. DEBRIERE: So we'll mark this as Exhibit 2. It's a copy of 59G-1.050.

(Plaintiff's Exhibit No. 2 was marked for identification.)

BY MS. DEBRIERE:

Q. If you scroll down to Subpart 7 -- scroll down; you're not a computer. If you follow down to Subpart 7 --

MR. PERKO: It's on the back of the page.
BY MS. DEBRIERE:
Q. So when I'm using the phrase "categorical exclusion of gender affirming care," I'm referring to that Subpart 7. Can we agree that that's the phrase that encompasses that portion of the rule?
MR. PERKO: I'm going to object to form.
But you can answer.
MS. DEBRIERE: Well, I think we do need -- Gary, I understand where you're coming from. But I think we just need to figure out a way to shorthand --
MR. PERKO: That's fine.
MS. DEBRIERE: -- that reference.
MR. PERKO: I'm just objecting to the use of "gender affirming care."
MS. DEBRIERE: Okay. How about "treatment for just gender dysphoria"? Would you --
MR. PERKO: That's fine.
BY MS. DEBRIERE:
Q. So we're going to use "categorical exclusion of treatment for gender dysphoria." And when I use that phrase -- categorical exclusion of treatment for gender dysphoria -- I'm referring to that Subpart 7. Can we agree to that?

A. Okay.

Q. I'm also going to use the term "EPSDT services"; which is an acronym for early and periodic screening, diagnostic, and treatment services. When I say "EPSDT," do you know what I mean when I say that?

A. Yes.

Q. So my name is Katy DeBriere. And I represent the plaintiffs August Dekker, Brit Rothstein, and Susan Doe and K.F.

I know you've been deposed before. I'm just going to go over some very brief instructions, just as a refresher.

If I ask a question ask and you don't understand it, don't try to, you know, understand what I'm saying and try to answer the question. Instead, just stop me and tell me to rephrase so that you understand the question. That's no problem at all.

A. Yes.

Q. And speaking one at a time -- I have a horrible habit of speaking over people. But we need to try and do our best to speak one at a time, so the court reporter can get down everything we say. I don't think you're going to have that problem, but I will. So please just let me finish my question before you answer. And I will do my best to do the same when you're

providing an answer back to me; okay?

A. Yes.

Q. Verbal answers -- again, it's clear that you understand. But as we move through, the court reporter can't record things like "uh-huh," or "huh-uh." So if you could just use "yes," or "no," or words whenever you are responding to a question; okay?

A. Yes.

Q. If you need to take a break for any reason, please feel free to ask me. Stop me; tell me you need to take a break. That's not going to be a problem at all. The only thing I ask is that you finish answering your question before we do.

A. Yes.

Q. Okay. Are you on any medications or other substances that can impact your memory today?

A. No.

Q. Can you state your name.

A. Ann Dalton.

Q. And, Ms. Dalton, what did you do to prepare for today?

A. I met with my attorneys.

Q. Okay. And how long did you meet with them for?

A. 45 minutes.

Q. Okay. Did you review any documents?

A. No.

Q. Okay. Can you describe your educational background for me.

A. I have master's degree in music from Florida State University and a bachelor's degree in music from Northern Kentucky University.

Q. What's your current position at the Agency for Health Care Administration?

MS. DEBRIERE: And, Court Reporter, probably throughout the deposition we'll be using "AHCA"; which is the acronym -- AHCA. Or I might reference "the agency" at times. And when I reference "the agency," I mean the Agency for Health Care Administration.

BY MS. DEBRIERE:

Q. So what is your current position at AHCA?

A. I'm the bureau chief of the Bureau of Medicaid Policy.

Q. How long have you worked in that role?

A. Since -- officially, since August 2021.

Q. Okay. What did you do prior to that role?

A. I was an AHCA administrator in the Bureau of Medicaid Policy.

Q. What does that mean to be an AHCA administrator?

A. I was a manager of a team -- the Program Authority Section in the Bureau of Medicaid Policy.

Q. What kind of responsibilities does that entail?

A. The Program Authorities Section was responsible for submitting and maintaining the Medicaid waivers, the Medicaid state plan with the federal partners at CMS; the promulgation of administrative rules; and the PACE program.

Q. And how long were you in that role for?

A. Since August 2018.

Q. What did you do prior to that?

A. I was a program administrator over a section in the Bureau of Medicaid Policy.

Q. And what responsibilities does that entail?

A. That section was titled Program Policy. And it was responsible for the Children's Health Insurance Program or CHIP Program; the provider enrollment policy; the eligibility rule; and a few other rule areas that I can't remember.

Q. What do you mean by eligibility rule? What's that?

A. The -- I don't remember the exact rule number. But it is the rule that outlines the eligibility criteria for recipients in the Medicaid program.

Q. Okay. Is that related to what category of

Medicaid someone would fall under in order to be eligible for Medicaid?

A. I believe so.

Q. Okay. And how long were you in that position for?

A. From January 2018 to August of 2018.

Q. And what did you do prior to that?

A. I worked at the Department of Elder Affairs as a senior management analyst in the Long Term Services and Supports Bureau.

Q. And how long were you in that role for?

A. From August 2017 to January 2018.

Q. Did that role require any knowledge about Medicaid?

A. Yes.

Q. And did that role require any knowledge about rulemaking?

A. Not the promulgation process itself, per Chapter 120; but the development of rule language, yes.

Q. Okay. And when did you start at DOEA?

A. June 2012.

Q. Okay. And so what other positions did you hold there between June 2012 and when you became the senior program management analyst?

A. I held various analyst positions within the

same unit.

Q. Okay. And did those other positions require knowledge of Medicaid?

A. Yes.

Q. And did those other positions require knowledge about rule promulgation?

A. The same as the senior management analyst would have.

Q. In your current role at AHCA, who is your direct supervisor?

A. Currently Brian Meyer is my direct supervisor.

Q. And who is that person's supervisor?

A. Jason Weida.

Q. And what is Brian Meyer's position at the agency?

A. These changes are recent. And I'm not sure of the exact title of his position.

Q. How is his position in relation to Tom Wallace? Or I should ask: What is Tom Wallace's position at the agency?

A. He's a deputy secretary at the agency.

Q. Does Brian Meyer supervise him?

A. No, I believe they're the same position.

Q. Okay.

A. But, again, these are recent changes, and I'm

not quite sure of the exact title.

Q. What was Brian Meyer's role before he changed into the role he currently is in?

A. He was assistant deputy secretary of operations.

Q. Okay. Is Brian within the Bureau of Medicaid Policy?

A. No.

Q. Okay. Is he within any specific bureau at the agency?

A. No.

Q. Describe your current role at the agency for me. What are the responsibilities?

A. I oversee the Bureau of Medicaid Policy. The Bureau of Medicaid Policy is responsible for the federal authorities; which are the contracts between us and the federal government that manage the Medicaid program in Florida. Promulgates -- we oversee the promulgation of all the rules and rule class 59G; which are the Medicaid rules. Oversee the coverage policy development; those coverage policies are promulgated in administrative rule, but outline the specific services and the criteria for reimbursement.

The administration of the CHIP program is also part of the bureau's responsibility. And the managed

care plan contracts -- the drafting of those contracts and policy actions related to the managed care program.

Q. What are coverage policies?

A. Coverage policies are documents that contain the information needed by providers and recipients that describes the service and also provides the information that they would need to be reimbursed -- providers would need to be reimbursed for a service. It describes who can provide the service, who can receive the service, and then any service criteria or details around that service.

Q. What do you mean "service criteria"? Can you explain that further.

A. A description of the service and then any exclusions, if there are any, pertaining to that service. It's different for each coverage policy.

Q. Okay. And what are coverage handbooks?

A. "Handbooks" is a term that we used to use at the agency. A lot of the coverage polices were -- they are now separate coverage policies, but they were contained in bigger handbooks that have since been kind of broken down to be more service specific. And so the term that we use now to describe the information that was previously contained in the handbooks is "coverage policy."

Q. Are the handbooks promulgated into rule?
A. Yes.
Q. And does the agency still rely on those handbooks in determining service eligibility?
A. If the information from a handbook was moved to a coverage policy, the coverage policy would be promulgated in the rule and the handbook would no longer be part of that rule.
Q. Can you give a recent example of the handbook information moving into a coverage policy rule.
A. It's not that recent, but it's the first one that comes to my mind -- is the Home Health Handbook was broken down into three coverage policies, I believe, around 2016. And those three policies are the Home Health Services Coverage Policy, Personal Care Services Coverage Policy, and the Private Duty Nursing Services Coverage Policy.
Q. Okay. And this will seem like a simple question. But where do those coverage policies -- can the public access those coverage policies?
A. Yes.
Q. And where would they access those coverage policies?
A. The agency has an external web page specific to all the coverage policies, fee schedules, reimbursement

policies.

Q. And the policies that are on that public facing website, are they all inclusive of the policies on which the agency relies for determining coverage? Strike that question.

Is it an exhaustive -- is what is contained on the agency's website, is it an exhaustive list of Medicaid coverage policies?

A. All the policies promulgated in class 59G. And the rules or links to the FAR notice are on our website, yes.

Q. Are there any coverage policies not on the website on which AHCA relies to determine coverage of Medicaid services?

A. Not that I'm aware of.

Q. What is a fee schedule?

A. A fee schedule is the document that provides information on billing codes, the description associated with a code, and the amount that Medicaid will reimburse for fee for service.

Q. What is fee for service?

A. Fee for service is a delivery system where the State pays providers directly -- reimburses them directly for the service provided.

Q. Is that in contrast to managed care?

A. It's a different delivery model.

Q. If a Medicaid service is listed on the fee schedule, does that mean Medicaid covers it?

I'll strike that. I think I can ask a question that well help here.

If a Medicaid service is on the fee schedule, does that mean Medicaid does not categorically exclude it?

MR. PERKO: Object to form.

MS. DEBRIERE: You can go ahead and answer if you understand. If you don't understand, please feel free to ask me to rephase.

THE WITNESS: I don't think I understand.

BY MS. DEBRIERE:

Q. If a Medicaid service is listed on a fee schedule, does that mean that Medicaid is willing to pay for it if the recipient meets all eligibility criteria for that service?

A. So the fee schedules have to be used in conjunction with the coverage policy. So, like I said, the fee schedule contains the coding that the provider needs to use in order to get reimbursed, and, in most cases, the amount and description. But the parameters of who can receive the service -- what kind of providers can get reimbursed for the service -- that's in the

coverage policy.

Q. Okay. What would it mean if a Medicaid service was not on the fee schedule?

A. So the fee schedule document and the term as we would use "fee schedule" does not include all of the services. Some of those are going to be found in the reimbursement methodology rules, if there's not a specific fee equated to a specific code. So there's also reimbursement methodology rules and documents as well.

Q. Are there services -- Medicaid services on the fee schedule that AHCA will not cover?

A. I don't know if there's any. But it would be -- any information about how the services covered would be included -- either on the fee schedule or in the coverage policy.

Q. Okay. Do your responsibilities currently include developing coverage policies for the Florida Medicaid program?

A. I oversee the teams that are responsible for that, yes.

Q. And who are those individuals? Or let's start with: Who are the teams?

A. The team primarily responsible for the majority of the coverage policies is the team managed by Jesse

Bottcher; he's the AHCA administrator. And he has three program administrators who report directly to him.

Q. And who are those people?

A. Christine Polacheck [phonetic], and she oversees the specialized services section. John Matson, he's the manager over at the primary and preventative services section. And then Tim Beaner is the manager over the behavioral health and behavioral analysis section.

Q. Are those the only teams over which you manage? Or are there other teams?

A. I have five AHCA administrator direct reports.

Q. Okay.

A. And then one program administrator direct report. So I have six direct management team reports.

Q. So who are the other ones?

A. Catherine Mcgrath is the AHCA administrator over the program authority section. Ashley Peterson is the AHCA administrator over at the pharmacy policy section. One of them is vacant -- the managed care contract AHCA administrator position. Devona Pickle, she is the AHCA administrator over the Canadian Prescription Drug Importation team. And Jesse Bottcher. And then Lakeva Campbell [phonetic] is a program administrator over the administrative unit who does the

administrative functions of the bureau.
Q. Who works under Jesse Bottcher?
A. That was Christine Polacheck, John Matson, and Tim Beaner.
Q. And do you know who Mr. Jeff English is?
A. Yes.
Q. And who is his supervisor?
A. His current supervisor is Cole Giering.
Q. Who is Mr. Giering's supervisor?
A. Catherine Mcgrath.
Q. And Mr. Bottcher -- does he supervise the person who undertakes GAPMS analysis?
A. The position that is designated to do the GAPMS is under Jesse Bottcher.
Q. Okay. And who does Ms. Peterson supervise?
A. The pharmacy policy team, which consists mostly of pharmacists within the bureau.
Q. How many pharmacists are there?
A. In Ashley's section, there are currently three.
Q. Do you know the names of any of those people?
A. Yes. Jessica Forbes, Kelly Rubin, Susan Williams.
Q. Are you familiar with a person named Nai Chen?
A. Yes.
Q. And who is his supervisor?

A. D.D. Pickle.
Q. And was Mr. Chen ever involved in the pharmacy policy? Did Mr. Chen ever work for the pharmacy policy unit?
A. No.
Q. How long has Mr. Chen been in that position?
A. I don't remember.
Q. More than a year?
A. Yes.
Q. More than two years?
A. I'm not sure.
Q. Okay. Does Mr. Chen in his position have any responsibilities over pharmacy coverage policies?
A. None that are currently promulgated.
Q. What about policies that are not promulgated?
A. I don't know if there's going to be the need for a coverage policy or what types of administrative rule we're going to need to implement the Canadian Prescription Drug Importation Program once that's federally approved -- which is why I answered how I did.
Q. Are there any other pharmacy related activities that Mr. Chen engaged in the past year?
A. Yes.
Q. What are those?
A. His -- he's part of the Canadian Prescription

Drug Importation Program team. And there has been pharmacy related activity regarding the SIP approval.

Q. What does SIP stand for? Or you can just describe it if that's easier.

A. It's the proposal or the importation program plan that the federal government authorized states to submit or request approval of in order to develop an importation program. And this was submitted to the FDA.

Q. What does the Canadian Prescription Drug Importation unit do?

A. Their primary responsibility is to implement the Canadian Prescription Drug Importation Program that was statutorily authorized -- and I think it was in 2019 -- which includes seeking that federal approval from the FDA and any implementation activities in managing the contract with LifeScience Logistics -- the agency's vendor who assists with that program.

Q. And did Mr. Chen over the past year have any responsibilities related to pharmacy activities that did not involve the Canadian Prescription Drug Importation Program?

A. Yes.

Q. And what were those?

A. I can't recall all the specific assignments. But he has helped with several research projects. I

No. 23-12155

In the United States Court of Appeals for the Eleventh Circuit

AUGUST DEKKER, BRIT ROTHSTEIN, SUSAN DOE, by and through her parents and next friends, JANE DOE and JOHN DOE, and K.F., by and through his parent and next friend, JADE LADUE,

Plaintiffs-Appellees,

v.

SECRETARY, FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, *et al.*,

Defendants-Appellants.

On Appeal from the U.S. District Court for the Northern District of Florida, No. 4:22-cv-00325, Honorable Robert L. Hinkle, District Judge

APPELLEES' APPENDIX
VOLUME 10 OF 10 (Tabs 230-4 – A)

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TAB 230-4 (continued)

think he has assisted Ashley's team with some questions or answering questions. And he's been available to assist with just different research projects.

Q. Was he involved at all with the categorical exclusion of treatment for gender dysphoria in developing the pharmacy coverage decisions related to that?

A. So when you ask that, you're specifically talking about the rule?

Q. I'm talking about the rule and the ways in which AHCA is implementing the rule.

A. I don't know to the extent -- I know that he assisted with research for the GAPMS report.

Q. Okay. And by GAPMS report, is that the report that is related to the categorical exclusion for treatment of gender dysphoria?

A. Yes.

Q. Why did Mr. Chen assist the pharmacy unit with the GAPMS report instead of the other pharmacists in the pharmacy policy unit? I'll strike that.

Why did Mr. Chen -- does the Canadian Prescription Drug Importation unit focus on pharmacy policies unrelated to the Canadian Prescription Drug Importation Program typically?

A. Since there's been such a long delay with the

federal approval of the Canadian Prescription Drug Importation Program, that team has assisted with various other projects within the bureau.

Q. Okay. Is that why Mr. Chen assisted with the GAPMS report for the exclusion of the treatment for gender dysphoria?

A. Yes.

Q. What types of services does AHCA develop coverage policies for? Actually -- I'm sorry; strike that. I apologize.

What does the Pharmacy Policy unit do?

A. Their job entails a lot of duties. Primarily they host and oversee the PNT and DUR meetings -- public meetings and the boards associated with that. They oversee the coverage policies specific to pharmacy. They assist with any contract language for the managed care contacts for pharmacy. They oversee the contract for our PBM contractor Magellan. Those are the primary duties.

Q. What does PBM stand for?

A. Pharmacy benefits manager.

Q. And what is that?

A. PBMs can have various duties. But the contract that I'm referring to is our rebate negotiation contract.

Q. Okay. And you said that PBM contract is with Magellan; is that correct?
A. Yes.
Q. Okay. What's DUR?
A. Drug Utilization Review Board.
Q. And I think you used one other acronym when you were discussing the public facing pharmacy meetings.
A. PNT.
Q. And what does that stand for?
A. I believe it's pharmaceuticals and therapeutics.
Q. Okay. And what is that?
A. All the responsibilities of that board are outlined in statute.
Q. Okay.
A. I can't think off the top of my head. But they meet quarterly. And we host those meetings and schedule them.
Q. Okay. A few more questions about Mr. Chen.
Is Mr. Chen a pharmacist?
A. I believe so.
Q. And is he the only pharmacist in the Canadian Prescription Drug Importation Program unit?
A. None of the other members of that team are pharmacists.

Q. So Mr. Chen is the only one?
A. Yes.
Q. Okay. Did any other pharmacist assist with the 2022 GAPMS relating to exclusion of treatment for gender dysphoria?
A. I don't know.
Q. What types of services does AHCA develop coverage policies for?
A. The coverage policies are -- outline the services that the State covers through the state plan -- Medicaid state plan or Medicaid waivers. So those are just any Medicaid related service.
Q. Does AHCA develop coverage policies for surgeries?
A. Yes.
Q. How about for prescription drugs?
A. Yes.
Q. Does AHCA develop coverage policies for every Medicaid service?
A. I don't know.
Q. Have you ever had a situation where a Medicaid recipient requests coverage for a service and there is no policy?
A. I personally have not, no.
Q. Okay. And what process does AHCA use to decide

whether to provide coverage of a Medicaid service?

A. That really depends on the specifics of what that service is.

Q. Does every service have a different process?

A. The process could vary based on what the service is that we are determining coverage for.

Q. Do you use the same process for developing pharmacy policy coverage?

A. I can't speak to the process or approach of the analysts. The process of promulgating the coverage policies into rule is always going to be in accordance with Chapter 120.

Q. During your time at AHCA, have you developed -- have you been involved in developing or has your team -- those you supervise -- been involved in developing new coverage policies to cover services?

A. Yes.

Q. Can you remember a specific service that you did that for?

A. Yes. We are currently in the process with promulgating the iBudget Waiver handbook. And as part of the updates to the handbook, one of those is to develop a new life skills development for Level 4 service. As part of that process, we also worked with our federal partners at CMS to get a waiver amendment

approved. That's a very recent example of a new service being developed.

Q. Do you have an example of a state plan service that you developed coverage for that's under current development?

A. Yes. We recently added some Puro Meno products to the DME fee schedule.

Q. And so in that instance, did you establish a coverage policy for those specific items of DME?

A. We did a coverage determination to determine if and how they could be included as a covered service as part of the DME service.

Q. And what is DME?

A. Durable medical equipment.

Q. And that includes medical supplies?

A. Yes.

Q. And Puro Meno would be a medical supply?

A. Yes.

Q. And you, to cover that service, incorporated it onto the fee schedule?

A. Yes.

Q. Did you do --

Okay. How did you assess whether to decide to incorporate Puro Meno into the fee schedule?

A. So I can't speak to all the steps that the

analyst -- the specific steps that they took. But just speaking overall, determined if we had the legislative and state plan authority to cover it; determined if it was -- if there would be a fiscal impact.

And we approach coverage like that example to, you know, try and make sure it's budget neutral since we are -- our coverage is driven by our general appropriations and our state general appropriations act. And then determined if and what types of updates would be needed to any of the Medicaid rules. That's the general process for determining that kind of coverage.

Q. So to make a coverage determination you look at your legislative authority -- authority under the state plan -- and you do a fiscal analysis and hope for budget neutrality. You check to see if there's any updates to Medicaid rules. Anything else?

A. Making sure that it's an allowable service under Medicaid, as well; which would entail that it meets all federal, state rules and regulations for coverage. But, like I said, all the details of the research that the team does -- I can't speak to exactly everything that they read or looked at.

Q. And if in that coverage determination you decide to cover that service, do you then incorporate it into the fee schedule?

A. In the example I gave, that's what we did, yes.
Q. Are there any situations where you would not incorporate it into the fee schedule?
A. Yes.
Q. What are those circumstances?
A. That would vary depending on what the actual request or coverage benefit is that we're looking.
Q. Can you think of an example?
A. Yes. Last legislative session, I believe it was, there was a specific language regarding the coverage of human donor milk and milk derivatives for inpatient use. Because it was under inpatient, that is a -- the reimbursement for that is different and isn't included in a fee schedule.
Q. Okay. That makes sense.
Once this coverage determination is made, do your responsibilities include reviewing that to determine whether to approve the decision?
A. Yes.
Q. And how do you go about doing that?
A. We usually meet with the team. We do a walkthrough, have discussions around the proposal and the recommendation. And then we put together -- depending on what the change is, put together a document to get approval from management -- upper management.

Q. Does that document have a specific title -- the same title every time?

A. No.

Q. How would you identify that document?

A. So if a fee schedule change was needed, there is a formal routing process for the rule promulgation process that would be routed through management and signed off on.

Q. Okay. Are there other documents that would be routed through management to be signed off on?

A. Yes.

Q. And what are the titles of those documents?

A. It depends on the situation. For example, we also have a steering committee at the agency for the division of Medicaid. And we call that a decision point that would be to the steering committee.

Q. Okay.

A. And the Medicaid director or agency leadership is part of that committee. And so that is also a way for us to get approval.

Q. For those coverage determinations that you reviewed and put together in a document for administrative review, who in the administration reviews that document?

A. Depends on what that is. So for administrative

rule -- that needs to be signed off by several agency leadership; including the general counsel, the agency secretary for a proposed rule. So it would depend on what the final document is who the final signatory would be.

Q. Distinct from implementation of the coverage determination, is there a review by the administration of just whether to cover the Medicaid service?

A. It depends on what the specific circumstances are.

Q. Okay. Can you think of an example of the administration reviewing a determination of whether to cover a service?

A. Can you be more specific? So the waiver example I used a while back would be signed to submit the waiver -- the iBudget waiver -- with the changes. That would have been signed by the Medicaid director prior to submission to federal CMS.

Q. How long have you been involved in the process of doing coverage determination?

A. Since my time at AHCA.

Q. Okay. So since -- I'm trying to take notes here. So since August of 2018?

A. January of 2018.

Q. January of 2018. Thank you.

And when you're making coverage determinations, you coordinate with AHCA rules unit if a rule change is needed; is that right?

A. Yes.

Q. Okay. Under what bureau does the AHCA rules unit fall?

A. Under the Bureau of Medicaid Policy.

Q. Okay. So under your unit?

A. In the bureau.

Q. I'm sorry. Under you're bureau?

A. Yes.

Q. And you coordinate with AHCA's pharmacy policy unit; which falls under your -- the pharmacy policy unit falls under your bureau as well; is that right?

A. Yes.

Q. Okay. Do you coordinate with other bureaus in developing coverage determinations?

A. Yes.

Q. Which ones?

A. All the bureaus in the division work closely together. And there have been some recent changes with that structure. But speaking prior to those changes, the Bureau of Medicaid Program Finance would be probably be the primary bureau; because they assist with determining or setting our fee schedules and our rates

and the methodologies and doing fiscal impact analyses -- data analytics -- Medicaid data analytics.

As part of the whole development package, we talk to all the bureaus because plan management operations can be affected if there is an update to the contracts. The Bureau of Medicaid Quality who monitors and oversees the provision of services through those contracts -- and they have various other duties. But depending on what the change is, we would communicate with most of the bureaus within the division.

Q. Okay. You just mentioned some recent changes in terms of that structure. What are those recent changes?

A. The Bureau of Medicaid Finance and Medicaid Data Analytics are reporting directly to Tom. And Plan Management Operations, Quality, and Policy are reporting directly to Brian Meyer.

Q. And why is that a change?

A. Previously I had been reporting directly to Tom Wallace.

Q. Is Brian Meyer's position a new one?

A. I don't know all the details of those changes.

Q. Okay. Who made the decision to make those changes?

A. I don't know.

Q. Okay. Who oversees the rules unit?
A. Cole Giering is program administrator of the rules unit.
Q. How long has he been in that position?
A. I'm not sure exactly. But it was since I've been bureau chief.
Q. Okay. So --
A. August of 2021.
Q. Thank you.
Do you coordinate -- in making coverage determinations, do you coordinate with the chief medical officer for AHCA?
A. Yes.
Q. Who is that?
A. Dr. Christopher Cogal.
Q. Can you describe how you coordinate with him, what that process looks like.
A. Again, it really depends on the specific question or policy we're reviewing. But it would consist of meetings or discussions.
Q. What types of things would you discuss?
A. So, for example -- I'm going to go back to the two examples of recent activity. So he wasn't involved in the iBudget Waiver changes at all. But for the human donor milk, he assisted when we had originally done the

legislative bill analysis when the legislation was first proposed. And so for the development of how to implement the changes, he was consulted. I don't know the specific conversation, but I do know that he was involved in that process.

Q. On what kind of expertise do you rely on him for? What kind of input does he provide in the process? Is it medical in nature?

A. I don't know.

Q. Okay.

A. To the extent -- I know he's an available resource for the team. But I don't know to the extent that -- of his involvement.

Q. When he gets involved, is it through a formal process? Or is it just a decision to reach out and ask him for advice? How would you characterize it?

A. From my experience at the bureau level, it's been more informal. I know that there have been -- he's been formally asked to review bill analysis or -- but how that process works, I don't know.

Q. Okay. Are there people under you who are more likely to communicate with Dr. Cogal?

A. I believe there's staff that communicate with him more than others, yes.

Q. What staff are those?

A. Ashley Peterson has been meeting with him on some projects lately. Again, it really depends on the project. But we are working with him on continuous glucose monitoring -- questions around coverage there. And Jesse Bottcher and his team.

Q. When you say Jesse Bottcher and his team, would that include the GAPMS process?

A. His team is responsible for it.

Q. In coordinating with Dr. Cogal -- in the coordination between Mr. Bottcher's team and Dr. Cogal, would that include the GAPMS process?

A. I don't know the extent to which he is involved in that.

Q. Okay. To your knowledge, has he ever been involved in that?

A. I don't know specifically.

Q. Have you and Dr. Cogal and anyone from Mr. Bottcher's team ever met to discuss the GAPMS process?

A. The process, yes. When I first took the role, we had met to talk through the process. But I can't remember the specific conversation.

Q. Okay. Switching gears a bit. When I use the term "Florida Medicaid managed care plan," do you know what it means?

A. Yes.
Q. What does that term mean?
A. Those are the managed care plans that the agency contracts with to provide the services through the managed care delivery model.
Q. Do Medicaid managed care plans have their own coverage policies?
A. The agency's coverage policies are incorporated into the managed care plan contracts by reference. And there are requirements outlined in the contract with how the managed care plans have to provide services.
Q. Are you aware of managed care plans having their own policies that incorporate Florida Medicaid's policies?
A. I don't know.
Q. Have you ever seen a copy of a Florida Medicare managed care plan document that discusses the coverage of a Florida Medicaid service?
A. I reviewed the plans' member handbooks or enrollee handbooks. And I've seen their resources available on their websites that weigh out what they cover. I can't remember if I've ever seen an official document titled "Coverage Policy."
Q. So my question is: Have you ever seen a document from a Medicaid managed care plan -- formal or

informal, it doesn't matter -- with information that contains the criteria used to determine if Florida Medicaid will cover a service?

A. I believe that information is in the handbooks. But I can't recall any specific documents drafted by the plans.

Q. What unit would be responsible for communicating with managed care plans about their coverage of Florida Medicaid services?

A. That would depend if they had a question for the agency on the agency's coverage of a covered service or a contractually required service. Those most likely would be sent to Medicaid policy.

Q. Okay.

A. To review.

MS. DEBRIERE: Okay. Yes. Definitely. Just a couple more questions, if that's okay.

BY MS. DEBRIERE:

Q. Are you okay Ms. Dalton?

A. Yes.

Q. Who would review those questions? Who specific -- like, what specific individuals?

A. It would depend on what the question was.

Q. Okay. If the managed care plan doesn't have a question, is there any process that exists that just

involves overseeing whether a Medicaid managed care plan is covering a Florida Medicaid service?

A. The Bureau of Plan Management Operations is the bureau that oversees the adherence to the contract. All the contract managers for the individual plans are housed there. So if it was a compliance question on if the managed care plan was following the requirements in the contract, that would be Plan Management Operations most likely who would be the first point of contact for the plans.

Q. Okay. Can MCOs create their own guidelines for implementing AHCA coverage policies?

A. I don't know.

Q. Who would know that?

A. It would be in the contracts.

Q. Okay.

A. The parameters around what their materials are allowed to contain and if the materials have to be reviewed and approved by the agency.

Q. Okay. And that would be the Bureau of Planned Management Operations who does that -- takes on that role? And if not, then who?

A. I believe it would depend on what the materials being reviewed are. Just like with reporting -- there are different report owners in different bureaus within

the division of Medicaid that review compliance with the -- the plan's compliance with the contracts. But the first point of contact for submitting those materials and making sure that they're submitted would be through Plan Management Operations.

Q. And who is that bureau chief? Remind me.

A. Pam Hall.

Q. Okay. One last question. Are you aware that MCOs have their own guidelines for specific types of Medicaid services?

A. I can't speak to that. I don't know.

Q. Do you know who would know?

A. Are you asking if it's a required -- or if they're allowed to --

Q. No. I'm just asking if you're aware. So are you aware that they have their own --

MR. PERKO: Asked and answered.

MS. DEBRIERE: -- criteria guidelines?

THE WITNESS: I would have to review the contract.

BY MS. DEBRIERE:

Q. Okay. So is that a no, you are not aware as we sit here today without having anything in front of you?

A. Correct. I don't know without seeing a specific example or reviewing the contract.

Q. Okay. Do you want to take a break?
A. Yes.
(Brief recess.)
BY MS. DEBRIERE:
Q. Ms. Dalton, just briefly -- when we took a break, did you discuss this deposition with anyone?
A. No.
Q. Did you discuss it with your attorneys?
A. Just briefly.
Q. Okay. When I use the term "quality improvement organizations" or QIOs, do you know what I mean?
A. Yes.
Q. What does that term mean?
A. Quality improvement organization.
Q. Yeah. Is eQHealth a QIO?
A. Yes.
Q. And what do they do?
A. I don't know the whole scope. But their main function in their contract with the agency is the -- to do prior authorization for fee for service services.
Q. Okay. What does prior authorization mean?
A. It's a utilization management tool to ensure that the services are in their scope, authorized, and appropriate.
Q. By "appropriate," what do you mean?

A. That the service that's being requested is allowable and delivered within the parameters of the Medicaid program.

Q. Who makes the request for prior authorization?

A. I don't know the details of how the process works.

Q. Okay. By parameters, do you mean the parameters set by AHCA's coverage policies?

A. Yes. And administrative rule.

Q. Okay. Is administrative rule distinct from a coverage policy?

A. Yes. Not all of the administrative rules incorporate a coverage policy by reference.

Q. Okay. So an example of that would be the definition of medical necessity -- would be an administrative rule that sets out the parameters for coverage but does not include a specific coverage policy?

A. The definition of medical necessity is actually in the definitions policy -- which is a document incorporated by reference into the text of the administrative rule.

Q. Okay. Do QIOs like eQHealth -- do they have their own coverage criteria they rely on?

A. Yes.

Q. Do you coordinate with QIOs regarding those coverage criteria?

A. I personally do not.

Q. Does anybody on your team?

A. The eQHealth contract is housed in the Bureau of Medicaid Quality.

Q. Okay.

A. So they would be a lead in managing of that contract and communicating with the vendor. But I do know that we have communicated with them in the past -- the Bureau of Medicaid Policy has.

Q. What types of things have you communicated about in the past?

A. The first example that comes to mind is recently the agency opened the definitions rule policy and did communicate that that rule was being opened with eQHealth.

Q. Okay. Are MCOs and QIOs bound by AHCA's coverage policies?

MR. PERKO: I'm going to object to form.

You can answer.

THE WITNESS: As I stated before, the contract for the managed care plans incorporates the coverage policies by reference. And the plans are not allowed to be more restrictive than the coverage

policies. I don't know the specific language off the top of my head with the requirements of how they adhere to the policies. But that is in the contract.

BY MS. DEBRIERE:

Q. Okay. So the MCO's obligation to adhere to AHCA's coverage policies is set forth in the contract?

A. Yes.

Q. Okay. What about QIOs?

A. I don't know the specific language off the top of my head. But that information is also in the contracts on how the managed care plans' contracted QIO vendors are expected to operate.

Q. Okay. Is there a formal approval process for the QIO's coverage criteria?

A. I don't know.

Q. Is Magellan a QIO?

A. I don't know.

Q. Okay. Does Magellan conduct prior authorization of Florida Medicaid services?

A. I don't know.

Q. Does Magellan review the request of a Medicaid recipient to authorize prescription drug services in the Fee for Service program?

A. I don't know.

Q. Do you know what -- do you know if Magellan plays any role in determining coverage of pharmacy services under Florida Medicaid?

A. I believe the agency has a contract with them to adjudicate the claims. But I don't know the scope of that contract.

Q. What do you mean by adjudicate the claims?

A. I don't know the whole scope of that process or the contract.

Q. When you just use that phrase, what did you mean by that?

A. That they're involved in the reimbursement process.

Q. Okay. And would the reimbursement process involve determining the eligibility for the service itself?

A. I don't know the extent of that process.

Q. Would anybody at AHCA know or be able to answer that question?

A. I don't know.

Q. Moving back to coverage determinations undertaken by your bureau, who is the final decisionmaker as to whether AHCA will adopt that coverage determination?

A. Can you repeat the question.

Q. So earlier we were talking about your bureau undertaking coverage determinations of Florida Medicaid services; correct?

A. Yes.

Q. Who is -- before AHCA or anyone at AHCA can act on that determination, who is the final decisionmaker?

A. Again, it depends on the circumstances. And I can only speak to the signatory of who needs to be -- to officially sign off. But the example I used before for a federal authority submission, that would be whoever was designated from the agency as the Medicaid director or the Medicaid state plan approver.

Q. Okay.

A. And then administrative rule to actually complete the promulgation process. That's actually signed off by the head of the agency, which here would be our secretary.

Q. Okay. When coverage policies are promulgated, are there multiple drafts of those policies? Are there ever multiple drafts of those policies?

A. Can you repeat the question.

Q. When you're developing a coverage policy, are there multiple drafts?

A. It would it depend on what the change was.

Q. So there are times when coverage policies have

multiple drafts?

A. Yes.

Q. And how do you track any changes to those policies during the drafting process?

A. So specific to the coverage policy, we typically use a document called a revisions template; which tracks the changes being proposed.

Q. Okay. Is there a limit to the people who can make changes to the revisions document?

I'm sorry; the revision just tracks who has made the changes; is that right?

A. So it tracks what the old policy said, what the new changes are, if there's a reason for the change. I'm not sure if it includes who the requester of the change is.

Q. Okay. Does it record who is making the change?

A. I can't recall if that's on the template.

Q. Is anybody at AHCA allowed to make a change?

A. So for most of the coverage policies, there's a subject matter expert assigned to that program area who any changes would filter through. And then they have to work with the rules unit who is actually making the changes to the coverage policy and promulgating that through the rulemaking process.

Q. Okay. Just switching quickly to some specific

Medicaid services. Are coverage policies regarding surgery adopted into rule?

A. Yes.

Q. And are they in handbooks or a handbook?

A. I don't believe it's one specific handbook.

Q. Do you remember the names of any of the handbooks they are contained in?

A. We have a transplant services coverage policy.

Q. Okay.

A. Which I would consider inclusive of surgical. We have an inpatient services coverage policy. Without seeing the list of policies, I can't recall off the top of my head.

Q. Give me one second.

Would coverage policies about surgeries be in the Ambulatory and Surgical Center Services Policy?

A. I don't know the content of that policy off the top of my head.

Q. Okay. You said inpatient hospital services would contain surgery policies?

A. I don't know all the content in the policy without looking at it. But it...

Q. If it mentions surgery in the handbook, is it going to have a coverage policy related to it?

How would you know if a handbook covered

surgery or contained a surgery coverage policy in it?

A. I would have to read the handbook. Depending on what the specific question was, what type of surgery.

Q. Okay. What about prescription drug coverage policies? Are those adopted into rule?

A. I believe there is a rule specific to pharmacy policies and prescription drugs, yes.

Q. Okay. And then I'm just going to flip my computer around here and go to this page. We're looking at what's titled Agency for Health Care Administration Drug Criteria. AHCA.myFlorida.com/Medicaid/prescribed_drug_criteria.shtml.

And I assume, Ms. Dalton, I'm seeing here -- are you just seeing a list of drug criteria?

A. Yes.

Q. Is this an exhaustive list of the drug criteria that AHCA relies on?

A. I don't know.

Q. Who would know that?

A. Ashley Peterson and her team may be able to confirm.

Q. Okay. And why wouldn't this be an exhaustive list?

MR. PERKO: Object to form.

THE WITNESS: I'm not personally very familiar with this page.

MR. PERKO: Counsel, for the record, can we read the URL.

MS. DEBRIERE: Absolutely. Well, I think I -- Gary, do I not know what a URL is?

MR. PERKO: The website address.

MS. DEBRIERE: So I think we read most of it. But I can start with https://AHCA.myFlorida.com/Medicaid/prescribed_drug/drug_criteria.shtml.

MR. PERKO: Thank you.

MS. DEBRIERE: Absolutely.

BY MS. DEBRIERE:

Q. Do you know what categorical exclusion means?

MR. PERKO: I'm going to object to form. I guess I'm a bit confused, Counsel. You already defined what categorical exclusion means at the beginning of this deposition.

MS. DEBRIERE: Well, that's categorical exclusion -- you're right, Counsel. It contained the statement "categorical exclusion"; just categorical exclusion of a very specific set of services. The treatment for --

MR. PERKO: That wasn't the definition at the

beginning. But go ahead.

BY MS. DEBRIERE:

Q. How about this, Ms. Dalton: Can you provide an example of a categorical exclusion under Medicaid?

A. I can't think of an example. I'm familiar with the term. I cannot think of an example.

Q. Okay. I'm trying to think of one too.

Does AHCA -- does Florida Medicaid cover private duty nursing service for individuals over the age of 21?

A. Not through the state plan.

Q. Okay. Do they cover it through home and community based services with a Medicaid waiver?

A. Yes.

Q. Okay. And if Florida Medicaid does not cover private duty nursing services for individuals over 21 under the Medicaid state plan, is that a categorical exclusion?

A. Yes.

Q. And does the agency categorically exclude any Medicaid service for beneficiaries under the age of 21?

A. Can you repeat the question.

Q. I'm sorry. Bear with me one second, Ms. Dalton. I'll come back to that.

Do your responsibilities include ensuring that

coverage policies meet the standards under EPSDT?

A. The Bureau of Medicaid Policy doesn't oversee the monitoring of the adherence to the policies or the provision of services. In terms of ensuring that the policy language complies with the federal EPSDT requirements, yes.

Q. And how do you ensure that compliance when developing coverage policies?

A. It depends on the specific coverage policy. But the majority of the service specific coverage policies include language incorporating EPSDT by reference and language from the federal regulation.

Q. Generally speaking, what is that EPSDT requirement?

A. That the State must provide all medically necessary services to children ages under 21.

Q. Does the State have to provide a service under EPSDT to a Medicaid recipient under 21 if that service is experimental?

MR. PERKO: Object to form.

BY MS. DEBRIERE:

Q. Do you know what I mean when I say experimental?

A. Yes.

Q. So same question. Does the State have to

provide coverage to children under age 21 if that health service is considered experimental?

MR. PERKO: Object to form.

THE WITNESS: The State is allowed to develop its own definition of medically necessary or medical necessity; which Florida has done and promulgated in administrative rule. And part of that definition does include the parameters by which a service would not be determined medically necessary; and, therefore, not required under the EPSDT.

BY MS. DEBRIERE:

Q. Okay. And that definition of medical necessity includes the requirement that the service not be experimental; correct?

A. I cannot recall the exact definition off the top of my head. But that is in -- promulgated in the definition coverage policy.

Q. When you say that is --

A. The definition of medical necessity.

MS. DEBRIERE: Okay. We can mark -- I have a copy of the rule so you can reference it. We can mark that as Exhibit 3. And that's 59G-1.010.

We might have forgotten to put a copy in. If we did, it's my fault.

MS. DUNN: I have a copy right here.

(Plaintiff's Exhibit No. 3 was marked for identification.)

MS. DUNN: Yeah. It's right there. Last definition on that page.

THE WITNESS: It doesn't seem to be the whole --

MS. DUNN: It's not.

MS. DEBRIERE: It's not. We ended it at "N," because it's a very large coverage policy and we are trying to save some trees.

BY MS. DEBRIERE:

Q. So if you look at the definition of "medically necessary" or "medical necessity," does that contain a requirement that the service not be experimental?

A. Yes.

Q. And so under EPSDT, can the agency deny a medical service to a child under 21 if they deem it to be experimental?

A. Yes.

Q. Okay. Who is responsible for compliance with EPSDT? Is it a specific person?

A. I don't know who is responsible.

Q. Is it someone within your bureau regarding EPSDT as it relates to the development of coverage policies?

A. There isn't a specific person in my bureau, no.
Q. Are there any written guidelines about ensuring compliance with EPSDT with developing coverage policies?
A. Can you repeat.
Q. Are there any written guidelines relied on to determine whether a coverage policy complies with EPSDT, other than that contained in the Federal Medicaid Act?
A. I don't know specific -- all the specific documents that the analysts rely on when developing the coverage policy. But as part of that process, the expectation is to review the federal guidelines and statute and other rules and regulations of governing the Medicaid program to ensure that the coverage policy adheres to the Medicaid program federally and state.
Q. And that's an expectation of the staff within your bureau?
A. Yes. It's the common practice when approaching research regarding changes to the policy -- a policy.
Q. Okay. When I use the term "comparability," do you know what I mean as it's laid out in regulations implemented in the Federal Medicaid Act?
A. You may have to give me some more context.
Q. So under the Federal Medicaid Act, there is a requirement that state agencies who administer Medicaid do so in a way that all Medicaid recipients receive

comparable services. Are you familiar with that requirement?

A. Vaguely sounds familiar.

Q. Is your bureau required to be familiar with that requirement in developing coverage policies?

A. I can't speak to that without more information.

Q. Okay. Is there anyone who can speak to the requirement -- is there anyone who can speak to ensuring that the policy comply with comparability under the Federal Medicaid Act?

A. So, again, I think it really would depend on what the specific question is regarding or which specific coverage policy. As I said before, a lot of the coverage policies have a specific subject matter expert with knowledge of that service area. So it just really would depend.

Q. Okay. I'm just going to make myself a note.

What is the purpose -- turning back to Exhibit 3 and the definition of medical necessity -- what's the purpose of AHCA's medical necessity standard?

MR. PERKO: Object to form.

BY MS. DEBRIERE:

Q. Does AHCA's medical necessity standard have a purpose?

MR. PERKO: Object to form.

THE WITNESS: I don't know what you mean.
BY MS. DEBRIERE:
Q. What is the purpose of the definition of medical necessity?
MR. PERKO: Object to form.
BY MS. DEBRIERE:
Q. What do you use it for?
A. The definition is relied on a lot. Most of the service specific coverage policies refer and incorporate by reference the definitions policy and make a statement that the service must be medically necessary as part of the requirement for reimbursement.
Q. If a Medicaid recipient makes a request for a Medicaid service, in order for that service to be authorized, does it have to be medically necessary?
A. Yes.
Q. Do managed care plans rely on AHCA's medical necessity standard in their prior authorization process?
A. I can't recall the exact contract language. But, yes.
Q. And what about QIOs?
A. I don't know.
Q. Regardless of the method in which Medicaid is delivering the service -- fee for service or managed care -- in order for that surface to be authorized, does

it have to be medically necessary?

A. I don't know the details of the actual authorization process. I do know that the expectation from policy prospective is that the services have to be provided in accordance with the agency's coverage policies and administrative rules.

Q. And that includes the definition of medical necessity?

A. Yes.

Q. If AHCA finds that a Medicaid service is experimental, would AHCA or a contractor or managed care plan still review whether service meets other portions of AHCA's medical necessity definition?

A. I don't know the extent of their review.

Q. What about your review at AHCA for fee service?

A. Again, I don't know eQHealth or QIO vendors' process.

Q. Do all Florida Medicaid services require prior authorization?

A. I don't know. I don't believe so.

MS. DEBRIERE: Okay. Can I have what we'll mark as Exhibit 4, which is the GAPMS Report on Cross-Sex Hormone Therapy, dated May -- I believe we did the May version.

So what I'm showing you is Bates stamped

beginning at Defendant 00126105. I should pull out my own copy.

And that continues through, Court Reporter -- this one is not Bates stamped. It's weird. This one doesn't have a copy. This copy is not Bates stamped. But it is entitled Cross-Sex Hormone Therapy GAPMS Determination Report With Recommendation.

That's very odd. Very odd. I don't think it's a huge deal.

(Plaintiff's Exhibit No. 4 was marked for identification.)

BY MS. DEBRIERE:

Q. So on the last two pages, Ms. Dalton, starting at "Coverage policy" -- and it starts, "Federal regulations."

"Federal regulations for Medicaid..." and continues on through the definition of medical necessity --

MR. PERKO: Can you give a page number.

MS. DEBRIERE: Oh, yes. Thank you, Gary.

So page 8, 9, and a tiny bit of the top of 10.

THE WITNESS: I'm there.

BY MS. DEBRIERE:

Q. Take all the time you need to read it. And

afterwards, if you can tell me if this is an accurate portrayal of the standard used to determine Florida Medicaid coverage for prescription drugs.

MR. PERKO: Do you have another copy?

Thank you.

BY MS. DEBRIERE:

Q. I think it starts at the top of page 8 -- middle of page 8. So reviewing that standard, is that what's used to determine whether Florida Medicaid will cover a prescription drug?

A. Can you direct me more to where you're referring. I read both pages 8 and 9, and I don't think I can speak to the specifics of all this information.

Q. Okay. When reviewing whether to cover a prescription drug, does AHCA look at -- here on page 8 it says AHCA is -- "The program is required to asses data on drug use against predetermined standards consistent with the following compendia." And then it lists three types of compendia and the peer reviewed medical literature. Is that an accurate statement of AHCA policy?

A. I don't know.

Q. Who would know that?

A. I don't know if I can speak for them. But I would ask one of the pharmacists.

Q. Would you ask Ashley Peterson? Or would you ask one of the pharmacists that works under her?

A. I specifically would go to Ashley, as she's my direct report. And then she would research the question for me.

Q. Okay. Would research involve asking one of her pharmacists?

A. I don't know. I can't speak for her process.

Q. So going to page 9, top of the page says, "In order to be reimbursed by Medicaid, a drug must be medically necessary."

Is that the same as the definition contained in the 59G-1.010 that we just reviewed -- Exhibit 3?

A. I don't understand what you mean by the same.

Q. Does medically necessary mean the same as the definition in the definitions policy?

A. I would think so.

Q. Okay. And it is, "Either prescribed for medically accepted indications and dosages found in the drug labeling or drug compendia in the Medicaid Act or prior authorized by a qualified clinical specialist approved by that agency."

Is this an accurate recitation of the standard AHCA uses to authorize prescription drug coverage?

A. I don't know.

Q. Would Ashley Peterson know that information -- her or her team?

A. I would think so, yes.

Q. Okay. The next thing it says, "The criteria that are utilized under the Florida Medicaid program in the authorization of drugs for off-label purposes are as follows." And then it lists three criteria.

Reading over that statement, are these currently the criteria AHCA uses in authorizing drugs for off label purposes?

A. Again, I don't know.

Q. Would Ashley Peterson know the answer to that question?

A. I would think her team would, yes.

Q. Is this the type of information -- looking at this, is this the type of information that would be contained in a coverage policy adopted in rule?

A. I'm not sure.

Q. Why aren't you sure? What's throwing you about it?

A. I don't know the content of the rules off the top of my head.

Q. But I think my question is a little different. So does this appear to be the type of information that would be contained in a coverage policy adopted into

rule?

A. I can't speak to that. I don't know because of the reason I stated. I will say the coverage policies traditionally do not repeat regulation or requirements or information that are found elsewhere; for example, in Florida statute or in federal regulation. And each coverage policy is structured somewhat similarly, but does contain very different information. So I don't know if this is information that's found off the top of my head in one of our policies.

Q. Okay. I think you -- do all prescription drugs require prior authorization to be reimbursed by Medicaid?

A. I don't know.

Q. Who would know that?

A. I would think Ashley Peterson and her team. Or it might be available on the information on our website regarding pharmacy policy and authorization criteria.

Q. Okay. So Ms. Peterson would be familiar with authorization criteria for prescription drugs?

A. Yes. Or she would know where to look.

Q. Okay. Specifically related to pharmacy coverage policies, how are they developed?

A. The coverage of the pharmacy services is a little different than the other coverage policies. I

don't know all the details that go from the analysts into the developments. But because there is different statutory requirements -- Florida statutory requirements around pharmacy services, including the PNT and DUR board -- the process for overseeing the coverage of pharmacy services is a little different.

Q. In reviewing whether a prescription drug requires a coverage policy -- strike that.

Do you use the GAPMS process to determine pharmacy coverage -- to determine whether coverage of a prescription drug is experimental?

A. I don't know specifically for determining if a prescription drug is experimental. I don't know.

Q. When you develop coverage policies in your bureau, does that include a determination as to whether a service is experimental?

A. So the coverage policies are drafted specific to the covered services that we've been approved to provide.

Q. Okay.

A. By the federal government. So that is the driving factor on how we would initially approach the coverage and organize or draft a coverage policy asserting a service that we are authorized to provide.

Q. So separate and apart from developing coverage

policies, the responsibilities of your bureau also include determining whether a service is experimental; is that correct?

A. So that would be part of the GAPMS process that is outlined in administrative rule.

Q. Okay. Do you use the GAPMS process for prescription drugs?

A. Without researching or consulting others on the team for a specific example, I don't know the interplay between the different authorities and how that works.

Q. Which team is responsible for the GAPMS process?

A. That position is within the Medicaid -- Bureau of Medicaid Policy.

Q. Earlier speaking about teams under the bureau, which teams is responsible for the GAPMS process?

A. Jesse Bottcher is the manager over the position that is primarily responsible for the GAPMS process.

Q. Are there any other teams that are primarily responsible for the GAPMS process? Or is it only Jesse's team?

A. So in terms of listing that as a primary responsibility on a job description, that would be Jesse's team.

Q. Should the people on Jesse's team be aware of

every GAPMS process that's undertaken?

MR. PERKO: I'm going to object to form.

You can answer.

THE WITNESS: So as the bureau chief of Policy, I do try to keep staff within the bureau aware of everything that's happening within the bureau -- especially when a determination has been made. Jesse's team would definitely need to be aware, because there could be potential impacts with a specific service coverage policy. But I do think every circumstance is different. So I can't say just in a general statement to your question.

BY MS. DEBRIERE:

Q. Would it be typical for Jesse's team to not be aware of a GAPMS report being developed?

A. I can't say if it would be typical. I have not overseen very many GAPMS in my time as bureau chief.

Q. So as the bureau chief with Jesse's team being primarily responsible for GAPMS, would you as that chief endeavor to ensure that Jesse's team was aware of all GAPMS reports being written?

A. Yes. We meet the managers on -- my direct reports and I meet regularly at least twice a week for an hour and discuss projects that are going on with each team and provide updates. So the ongoing bureau

activities are regularly discussed with the management team.

Q. Okay. Do you know what a drug compendium is?

A. I recognize the term, but don't think I can define it.

Q. Do you know which compendia are listed in the Federal Medicaid Act?

A. No.

Q. I'm just going to screen share again. I'm showing right now on my screen -- the URL is https://AHCA.myFlorida.com/Medicaid/prescribed_drug/pharm_thera/pdf/PDL.pdf. The title of this document is Preferred Drug List, Effective January 21st, 2023.

Do you know what the preferred drug list is?

A. Yes.

Q. What is it?

A. It's list of drugs developed that the managed care plans must adhere to. And it has to do with rebate negotiations and is recommended by the PMT committee.

Q. Perhaps you just answered this. But who develops the PDL?

A. The agency.

Q. What is the PMT committee's role in it?

A. Per statute, they make recommendations to the agency.

Q. Okay. Does the DUR have any role in developing the PDL?

A. I don't know. I don't believe so.

Q. And this PDL applies to managed care plans; is that correct?

A. And fee for service.

Q. Okay. So on here -- I'm going to have to do Control+F. Pardon; one second.

It's very small. So tell me if you need to make it any bigger.

Okay. On here you will see the drug estradiol -- e-s-t-r-a-d-i-o-l -- listed. And there is many versions here starting at it looks like this line continuing all the way down until we hit norethindrone AC. So the fact that estradiol is lied on the PDL, does that mean Florida Medicaid will cover it if the eligibility criteria are met? Excuse me. Scratch that.

Since estradiol is listed on this PDL, does it mean that Florida Medicare will cover it?

MR. PERKO: Object to form.

THE WITNESS: I don't know.

BY MS. DEBRIERE:

Q. If any drug is listed on the PDL, does that mean Florida Medicaid will cover it?

A. I don't know the interplay between the PDL and

the other rules and regulations covering pharmacy services.

Q. Okay. Over in this column at the top of page, it reads "Clinical PA required." And it also has a column for a minimum and a maximum age. What does clinical PA required mean?

A. Operationally, I don't know.

Q. Do you know it in any other version?

A. I understand the words. But I don't know in the context of the program or the PA process what that means.

Q. What does "PA" stand for?

A. Prior authorization.

Q. Okay. Is it possible that clinical PA -- so if we scroll down to estradiol -- this version with a minimum of an age of zero, maximum age of 999 -- and it says "no" under the column of clinical PA required, do you know what that means?

A. No.

Q. Who would know that?

A. Ashley Peterson and her team are lead on this.

Q. Do you know what it means to have a minimum age column? Why that's significant or why it's on there?

A. Specific to this document, no.

Q. Same with maximum age?

A. No, I don't know the reason why it's on there.
Q. Since you've been at the agency -- January 2018?
A. Yes.
Q. How many GAPMS processes have you been involved in?
A. Two completed. And maybe one or two discussions.
Q. How many pending?
A. I don't know.
Q. Do you know currently how many GAPMS are pending?
A. Clarify "pending."
Q. Why don't you tell me what you meant by completed.
A. Two that have been signed by agency leadership.
Q. Okay. And how many reports are in the stage of being written and not yet signed?
A. I don't know.
Q. To be clear, though, as bureau chief you meet weekly with Jesse Bottcher and his team who are primarily responsible for GAPMS.
A. I meet weekly with Jesse Bottcher and my team.
Q. Okay.
A. I don't regularly meet with the individual

teams, but with the managers.

Q. When you meet with Jesse, do you discuss GAPMS?

A. Not routinely. We have before.

Q. What are the other responsibilities of Jesse's team?

A. The three managers under Jesse each have units that are responsible for the developments of the service specific coverage policies. His team also oversees the eligibility policy and the provider enrollment policy, updates all the fee schedules -- so works closely with fiscal agent operations to ensure updates are made to the MMIS system and with Medicaid program financing the development of fee schedules. And that's the bulk of their responsibilities.

Q. So when you're meeting with Jesse weekly, what are you discussing about his team?

A. It depends on what -- the highest priority assignments are usually up first; things that are due that week.

Q. Okay. So you do not routinely discuss GAPMS -- that was your testimony just a second ago?

A. Yes. I wouldn't say that it's a subject that we discuss at every meeting or routinely at our individual meetings, no.

Q. And you organize what you discuss based on what

has the highest priority?

A. Yes, typically.

Q. Okay. How familiar with you with the GAPMS process?

A. In terms of all the research and everything that goes into developing, I'm not as familiar. But I am familiar with the routing process, the rule, the authority for that process.

Q. Okay. So just generally, what does AHCA use the GAPMS process for?

A. So if the agency receives a request for coverage -- typically that's how the process would be initiated. If the coverage was determined to not be something that the agency could proceed with -- possibly adding to the fee schedule or incorporating into a service definition -- then the GAPMS process would be used.

Q. Okay. How is the GAPMS process initiated?

A. I believe it's a rule how to.

Q. Would it be helpful if you had the rule in front of you?

A. Yes.

MS. DEBRIERE: Okay. Let's mark that as Exhibit 5. That's Rule 59G-1.035.

(Plaintiff's Exhibit No. 5 was marked for

identification.)
BY MS. DEBRIERE:
Q. So how is GAPMS initiated?
A. A request is submitted to the health services research inbox in the Medicaid Policy Bureau.
Q. Who can submit a request to that inbox?
MR. PERKO: Object to form.
THE WITNESS: I believe anyone can.
BY MS. DEBRIERE:
Q. Okay. Is that the only way that a request is submitted for AHCA to undertake a GAPMS?
A. No.
Q. What are other ways?
A. So in the contracts with the plans, there's also language on how a managed care plan can submit a request to the agency for review -- not necessarily through the health services inbox. I can't recall the exact direction. But there's also the opportunity for the clients to request a review.
Q. When that review is requested, is it -- is the standard process used? Is the standard GAPMS process used?
A. I'm not sure. I believe it may be expedited. But I'm not sure to the specifics of the process.
Q. Who would be most familiar with that process?

A. Either Jesse Bottcher or Jeffrey English.
Q. Okay. So you mentioned managed care plans can submit a request -- or anyone can submit a request through the health services inbox. Are there any other ways that a request can be submitted to the agency to undertake a GAPMS?
A. Yes.
Q. And what are those ways?
A. I don't know all the ways. But I can't think of us not approaching the process if we received a request outside of getting it specifically through the health services research inbox.
Q. How often --
A. Which is -- I'm hesitating because I couldn't see us not -- like, refusing to complete the process if it was received another way.
Q. How often does that happen?
A. So, like I said before, in my time as bureau chief, there haven't very many finalized GAPMS. Or that process has not been a part of my day-to-day work. So I'm not sure.
Q. Okay. So you cannot recall another way that a GAPMS request came to the agency, other than through a managed care plan or the health services inbox?
A. So for the most recent GAPMS report, that was a

request from -- I believe it was the secretary. But I don't know if it went through the inbox specifically or not.

Q. Okay. So that's another way that the GAPMS process can be requested -- is through the secretary?

A. That's the way that it has been.

Q. Okay. How many times?

A. I don't know.

Q. And when you say the most recent GAPMS report, do you mean the GAPMS report related to gender dysphoria?

A. Yes.

Q. When that request came in through the secretary, did the secretary identify why she was making that request?

And, I'm sorry, do you mean Secretary Marstiller?

A. Yes.

Q. Okay. Did she identify why she was making that request?

A. I can't recall the contents of the specific request.

Q. Did the request come -- who did the request from Marstiller go to?

A. I don't know.

Q. How did you find out about it?
A. I just can't remember if I was sent the letter in an email. But it was then discussed by my manager.
Q. And that manager was? Is?
A. At the time was Jason Weida, who is the assistant deputy secretary.
Q. And did you receive the letter from Secretary Marstiller before that discussion occurred?
A. Yes.
Q. And how long between receiving the letter and having -- how long past between receiving that letter and having that conversation with Mr. Weida?
A. I don't remember.
Q. Was it, like, hours? A day? Several days? Within the same week?
A. I don't remember.
Q. Okay. Was that discussion just between you and Mr. Weida? Or were there other people?
A. I don't remember in the initial conversation if there was anybody with me.
Q. Okay. Was it -- where did it take place?
A. I believe it was in Jason's office.
Q. Okay. Did Jason ask you to come to his office to have the conversation? How were you notified of the meeting?

A. I don't remember. We had standing meetings in his office; he was my -- or I was his direct report. So I don't remember if it was part of that when we were talking about assignments and priorities or separate. I can't remember.

Q. What was Mr. Weida's position at the time at the agency?

A. He was the assistant deputy secretary for Medicaid policy and quality.

Q. And then who is in that position prior to him?

A. I think Shevaun Harris.

Q. Okay.

A. There was a gap in between. But I think she was the last person.

Q. Okay. And who took that position after Mr. Weida?

A. That position is currently vacant.

Q. Okay. And has Brian Meyer ever held that position?

A. No.

Q. Okay. Prior to your meeting with Mr. Weida but after your received the request from Secretary Marstiller, did you communicate with anybody else about the request?

A. Can you repeat the question.

Q. Between the time that you received the request from Secretary Marstiller -- the letter -- and meeting with Mr. Weida, did you have a conversation with anyone else about the request?

A. I don't believe so.

Q. Okay. Were you surprised to see the request?

A. No.

Q. Why not?

A. Medicaid Policy -- I think we're unique in that bureau because no one day is exactly the same. There's always something new coming out from the federal government, from legislative action, from leadership. So I think that's kind of part of the job of being the bureau chief of Medicaid policy.

Q. Okay. What was -- when you met with Mr. Weida, did you develop a plan about how to honor the Secretary's request?

A. Yes.

Q. And what was that plan?

A. The team that was going to work on it was the Canadian Prescription Drug Importation Plan team; following the regular GAPMS process in terms of research and report and development.

Q. Did you identify who was going to be on that team?

A. Yes.
Q. And who did you identify?
A. Matt Brackett, Nai Chen, and D.D. Pickle.
Q. As part of that plan -- and to be clear, the secretary's request was specifically a request to undertake a GAPMS investigation?
A. Yes; to review through that process.
Q. Okay. And the team identified was Brackett, Chen -- and I forgot the --
A. Their manager, D.D. Pickle.
Q. D.D. Pickle. Thank you.
So you previously testified that the team primarily responsible for GAPMS was led by Jesse Bottcher. Why was Jesse Bottcher not part of the team to undertake this GAPMS?
A. So there was several factors considered. Matt Brackett has worked with the bureau a long time and previously had the position responsible for -- primarily responsible for the GAPMS. D.D. Pickle has also been with the bureau and agency a very long time. So I would say that the historical knowledge, the bandwidth -- having bandwidth to focus on completing the GAPMS -- were probably the two biggest factors.
Q. When you say bandwidth, what do you mean?
A. So that team -- their primary responsibility is

the Canadian Prescription Drug Importation Program, which is not approved federally. So our ability to move forward with the day-to-day operations and implementation of that program is stalled. Due to that, that team has been available to assist in other areas within the bureau when needed.

Q. Was the team that's primarily responsible for GAPMS -- were they overwhelmed with doing GAPMS at the time?

A. I don't know.

Q. But you used the fact that Mr. Brackett and D.D.'s team generally would have a lot of time to work on GAPMS as a deciding factor to pick the team for this report; is that right?

A. Yes.

Q. But you didn't first check whether the team that's primarily responsible for GAPMS would have the time to do the report?

A. No.

Q. Okay. How long has Mr. Chen been with the agency?

A. I don't remember.

Q. Would you classify him -- as you did Ms. Pickle and Mr. Brackett -- as being with the agency for a long time?

A. No.
Q. So he did not have that historical knowledge that Mr. Brackett and Ms. Pickle have with the agency?
A. No.
Q. And that was a deciding factor in picking the team?
A. Yes.
Q. When you met with Mr. Weida to pick this team, did Mr. Weida suggest the names or did you?
A. I believe I did.
Q. Okay. Other than the length of time at the agency and bandwidth, what criteria -- did Mr. Weida give you any criteria in terms of picking the team?
A. I don't think so, no.
Q. Did you use any other factors other than the length of time at the agency and bandwidth to select this team?
A. I think it's still the same as historical knowledge. But I have worked very closely with D.D. and Matt in my various positions. I knew Matt had some knowledge of previous similar requests, as well extensive knowledge of the standard GAPMS process. And it was a team of three that was available. So I think that still kind of historical knowledge and bandwidth were really the biggest factors.

Q. You said Mr. Brackett had experience with previous similar requests. What were those previous similar requests?

A. I believe there was a GAPMS request in the past before my time with the agency that had to do with hormone treatment.

Q. Would it be -- and it was hormone treatment. When you say a similar request, was it for GAPMS?

A. Yes.

Q. Would it have been the cross-sex hormone therapy GAPMS that is Exhibit 4?

A. No.

Q. How do you know?

A. The date on this. The one I was thinking of was much earlier before my time.

Q. Before your time -- do you have any sense of when that might be?

A. Maybe 2016 or 2017.

Q. Do you know who the Governor of Florida was in 2016 or 2017? I'm sorry. It's not a test, I promise.

Was it Rick Scott?

A. Yes.

Q. Okay. And was the interim secretary at the time at AHCA, was it Justin Senior?

A. Yes.

Q. And was Beth Kidder there at that time at AHCA?
A. Yes.
Q. And all of those people are listed on this Exhibit 4 --
A. So my document has Beth Kidder crossed out and looks to be a draft document from May 20th, 2022.
Q. Is there a name that replaced Beth Kidder on that?
A. Ashley Peterson.
Q. Okay. Do you know when Ashley Peterson joined AHCA?
A. I believe it was 2021.
Q. Okay. And is it --
MR. PERKO: Counsel, it's 1:30. Are we going to stop for lunch?
MS. DEBRIERE: We can if you want to.
MR. PERKO: Do you want to? It's up to you.
THE WITNESS: At some point.
MS. DEBRIERE: That's fine. Can I just finish up here real quick.
BY MS. DEBRIERE:
Q. So is it possible that this document was created in 2017?
A. I'm looking at a document that has track changes that appear to be since then. But I don't know.

Q. Why do those track changes appear to be since then?

A. Since the date was updated to May 20th, 2022.

Q. Okay. There's some editing in the column. It's very faint. Can you see it?

A. Yes.

Q. And the initials of editor appear to be GS.

A. Yes.

Q. Do you have any idea who that would be?

A. No.

Q. Do you know anybody here with the initials GS?

A. I'm sure somebody here has those initials, but I don't know off the top of my head.

Q. So Mr. Brackett was involved with a GAPMS related to cross-sex hormone therapy, but it wasn't necessarily this one; is that right?

A. I don't know the level of his involvement, but I know that he had some knowledge or knew about it.

Q. Okay. Did he do any other GAPMS related to the treatment of gender dysphoria?

A. I don't know.

Q. Mr. Chen -- did he have any previous experience with GAPMS?

A. I don't know.

Q. Ms. Pickle -- has she had any previous

experience with GAPMS?
A. I don't know.
Q. And you've explained why Mr. Brackett, Ms. Pickle, and Mr. Chen were selected for the team. Why was Mr. Bottcher not selected?
A. I can't recall all the details of the decision. But Jesse Bottcher's team is one of the busiest in the bureau, and has a lot of time sensitive work that they are constantly working on. So I think that had something to do with it, since he is the manager of an entire section.
Q. I think you had previously testified there weren't a lot of GAPMS pending at the time this request come through; is that right?
A. I didn't know the bandwidth or the workload.
Q. Okay. You didn't know the bandwidth. So you didn't know if, for example, Mr. English had the bandwidth to handle the GAPMS report?
A. No.
Q. Do you want to take a break?
A. Yes.
(Brief recess.)
BY MS. DEBRIERE:
Q. Previously before break we were talking about the selection of Mr. Brackett to be on the GAPMS report

team for gender dysphoria. And you mentioned that he had drafted previous similar GAPMS in the past. And I believe you used the example of cross-sex hormones.

Were there any other similar requests that he drafted related to gender dysphoria in the past?

MR. PERKO: Object to form.

THE WITNESS: Just to clarify, I'm not sure if he drafted it.

MS. DEBRIERE: I'm sorry; yes.

THE WITNESS: I know he had some historical knowledge of previous GAPMS.

MS. DEBRIERE: Okay.

THE WITNESS: So can you repeat your question.

BY MS. DEBRIERE:

Q. Did he have hysterical knowledge of previous GAPMS related to gender dysphoria?

A. Outside of the one that I referred to earlier?

Q. No, including that one.

A. Yes, I believe he had some historical knowledge of previous GAPMS.

Q. Other than the one you referenced earlier, are you aware of any other GAPMS that he was involved in related to gender dysphoria?

A. I don't know the extent of all the GAPMS he was involved in.

Q. Also earlier when you were discussing your responsibilities under GAPMS, you mentioned routing.

A. Yes.

Q. Can you describe that a little bit.

A. As the bureau chief of Bureau of Medicaid Policy, any official documents that leave the bureau are usually reviewed by me. And so routing process is the hierarchy of reviewers through wherever the final reviewer or signatory or approver. That's what I was referring to by routing process.

Q. Okay. Does every GAPMS report have a routing process?

A. Yes.

MS. DEBRIERE: Okay. Can I have the 2016 GAPMS routing form. And we'll mark it as Exhibit 6.

MS. DUNN: I can tell from this exhibit that when we printed these the Bates numbering got cut off. So I will look it up and read --

MS. DEBRIERE: That's a bummer.

MS. DUNN: I know.

(Plaintiff's Exhibit No. 6 was marked for identification.)

BY MS. DEBRIERE:

Q. Okay. So do you recognize this document?

A. Not this specific document. But this appears

to be a policy routing and tracking form.

Q. And is that form the same as the form you currently use to track -- to route and track?

A. Sometimes.

Q. What other forms do you use?

A. Prior to the pandemic, we used this form primarily. Since returning to the office there have been different variations of routing and tracking forms developed for different teams or documents -- types of documents.

Q. Do you use the same routing and tracking form for GAPMS?

A. So I've only approved two GAPMS in my time. And I can't remember if this was the -- this format was what was used to route it to me.

Q. Okay. But there was a form used to route it to you when you approved -- when you approved your two GAPMS?

A. I believe so.

Q. Okay. And on this GAPMS form, it says prepared by Monique Johnson. What does it mean to be prepared by? Was the form prepared by Ms. Johnson? Or was the GAPMS report prepared by Ms. Johnson?

A. I don't know.

MS. DEBRIERE: Okay. Could I see the 2022

GAPMS. This will be Exhibit 7.

(Plaintiff's Exhibit No. 7 was marked for identification.)

BY MS. DEBRIERE:

Q. So I'm handing you -- and Gary will want to take a look at it too -- again, the first page of the document is entitled "Medicaid Policy Routing and Tracking Form." If you go through the entire document, it should also include the June 20, 2022, GAPMS report on treatment of gender dysphoria.

MR. PERKO: I believe it was June 2nd.

MS. DEBRIERE: June 2nd. Excuse me.

BY MS. DEBRIERE:

Q. So looking at the document -- the first page, is this the Medicaid Policy Routing and Tracking Form that was associated with the GAPMS report on the treatment of gender dysphoria?

A. Yes.

Q. How do you know?

A. These are my initials.

Q. Okay. So you've seen this before?

A. Yes.

Q. I do want to point out "prepared by" here. What does that mean?

A. That Matt Brackett prepared the routing

package.

Q. Okay. Did he also prepare the GAPMS report itself?

A. Yes.

Q. Do you know if the person who prepares the routing and tracking form -- if they are the person who also prepares the GAPMS report?

A. Can you repeat the question.

Q. The person who prepares the Medicaid Policy Routing and Tracking Form, do they also prepare the GAPMS report itself?

A. I don't know how all the team members are instructed to fill out the report or -- I'm sorry -- fill out the tracking form.

Q. Is there any other way to determine who has prepared a GAPMS report?

A. I don't know. But speaking in general assignments -- these forms are used for other assignments. And there are a lot of assignments that are done collaboratively. So, yeah. I don't know specifically how else you would know just looking at documentation.

Q. Would that information be contained on an AHCA shared drive?

A. It's possible.

Q. Okay. Is there a reason the GAPMS report doesn't identify an author on the report?
A. I don't know.
Q. Okay. A couple other things. On the section line here, it says Canadian Prescription Drug Importation Program. But we have established this was the routing and tracking form for the GAPMS report related to the treatment of gender dysphoria. Are those two things related?
A. So the Canadian Prescription Drug Importation Program is the section of who developed the report. And it lets us know how the hierarchy of the routing should go through the management levels within the bureau and outside.
Q. So it was the Canadian Prescription Drug Importation unit who prepared the GAPMS report on the treatment for gender dysphoria?
A. So that's what I would interpret this section -- why it's listed there next to this section. It's the section responsible for routing and lets us know the hierarchy of the management.
Q. Okay. And then just looking down at the "Reviewed by and Routing Timelines," the start date is June 1st, 2022, for everybody except Mr. Wallace; who has a date of June 2nd, 2022. And the end date is June

1st, 2022, except for Mr. Wallace. Does that indicate that you Mr. Weida and Ms. Pickle all reviewed the report and signed off on it on the same day?

A. That the official routing and the signature occurred on the same day, yes.

Q. What do you mean by official routing?

A. So the date that this form and the final routing package was ready for signature.

Q. And what was continued in the final routing package?

A. I believe it was just the report.

Q. Okay. So the final report -- what was being tracked through this routing and tracking form?

A. Yes.

Q. Were there any attachments to the final report that were also reviewed?

A. The expert witness reports were also reviewed. But I can't remember if they were included in this routing package at the same time.

Q. Who reviewed those final expert reports?

A. I don't remember.

Q. Did you review them?

A. I don't remember if I reviewed them all. But I had seen them -- at least some of them. I can't remember if I reviewed them all formally.

Q. Okay. Turning just back to the general GAPMS process. Is the GAPMS process ever initiated to assess existing coverage of Medicaid services?

A. Can you repeat the question.

Q. Is the GAPMS process ever used to assess existing coverage of Medicaid services?

A. I don't know specifically.

Q. Okay. Who would know that?

A. Are you asking if it ever has or ever would?

Q. Ever would.

Would Ms. Pickle know that?

A. So my personal experience with the GAPMS process is somewhat limited. But it is such a unique process. I feel it's hard to answer that without each situation or each request that we would get would be unique, because that process is dealing with questions that fall outside of something that's easily answered policy question.

MS. DEBRIERE: Have we entered the GAPMS rule into evidence yet? Can we do that now. And that's to be 59G-1.0 -- I thought we had. Oh, it's 5. Okay. Sorry. That's my fault.

MR. PERKO: That's fine.

BY MS. DEBRIERE:

Q. So a couple questions about the language of the

rule. First under (1)(b), "health services" is defined as diagnostic tests, therapeutic procedures, or medical devices or technologies.

Under what category would prescription drugs fall in this definition?

A. I don't know.

Q. You are familiar with the GAPMS rule, though; correct?

A. Yes. I've read the GAPMS rule.

Q. Would prescription drugs fall under any of these categories?

MR. PERKO: Object to form.

THE WITNESS: I don't know. I wasn't part of the original drafting of this rule text. So in order to interpret the policy, I would need to do research.

BY MS. DEBRIERE:

Q. Who would you ask?

A. I would probably start with Ashley Peterson.

Q. Okay. And going down to 3, the second sentence -- "The public may request that a health service be considered for coverage under the Florida Medicaid program by submitting a request."

What does this sentence mean to you?

A. There's much room for interpretation. It says

the public may request a public health service be considered for coverage.

Q. Does this sentence mean that the public may request that Florida Medicaid consider whether to exclude a service previously covered?

MR. PERKO: I'm going to object to form.

THE WITNESS: So I think it could. Not only do we update the coverage policies to include new services, but we do change the scope of a service as part of that process. So if there was a question that was not clear within the scope of the service, I can see how that might apply.

Or the example that you used earlier with a service that's only provided to under 21. If that service was -- if we received a request to make that service available for over 21. So I can think of examples where it wouldn't have to be a new service.

BY MS. DEBRIERE:

Q. Does this rule cover a public's request to take a service away?

MR. PERKO: Object to form.

THE WITNESS: I don't know.

BY MS. DEBRIERE:

Q. Okay. Who would know?

A. Public -- that would be a legal interpretation

or policy interpretation that would need consultation with the agency for me to answer.

Q. As the bureau chief of Medicaid Policy, you're responsible for developing coverage policies; correct?

A. I oversee the teams that develop coverage policies, yes.

Q. And you are responsible for overseeing the teams that develop administrative rules to implement those coverage policies; correct?

A. Yes.

Q. So you would be responsible for understanding how rules that implement coverage policies should be interpreted.

MR. PERKO: Object to form.

BY MS. DEBRIERE:

Q. Is it your responsibility to understand the content of this rule?

A. Yes.

Q. Okay. But you can't tell me how to interpret that second sentence in Subpart 3?

A. So if we received a request and I wasn't clear on the authority, there's several steps I would take to confirm that the agency's position is we have authority -- which would be to review any other applicable laws or regulations; would be to consult with

my team and with agency management and perhaps with legal if I was not sure whether a specific question or scenario that was received. We may not have the authority to take an action.

Q. So when reading the second sentence in Subpart 3 -- "The public may request a health service be considered for coverage" -- in order to understand what that sentence means, would you undertake any of the steps you just described?

A. It would depend on the exact question. If I wasn't clear with what the request was and how that authority applied, then I would take further steps to make sure that I understood how the rule applied to the request.

Q. Did you do that for -- okay. Okay. Let me make a note.

In the legal consultation part, it trigged me to remember just a housekeeping question. At lunch did you speak with your attorneys --

A. No.

Q. -- about the deposition?

A. No.

Q. Okay. Does the GAPMS process typically look at an individual service when you're undertaking analysis?

A. I don't know.

MS. DEBRIERE: Okay. Can I have either the Van Mol or Van Meter ATF. It doesn't matter. And we'll mark that as Exhibit 8.

(Plaintiff's Exhibit No. 8 was marked for identification.)

BY MS. DEBRIERE:

Q. So at the top of the page you have a -- did you approve this document?

A. Yes.

Q. Okay. So under "Reason for Occurrence," it says, "On April 20th, 2022, the Bureau of Medicaid Policy received a request for a time-sensitive analysis of service coverage. While such requests are typically for a single service or good --" Is that a correct statement?

A. I don't know.

Q. But you wrote this?

A. No. I signed this.

Q. Okay. Were you the one making the request?

A. No.

Q. Who was making the request?

A. Devona Pickle.

Q. Okay. Before you sign something, do you have to agree with the language contained therein?

A. Yes.

Q. So at the time you signed this, you agreed with the statement that such requests are typically for a single service or good?

A. Yes.

Q. Okay. But now you don't know if GAPMS are typically used for a single service or good?

A. My experience with GAPMS is limited. And I trust the expertise of my staff. And one of the reasons I asked or had recommended that this team be responsible was because of their historic knowledge of the GAPMS process.

Q. And when you say that, that includes D.D. Pickle; correct? You trust her expertise on the GAPMS process?

A. Yes.

Q. Okay. Are you aware of a standard operating procedure used for the GAPMS process?

A. I've heard mention of it. But I don't believe I've ever seen it.

Q. Who did you hear mention of it from?

A. I can't remember. Either Matt or Jesse.

MS. DEBRIERE: Okay. Can I have what we'll mark as Exhibit 9, which is the GAPMS Decision Tree Checklist.

(Plaintiff's Exhibit No. 9 was marked for

identification.)
BY MS. DEBRIERE:
Q. Do you recognize this document, Ms. Dalton?
A. I believe I've seen this before.
Q. Do you know what it's used for?
A. I believe this was developed to determine if a request just goes through the coverage determination process or should be handled as a GAPMS.
Q. Okay. And tell me the difference between a coverage determination and something that needs to go through the GAPMS.
A. I don't know everything that goes into how that decision is concluded. But in general, a coverage determination is when it's very clear that the agency has the authority to add a service and that it meets all of the agency's rules and -- for example, an optional state plan service that the agency currently doesn't cover but is clearly allowed through federal CMS would be a coverage determination. Where the GAPMS process is driven by the rule you referenced earlier that describes when it's not clearly meeting all the requirements and laid out in the current coverage policies.
Q. So much earlier in the deposition you gave an example of a coverage determination of a medical supply for -- was it Amino Foods?

A. Puro Meno.
Q. Puro Meno Foods. Why didn't you use the GAPMS process for that? Did you use the GAPMS process for that?
A. No.
Q. Why not?
A. Because the agency already covered similar products.
Q. Okay. Was that the only factor in determining whether to assess it using GAPMS?
A. I don't remember the conversations with the team when I was briefed on the recommendation.
Q. Was a GAPMS Decision Tree Checklist done for Puro Meno Foods?
A. I don't believe so. I never saw one, no.
Q. Okay. Who undertakes the process to fill out the decision tree?
A. I don't know.
MS. DEBRIERE: I apologize. Can we take just a two-minute break.
MR. PERKO: Sure.
(Brief recess.)
BY MS. DEBRIERE:
Q. Do you know how to interpret the answers on a decision tree checklist?

A. No, I don't believe I've ever seen one filled out.

Q. Okay. There's a space here that says "GAPMS Topic." What would go in that space? Do you know?

A. I don't know.

Q. Would a decision tree checklist be generated for every GAPMS request that comes in?

A. I don't know.

Q. Who would know that?

A. I don't know. I don't know if this is still the internal process. I don't know.

Q. Who would know whether it was still the internal process?

A. Jesse Bottcher.

Q. Okay. Would the members of Jesse Bottcher's team also know?

A. No, I don't think anyone currently on his team would know.

Q. How about anybody previously on his team -- I'm sorry; back up.

So no one on Jesse Bottcher's team is in charge of the GAPMS process?

A. The GAPMS position is currently vacant.

Q. Would anybody who was in charge of the GAPMS process at some point know whether the decision tree

checklist is used in the GAPMS process?
A. I don't know.
Q. And there's only one position that would know that, and that is currently vacant; correct?
A. I believe so, yes.
Q. And what is that position called?
A. I believe it's a Government Analyst II.
Q. And so there's just that one position in charge of knowing the GAPMS process?
A. As far as I know, yes.
Q. Okay. We touched on this a bit earlier. Does AHCA use the GAPMS process for prescription drugs?
A. I don't know.
Q. When you were giving an example of similar requests that Mr. Brackett handled for GAPMS, the example you gave was cross hormone therapy; correct?
MR. PERKO: Object to form.
THE WITNESS: I believe that was the example I gave.
BY MS. DEBRIERE:
Q. And what is cross-sex hormone? What is a hormone?
A. I don't think I can recite the clinical definition.
Q. Is the hormone a prescribed drug?

A. I believe so.
Q. So then you're aware of one instance in which GAPMS was used for determining -- for assessing a prescription drug?
A. Yes.
Q. But you don't know generally if GAPMS is used to assess prescription drugs?
A. My knowledge of GAPMS is limited. So to speak in generalities -- but I do see where in 2016 there was the GAPMS on hormone suppression.
Q. Okay. Is GAPMS the only method AHCA relies on to determine whether a Medicaid service is experimental?
A. I don't know. I know we have a clinical trials coverage policy. So there may be circumstances where it's clear that coverage would be -- that coverage policy or the clinical trials rule would apply. And I don't know all the details of how the QIO vendors -- what that process, all that entails.
Q. Whether the QIO venders would determine whether something is experimental?
A. Or if it was clear the clinical trial policy would apply instead. So I don't know to the extent of if there could possibly be.
Q. What is the clinical trials policy?
A. It's a rule that outlines the agency's coverage

for recipients participating in a clinical trial.

Q. And what does that type of authorization entail?

A. I don't know the specifics.

Q. Is GAPMS the only method that AHCA relies on to determine whether a Medicaid service is experimental and therefore should be excluded?

A. Can you repeat the question.

Q. Is GAPMS the only method that AHCA relies on to determine whether a Medicaid service is experimental and therefore should not be covered?

A. I don't know the specifics. But if, for example, a pharmaceutical is not FDA approved, there would be perhaps, like, a different process where it wouldn't have to go through the process.

Q. What is the significance of a drug being FDA approved for the purposes of coverage?

A. I don't know the details.

Q. What do you know about it?

A. I believe there's federal requirements on if a drug is not FDA approved -- there is certain coverage requirements.

Q. Do you know if that relates to the compendia we were earlier talking about?

A. I don't know.

Q. Okay. If AHCA is determining whether a production drug is experimental, does AHCA consider whether the drug is FDA approved?

A. I believe so.

Q. If a particular use for a drug has been FDA approved, can AHCA deem the drug experimental for that use?

A. Can you repeat the question.

Q. If a particular use for a drug has been FDA approved, can AHCA deem that drug experimental for that use?

MR. PERKO: I'm going to object to form.

THE WITNESS: I don't know.

BY MS. DEBRIERE:

Q. But FDA approval bears on a determination as to whether AHCA will cover a drug; is that correct?

A. Yes, I think it's considered.

Q. If it's not -- if a drug is not FDA approved, are there circumstances under which AHCA will still cover the drug?

A. I don't know. But I think there is federal regulations around what's allowable.

Q. In the Federal Medicaid Act?

A. I believe.

Q. You mentioned just a second ago, a clinical

trials coverage policy. Where does that policy live?
A. In Rule Class 59G on our website.
Q. If it's not there where would we find it?
A. In the Florida Administrative Code.
Q. It should be in Chapter 59G?
A. But it should be on our website.
Q. Okay. And it is adopted as a rule?
A. Yes.
Q. Okay. Once AHCA reaches a decision through the GAPMS process, describe the implementation of that decision.
A. So, again, in my experience -- I've only been bureau chief for two finalized decisions that were different. And I can't remember all the steps to implementation. But once a determination of any coverage is made, then there's a process of how to notify the public. There's a process for notifying the plans of changes if it affects the plans. There's a process of making sure that the -- any other associated rules that may be impacted are updated.
Q. Anything else?
A. If a training is needed, it depends on what it is. But there could be other.
Q. Who would you train?
A. So, again, just speaking generally -- the

managed care plans; the public; if it's fee for service, the providers; especially if it has to do with submitted claims.

Q. What are the two final reports that you have overseen as bureau chief?

A. So it was the GAPMS that we're discussing today.

Q. And, again, that's the one that relates to treatment of gender dysphoria?

A. Yes. And then the -- I can't remember the exact name of the other GAPMS. But it was through a managed care plan request.

Q. Was it an expedited GAPMS?

A. I don't believe so.

Q. Do you remember what the service was at issue?

A. I do not.

Q. Okay. And the process for an expedited GAPMS, that's different from the traditional GAPMS process?

A. I'm not sure of the differences outside of the timeframe.

Q. Is it different as to how you would inform the public about it?

A. I don't know. I can't recall what steps we took after notifying the plans of the final decision.

Q. Okay. Through the traditional GAPMS process --

do you have any GAPMS right now that are in the final stages?

A. No.

Q. Okay. And you don't know how many requests are currently pending?

A. I don't know.

Q. So the last GAPMS that was finalized was in June of 2022?

A. Yes.

Q. Okay. And now we're in February of 2023. And there's no GAPMS that are ready for finalization at this point?

A. I don't know what stages of development they are.

Q. Okay. Is there anything on your desk to review?

A. I don't know. I don't remember if I have anything pending.

Q. Okay. When you were meeting with Mr. Weida about the June 2022 GAPMS report related to the treatment for gender dysphoria, that report had not been drafted; correct?

A. Sorry. Can you repeat that.

Q. Yeah. Absolutely. So earlier you spoke to meeting with Mr. Weida once you received the request

from the secretary to undertake the GAPMS for treatment of gender dysphoria; do you remember?

A. Yes.

Q. During that meeting had the GAPMS report been drafted yet? I know it seems like a silly question. But I'm asking at face value.

At the time you met with Mr. Weida, had the GAPMS report been drafted yet?

A. The GAPMS report I was discussing with him? No.

Q. Okay. But you have a good memory of that report before it was even drafted; is that right? You were able to recount details to me about discussing that report about before it had been drafted; is that right?

A. Throughout the process there had been discussions. But I don't know if I remember all the details.

Q. What I'm wondering is just why that report sticks out in your mind, but now you can't recount any other GAPMS reports that are pending. Is there a reason for that?

A. I have a lot of documentS in my queue at any one time. And it's really on the onus of the analyst -- part of their job responsibilities -- to make sure assignments are completed and finalized and routed and

closed. So because there was discussion and updates on the status and progress of the report -- and it was not that long ago -- I remember having conversations about the report.

Q. There are GAPMS reports pending right now, though; right?

A. I don't know. I don't know what the GAPMS queue is right now.

Q. Okay. So you don't know if there's anything in the queue right now?

A. Correct.

Q. But you do remember details about the GAPMS report related to treatment of gender dysphoria?

A. Details on the process?

Q. Yeah.

A. Yes.

Q. Okay. When I say "rulemaking process," do you understand what I'm referring to?

A. Yes.

Q. And do your current responsibilities at AHCA include the rulemaking process?

A. Yes.

Q. Can you describe those responsibilities.

A. I review drafts of the coverage policy and the documents that go along with the rule promulgation

process. I sometimes participate in the public meetings and review provider alerts or other notices associated with the process.

Q. Anything else?

A. Not that I can think of.

Q. Okay. Do you ever review public comment associated with the rule?

A. It depends.

Q. So you have before?

A. More in my old role as the AHCA administrator.

Q. Okay. Can you remind me the dates you were in that role.

A. August 2018 to August 2021.

Q. And in your previous roles at AHCA as well as DOEA, you had rulemaking responsibilities; is that right?

A. DOEA was more of the drafting of the policy and not the promulgation process.

Q. Okay.

A. And then AHCA has been more on the promulgation process -- administrative process.

Q. So you'd say you had experience with Florida agency rulemaking?

A. Yes.

Q. When I say "rule workshop," do you understand

what I'm referring to?

A. Yes.

Q. When I say "rule hearing," do you understand what I'm referring to?

A. Yes.

Q. What is the difference?

A. Chapter 120 has different public meetings outlined in different stages of the process. The workshop as we use it here is primarily for the rule development stage of the administrative process. And the hearing occurs at the proposed rule stage.

Q. Okay. When you say the development of the rule, does that mean generally the rule language itself has not yet been drafted or proposed?

A. It depends.

Q. Okay. So is there a difference between workshop and hearing?

A. They're both public meetings meant to garner input from the public and make the public aware of the changes. But per Chapter 120, there are differences because of the different stages of the process.

Q. Okay. Why was there no public workshop held for the rule development of the change to Rule 1.050 excluding the treatment for gender dysphoria?

A. I don't know.

Q. Were you here were when that happened?
You were?
A. Yes.
Q. Okay. While here, have you had public comment on rule workshops for other rules?
A. Can you repeat the question.
Q. Since you've been here at AHCA, have you -- let me ask this question: When the rule was developed to exclude treatment of gender dysphoria per 1.050, were the you bureau chief for Medicaid Policy?
A. When the rule was promulgated?
Q. Well, when you were having the -- when you noticed the proposed rule and had the rule hearing.
A. For this specific rule?
Q. Yes.
A. Yes.
Q. Okay. In your role as bureau chief, have you ever -- in your role as bureau chief, have you been involved in rule workshops for other rules?
A. Yes.
Q. So why weren't you involved in the rule workshop for the exclusion of treatment for gender dysphoria; do you know?
A. I can't remember. I believe I was out of town.
Q. Okay. If you weren't out of town, would you

have been involved in it?

A. I don't remember the discussion around that. But I'm not always involved in the workshops or rules.

Q. How is that determined?

A. It depends on the circumstances and the content of the rule. But I can't remember the specific conversation when that was determined.

Q. Was there a public workshop for the exclusion of the treatment for gender dysphoria? There was only a public hearing; correct?

A. I know there was only one public meeting. I can't remember.

Q. Generally what's the process for planning a rule hearing?

A. We determine a date, a location, and who will be in attendance. And the date and location is included in the notice.

Q. And when you say who will be in attendance, who does that mean?

A. Who the subject matter experts or other agency staff will conduct the public meeting.

Q. Okay. And what do you mean by subject matter expert?

A. So I think I described it a little before how for most of the coverage areas there is a specific

analyst responsible for the development of that policy. So, for example, if there was a change to respiratory services, whoever that suggest matter expert or analyst is would typically be present at the workshop since they have the in-depth knowledge on the changes being proposed.

Q. Is that person always a person employed by the agency?

A. The subject matter expert for all our coverage policies are individuals employed with the agency.

Q. Okay. Are there any written protocols regarding the planning of a rule hearing?

A. I know we've developed process maps and procedures. But I don't know the details of planning a hearing specifically and how detailed those documents are on that process.

Q. What's a process map? What does that entail or detail?

A. There's a graphic that was created before my time that -- it's a real nice layout of the administrative rulemaking process.

Q. Okay.

A. And so it has -- it's a graphic, and it's one page. So it's easy to put on your wall.

Q. And your responsibilities include sometimes

attending rule hearings?

A. Yes.

Q. Since you've been the bureau chief, how many rule hearings have you attended?

A. I don't think I've attended any hearings.

Q. As a State agency employee -- either at DOEA or AHCA -- how many rule hearings have you attended?

A. So at DOEA I attended several AHCA rule hearings in the audience. In my previous position with the agency, I think it was only a handful.

Q. Does that mean five?

A. Yes; I'd say five or less.

Q. Okay. Who else from AHCA attends rule hearings? Let me ask this: Are there AHCA staff who attend rule hearings as part of their job description -- they have to be at every rule hearing?

A. I don't know if that's actually in the job descriptions. But Cole and his team -- since they set up the workshop or hearing or the public meeting -- their responsibilities include making sure they have the speaker list, making sure that everybody is escorted into the building, that the speakers can be heard. So they're in attendance for all of the public meetings.

Q. Okay. And do you know if they have any protocol off which they operate -- written protocol for

conducting the hearing?

A. I believe there's an internal process and process map. But I don't know the details off the top of my head what's included in that document.

Q. Is it the rules unit that is in possession of that document?

A. I would think so, yes.

Q. Okay. In your experience, aside from the agency who attends the hearing?

A. From the public?

Q. I mean, I think that would be the only other option; right?

What types of people from the public?

MR. PERKO: Object to form.

THE WITNESS: That would really depend on what the change is and who is impacted.

BY MS. DEBRIERE:

Q. In your experience attending public hearings -- rule hearings -- are there typically more than 25 people from the public that show up at the rule hearing?

A. I would say yes. Especially since the hearings are now -- have a virtual option. The majority of them are virtual and in person.

Q. Are there typically more than 25 people who show up in person?

A. So I haven't participated in all of them. In the last few that I participated in, there was not 25.

Q. In the last one you participated in how many were there?

A. Less than ten.

Q. Does AHCA ever invite specific persons from the public to attend the rule hearings?

A. Yes.

Q. And how do they do that invite?

A. A provider alert is sent out to the providers. Usually that goes along with the FAR notice that was posted and the public was noticed. If it's a sister agency, it might be by email. So if we believe a rule might impact a sister agency, we might reach out specifically.

Q. So other than posting the public notice and the FAR provider alerts and emails to potentially impacted sister agencies, is there any other way the agency invites specific people to attend the hearing?

A. I believe we sent calendar invites before.

Q. To what people? How did you decide on sending calendar invites?

A. The specific example I'm thinking of is a sister agency for the iBudget handbook. We invited ADP to participate and sent them a meeting invite so they

can block that time.

Q. Okay. Have you ever invited Medicaid recipients other than through the public notice to attend a rule hearing?

A. I don't know, outside of the public notice process.

Q. In your experience?

A. I personally have not.

Q. Okay. Do any State agencies in hosting a rule hearing, do they arrange for transportation for individuals from the public to attend that hearing?

MR. PERKO: Object to form.

THE WITNESS: I can't speak for any other agency. I don't know.

BY MS. DEBRIERE:

Q. What about at DOEA? Did that ever happen?

A. I don't believe I ever participated in an actual public meeting hosted by DOEA.

Q. That's right. You said that.

What about AHCA? Are you aware of AHCA ever arranging transportation for individuals from the public to attend a hearing?

A. Not that I'm aware of.

Q. Are you aware of anyone from the public being paid to attend a hearing?

A. No.
Q. Are you aware of anyone who is a subject matter expert being paid to attend a hearing?
A. I know we've reimbursed the subject matter experts. But I'm not sure if that was specifically -- attending the hearing was specifically included.
Q. And these are subject matter experts that are employed with the agency?
A. I don't know how that process works. But they're not full-time employees with the agency. I believe it's like consultants.
Q. Okay. What's the average length of a hearing?
A. I don't know the average. I know our public meetings typically range between 30 minutes and two hours.
Q. Okay. On average how many comments do agencies receive for a rule hearing? Is there an average?
MR. PERKO: Object to form.
THE WITNESS: I don't know.
BY MS. DEBRIERE:
Q. Do you think 100 comments is a lot of public comments to receive at a hearing?
MR. PERKO: Same objection.
THE WITNESS: I really don't know.
BY MS. DEBRIERE:

Q. In your experience, does a State agency ask outside legal counsel to attend and perhaps in rule hearings?

A. Can you repeat the question.

Q. In your experience, does a State agency normally ask that outside legal counsel attend a rule hearing?

A. I don't know.

Q. When you planned this last rule hearing, did you ask outside legal counsel to attend?

A. Can you specify which hearing.

Q. Yeah. There was a hearing a couple of weeks ago on the change to the medical necessity definition.

A. Yes. The workshop.

Q. Workshop. Did you ask outside legal counsel to attend that workshop?

A. I personally did not.

Q. Did outside legal counsel attend that workshop?

A. I don't believe so.

Q. And have you ever attended a rule hearing where outside legal counsel was asked to participate in?

A. I can't recall if that circumstance has ever happened.

Q. So it's not usually -- it's not the standard course of things for outside legal counsel to attend?

A. Correct.

Q. All right. Turning to the exclusion for treatment of gender dysphoria under Rule 59G-1.050. Prior to the adoption of this exclusion, did any coverage policies regarding any of the services listed there -- sorry. Strike that.

Prior to the adoption of the exclusions set forth -- I'm not sure you're looking at the right rule. 59G-1.050. Exhibit 2. It would help me to tell you the exhibit number. And then it's Subpart 7.

So prior to the adoption of that rule -- that Subpart 7 -- did any coverage policies exist regarding the services that are now subject to that exclusion?

A. Can you repeat that question.

MS. DEBRIERE: Court Reporter, can you read back that last question.

(The preceding question was read back by the reporter.)

THE WITNESS: There was not a specific coverage policy for services for the treatment of gender dysphoria.

BY MS. DEBRIERE:

Q. Does that mean those services were never covered to treat gender dysphoria by Florida Medicaid?

A. I don't believe there was any policy language

that specifically outlined coverage of the services listed in this section.

Q. If there was no specific policy language, does that then mean those services were not covered to treat gender dysphoria by Florida Medicaid?

A. I don't know the extent to what providers were reimbursed for providing the services.

Q. So even if there wasn't a coverage policy specifically related to these services, it's possible that Florida Medicaid was covering the services for the treatment of gender dysphoria?

A. It's possible Florida Medicaid reimbursed for these.

Q. Are there circumstances in which AHCA might not have an explicit or affirmative coverage policy, but would consider a request for a service on a case-by-case basis?

A. Can you repeat the question.

Q. Are there circumstance in which AHCA might not have an explicit coverage policy regarding those services -- or any service -- but would consider a request for a service on a case-by-case basis?

A. I don't know specifically if it's case-by-case basis. But I believe that the plans -- that some of the request from the managed care plans may be specific to a

request for a specific coverage. So when plans request for a GAPMS to be provided, it could be being driven by a specific case.

Q. Okay. So even though a coverage policy does not exist regarding the coverage of a specific service, there are circumstances in which AHCA might still cover that service?

A. Yes.

And I apologize. On your last question I think I heard you specific about GAPMS, which is what I answered. So I apologize.

Q. That's okay. No, that's fine. You're referring to not the last question, but the question before that; is that right?

A. Yes.

Q. Okay. But your response on that last question, you understood the question?

A. Yes.

Q. Okay. Will Florida Medicaid cover an EPSDT service if that service is experimental?

A. So in order for an EPSDT service to be covered, it has to meet the definition of medical necessity.

Q. And that medical necessity definition includes the requirement that the service not be experimental?

A. Yes.

Q. Okay. So you received a request from Secretary Marstiller via email to engage in a GAPMS regarding treatment for gender dysphoria; correct?
A. I can't remember if it was email.
Q. Right. But you received the request somehow?
A. Yes.
Q. And roughly when was that; do you remember?
A. I don't remember.
Q. And then the next step was speaking with Mr. Weida about the letter?
A. Yes.
Q. And developing the plan as to who was going to --
A. Yes. Developing how the process would work.
Q. Were all the decisions reached in that one meeting with Mr. Weida?
MR. PERKO: Object to form.
THE WITNESS: No.
BY MS. DEBRIERE:
Q. Okay. So after that meeting with Mr. Weida, what happened next?
A. I can't remember the exact timeline of events. I know we met at some point with the Canadian Prescription Drug Importation team.
Q. And they were the ones who were put in charge

of doing this GAPMS?
A. Yes.
Q. Okay.
A. And there was several conversations following that.
Q. Were those conversations limited to yourself, Mr. Brackett, Mr. Chen, and Ms. Pickle? Or were there other people involved?
A. I can't remember the chronology. I know after the report and then into the rulemaking Cole Giering was brought into the conversation. Legal counsel -- there was conversations with the experts.
Q. Who were the experts?
A. I can't remember all their names. I don't know if we have that list here.
Q. Did you ever personally speak with any of the experts?
A. No.
Q. Are all the experts listed here on what would be will be your Exhibit 7 on page 45?
A. I believe so, yes.
Q. Was a Dr. Von Mol ever involved as an expert?
A. I believe so.
MS. DEBRIERE: And let me just mark this as Exhibit 10.

(Plaintiff's Exhibit No. 10 was marked for identification.)

BY MS. DEBRIERE:

Q. And this is a document -- an After the Fact Request Form Under 35K. This form is indicating what?

A. Consultant services for vendor name Andre Van Mol.

Q. And what kind of consulting services did Dr. Van Mol provide?

A. I don't know all the details of that -- what the contractor provided. But it was as part of the GAPMS process.

Q. Okay. Why was it time sensitive? It indicates on that form it was time sensitive. Why?

A. I don't know why the request was time sensitive.

Q. Who would know that?

A. I don't know.

Q. Okay. At any time throughout the process did you feel like there was an urgency to the development of the report and rule?

A. Yes. The time sensitive nature was communicated.

Q. By?

A. I don't know remember if it was in the original

request or if it was later in conversations with leadership. I can't remember exactly who. But I think the expectation to follow the process but work as quickly as possible was apparent.

Q. Okay. But you cannot provide me an explanation as to why it was identified as time sensitive?

A. Correct.

Q. I believe we already marked ATF to Dr. Van Meter as Exhibit 8.

Dr. Van Mol -- do you know if he attended the rule hearing for the exclusion of treatment for gender dysphoria?

A. I don't know.

Q. Okay. What does this document, Exhibit 8, indicate to you?

A. An approval for consultant services for vendor named Quintan Van Meter.

Q. Okay. And what kind of services did he provide in exchange for that reimbursement?

A. Consultant services.

Q. Consulting on what?

A. As part of the GAPMS process.

Q. Do you know what specific stages he provided consultation on?

A. I don't.

Q. Do you know whose idea it was to use him?
A. I don't.
Q. Do you know whose idea it was to retain any of the outside experts?
A. No.
Q. Was it internal to AHCA, that decision? Did someone at AHCA decide to retain outside experts?
A. I don't know.
Q. Who would have made that decision?
MR. PERKO: Asked and answered.
THE WITNESS: I don't know.
BY MS. DEBRIERE:
Q. Are you aware of AHCA retaining outside experts for any other GAPMS report?
A. I don't know.
Q. Other than Dr. Van Meter and Dr. Van Moll -- I'm sorry.
Was there a Dr. Grossman involved in the process?
A. Yes.
Q. And what was Dr. Grossman's role?
A. I believe it was the same -- consultant services.
Q. For the development of the report?
A. Yes.

Q. Okay. Do you know if they were reimbursed to participate in the hearing?
A. I don't know.
Q. Okay. Were any of the -- other than Dr. Van Mol and Dr. Van Meter -- was Dr. Brignardello-Petersen reimbursed by AHCA for consultant services related to the development of the exclusion of treatment for gender dysphoria?
A. I don't know off the top of my head.
Q. What about Dr. James Cantor?
A. I don't know off the top of my head without consulting if there was an invoice.
Q. Is that true for all the experts?
A. I can't remember how exactly the contracts -- the contracted services were reimbursed.
Q. Were they reimbursed?
A. They were.
Q. Looking at Van Meter's form -- why did you sign that form for a $34,000 reimbursement if you didn't know what Van Meter was doing?
MR. PERKO: I'm going to object to form.
THE WITNESS: So I know that Van Meter was consulting as part of the project. I just don't know throughout the process all the specific details of that consultation.

BY MS. DEBRIERE:

Q. Would you assume each expert listed was similarly compensated for the amount that Dr. Van Meter and Van Mol were compensated?

A. I'm not going to assume. Just looking at the two invoices, they are very different.

Q. In what ways?

A. This one has a not to exceed amount. And then this one has as dollar amount.

Q. Okay. Is that the only way they're different?

A. No.

Q. How else are they different?

A. The one for Quinton Van Meter has specific information regarding his MFMP registration.

Q. What is MFMP?

A. My Florida Market Place.

Q. Okay. Any other ways that they're different?

A. Some of the other language is different. The dates are different. But aside from that, no.

Q. How often do you approve an After the Fact Request Form for reimbursement of outside expertise?

A. Not often.

Q. How many times have you done it for expertise not related to the treatment of gender dysphoria?

A. I can't recall if I actually approved the

invoice; but I believe there was a consultant for the Canadian Prescription Drug Importation Program at one point. And I just can't remember the time.

Q. Is that the only time you can remember?

A. Yes.

Q. Okay. So when you were approving these forms that don't come across your desk often, do they strike you as something that needed careful review?

A. The invoice itself?

Q. The reason for reimbursement.

A. Yes. But the invoice itself seems pretty straightforward that a reimbursement based on services provided -- that had already been provided would be signed.

Q. Did you do a carful review of the reason for reimbursement?

MR. PERKO: Object to form.

THE WITNESS: I guess I'm not sure what you mean by careful review. I personally was not involved in all of the consultation services provided. But I did meet with the team and knew that services were provided.

BY MS. DEBRIERE:

Q. Prior to you receiving this request for reimbursement, did you know these experts were being

relied on for consultation?
A. Yes.
Q. Did you have to approve that request?
A. I don't know if there was a request initiating the services. I don't remember.
Q. Was there a need to approve the decision to rely on outside experts?
MR. PERKO: Object to form.
BY MS. DEBRIERE:
Q. Was there a requirement that consulting with outside experts be approved prior to the consultation?
MR. PERKO: Object to form.
THE WITNESS: Can you repeat that question.
BY MS. DEBRIERE:
Q. Was there -- who consulted with the outside experts?
A. Again, I don't know the extent of what the consultation services were or who all was part of that.
Q. In order for them to -- in order for the team to develop the GAPMS report -- who wrote it -- in order for them to consult with outside experts, did it require your approval?
A. I don't recall ever approving them.
Q. And the team relying on outside experts to write the GAPMS report on gender dysphoria, did it

require the approval of D.D. Pickle?

MR. PERKO: Object to form.

THE WITNESS: I can't recall how the formal process was initiated.

And I do want to say relying on experts -- there was a lot of additional research done as well as part of the GAPMS process. So I wanted to clarify that.

BY MS. DEBRIERE:

Q. But part of writing the report was consulting with these outside experts; correct?

A. Yes.

Q. And you don't know who made the decision to consult with those experts; is that right?

A. Correct.

Q. Whoever made the decision -- we don't know who that is. But whoever made the decision, did they require approval before they could implement that decision?

MR. PERKO: Object to form.

THE WITNESS: I don't know.

BY MS. DEBRIERE:

Q. Okay. As the bureau chief who oversees the team who wrote this GAPMS report, did you have an expectation that they would come to you for approval to

consult with outside experts that would then be paid?
A. Can you repeat that.
Q. As the bureau chief, the person who oversees the team that wrote the GAPMS report on treatment for gender dysphoria, did you have an expectation that they first ask you permission before they consulted with outside experts who charged for their services?
A. No.
Q. Why didn't you have that expectation?
A. I can't really answer that, as I was not part of the decision to consult with the experts.
Q. Who was part of the decision?
A. I don't know.
Q. But you know you were not part of it. Okay.
At the bottom of the After the Request Form, it states -- for Dr. Van Mol, which is Exhibit 10 -- it states supervisor approval is required. What does that mean?
A. In the routing hierarchy for approval.
Q. Approval of what?
A. For invoices for My Florida Marketplace. I'm the direct supervisor of D.D. Pickle.
Q. So your approval is required for D.D. Pickle to pay this bill?
A. Yes.

Q. Okay. But your approval was not required for D.D. Pickle to incur this bill?

MR. PERKO: Object to form.

THE WITNESS: I don't remember if there was a formal approval to initiate the services.

BY MS. DEBRIERE:

Q. Did you have to have approval to authorize this payment to Dr. Van Mol?

A. I can't remember. I don't know where this goes next in the routing.

Q. Okay. Did you ask permission to approve this from anyone?

A. I can't remember a specific conversation. But I knew it was approved by the agency to consult with -- to have the consultant services.

Q. Okay. Related to that, the last sentence is -- how did you know that?

A. How did I know what? Can you repeat that.

Q. I think you had responded that you knew the agency had approved it. And so my question was: How did you know that?

A. I don't remember the specific conversation. But I do know that it was approved by leadership.

Q. And how do you know that?

A. There must have been a conversation. I just

can't remember an exact -- if there was an exact conversation or a document I signed. I can't remember.

Q. Okay. Do you remember who you had the conversation with or had the document signed by?

A. I don't remember.

Q. The last sentence under that first paragraph, it says, "Verification of the availability of funding and approval from executive leadership was obtained prior to any work being conducted for this project."

Who was that executive leadership?

A. The majority of my discussions were with my direct supervisor. But Tom Wallace ultimately signed the report. And I don't know outside of that who all was involved.

Q. Do you need a break?

A. Yeah.

(Brief recess.)

BY MS. DEBRIERE:

Q. Who decided the amount in those forms?

A. I don't know how the amount was negotiated.

Q. Did you follow up on the amount being requested -- ask any questions about it?

A. I can't remember if I asked any questions. But, again, as it states on the form -- the availability of funding approval for leadership.

Q. So you think whoever that leadership was had approved that amount?
A. I don't know how the reimbursement for the services was negotiated.
Q. Okay. So you didn't ask any questions about the amount or what it was being used for?
MR. PERKO: Object to form.
THE WITNESS: I knew what it was being used for. But I can't remember if I asked any questions about the amount.
MS. DEBRIERE: Okay.
THE WITNESS: I can't recall any.
BY MS. DEBRIERE:
Q. Are there any subject matter experts for the services listed in that exclusion that are full-time employees with the agency?
MR. PERKO: Object to form.
THE WITNESS: I don't believe so, since the services outlined in the policy were not clearly outlined in any existing coverage policy that would have had any subject matter expert assigned to the coverage policy.
BY MS. DEBRIERE:
Q. Do you have a subject matter expert in surgery?
A. I don't know if it's one person or more than

one. We have an area that's responsible for the coverage policies we talked about earlier that contain coverage for surgical procedures.

Q. So you have a subject matter expert for outpatient hospital services?

A. Yes.

Q. And do you have a subject matter expert for inpatient hospital services?

A. I don't know if it's the same person.

Q. Okay. But do you have a subject matter expert in inpatient, it just might be the same person?

A. There's a team responsible for oversight of those policies, yes.

Q. Was that team involved in the development of this GAPMS report?

A. Not to my knowledge. But I can't speak to all of the research and activities that were part of the completion of the project.

Q. Who is that team -- that team that are the suggest matter experts in inpatient and outpatient hospital services?

A. That would be John Matson under Jesse Bottcher who is responsible for primary and preventive surgeries, including dental.

Q. Okay. You had mentioned before the break that

you had communications about the development of the GAPMS report with legal counsel; is that correct?

A. I believe so. I can't remember if it was part of the report or part of the rule. I know for sure with the rulemaking process that legal is involved in that process normally. And they were in this instance as well.

Q. Did that legal include outside counsel?

A. I don't know. I don't remember meeting with outside counsel.

Q. Okay. You don't remember with meeting with Holtzman & Vogel, the law firm?

A. No.

Q. Did you communicate with any other State agencies like the Florida Department of Health about the GAPMS report?

A. I personally did not.

Q. Did anybody at the Agency for Health Care Administration?

A. I don't know.

Q. Did you communicate -- were there any communications between AHCA and the Governor about the development of this report?

A. I don't know.

Q. Did you personally communicate with the

Governor's office about the development of this report?

A. No.

Q. Did you personally communicate with the Governor's office about the exclusion of treatment for gender dysphoria?

A. No.

Q. Were there any communications between AHCA and people that provided public comment at the hearing?

A. I'm sorry; can you repeat the question.

Q. Were there any communications between AHCA -- prior to the hearing, were there any communications between AHCA and the people who provided public comment at the hearing?

A. I don't know.

Q. Did you personally communicate with anyone who provided public content at the hearing prior to the hearing?

A. No.

Q. Was anyone at AHCA aware that specific people would provide public content at the hearing prior to the hearing?

A. I don't know.

Q. Were you aware that there were any specific members of the public who would provide public comment at the hearing prior to the hearing?

A. No.
Q. The person who is identified as authoring the GAPMS report on gender dysphoria is Matt Brackett; correct?
A. Yes, he was the primary author.
Q. Do you recall a meeting between you, Mr. Weida, and Mr. Bottcher discussing who the author of the report would be?
A. I don't remember if Jesse was in any of the conversations.
Q. Okay. Did Jesse ever express a concern to you about someone -- anyone on his team drafting the GAPMS report on gender dysphoria treatment?
A. Prior to?
Q. At any time.
A. Can you say that again.
Q. Did Mr. Bottcher ever express to you concerns over someone on his team drafting the GAPMS report on the treatment for gender dysphoria?
A. Not that I can recall.
Q. Was the GAPMS decision tree used before you decided to undertake the GAPMS analysis that is contained in the June 2022 report?
A. I don't know.
Q. Who would have that information?

Did Secretary Marstiller in her letter to Tom Wallace -- did she direct Tom Wallace to undertake the GAPMS process?

MR. PERKO: Object to form.

THE WITNESS: I can't recall the details of the letter.

MS. DEBRIERE: Me neither. Do we have a copy?

MS. CHRISS: It's the last page right there. It's Attachment A.

MS. DEBRIERE: Oh. It's the very back of Exhibit --

MR. PERKO: It's not attached to ours.

MS. DEBRIERE: Okay.

MS. DUNN: Why don't you pull it off and mark it as a separate exhibit.

MS. DEBRIERE: So we'll mark the letter from Simone Marstiller dated April 10th, 2022, as Exhibit 11. And that's Attachment A to the June 2022, GAPMS report related to the treatment for gender dysphoria.

(Plaintiff's Exhibit No. 11 was marked for identification.)

BY MS. DEBRIERE:

Q. So in this letter is Secretary Marstiller directing Mr. Wallace to undertake the GAPMS process?

MR. PERKO: Object to form.
THE WITNESS: Yes.
BY MS. DEBRIERE:
Q. Do you think that Secretary Marstiller undertook a decision tree prior to writing this letter and sending it to Mr. Wallace?
MR. PERKO: Object to form.
THE WITNESS: I don't know.
BY MS. DEBRIERE:
Q. Has the secretary of AHCA ever personally completed a decision tree on the GAPMS process?
A. I don't know.
Q. Would it be unusual if the secretary of AHCA completed a decision tree on the GAPMS process?
A. I don't know.
Q. Looking at the GAPMS report itself, does it contain a fiscal analysis?
A. I don't know off the top of my head.
Q. Yeah. No, take your time.
A. No, I do not see a fiscal analysis.
Q. Do you see anything related to cost effectiveness?
A. No.
Q. Do you know why that was not included?
A. No.

Q. Is budget neutrality in reaching a GAPMS decision important?

MR. PERKO: Object to form.

THE WITNESS: I don't know. I know that that's something when determining a coverage determination that is taken into consideration. But specific to the GAPMS process, I don't know.

BY MS. DEBRIERE:

Q. Okay. Who would know that? Would the person responsible for writing GAPMS reports know that?

A. Yes. Or Jesse Bottcher or Matt Brackett.

Q. Or Jeff English?

A. Yes.

Q. Who decided which services would be assessed in the GAPMS report?

A. I don't know.

Q. So typically a request comes in from the public for a specific service. In this instance, the request came from the secretary; correct?

A. Yes.

Q. So would it have been the secretary who decided which services should be assessed?

A. I can't recall how the decision was made. I do know that that was part of conversations we had during this process. But I can't recall exactly how the

decision was finalized.

Q. Was there ever a discussion about narrowing the types of services to be included?

A. I don't recall specifically. I know that the coverage of behavioral health services was something that was always covered. But outside of that specifically, I can't remember.

Q. Was there ever any discussion about undertaking the GAPMS process for a set of services simultaneously as opposed to a single service?

A. Can you clarify.

Q. In the discussions about writing the report or assessing the services, were there ever any concerns raised about undertaking the process for a set of services as opposed to a single one?

A. I don't recall specifically.

Q. Was there any discussion about EPSDT?

A. I can't remember if it was specific to the development of the report or the rulemaking more specifically. But I believe there was.

Q. And what was discussed?

MR. PERKO: I'm going to object for a second. Did that include counsel? Did those discussions include counsel?

THE WITNESS: Yes.

MR. PERKO: And who was that?
THE WITNESS: I don't remember.
MR. PERKO: But it did include counsel?
THE WITNESS: I believe it was a discussion on the rulemaking with counsel.
MR. PERKO: I'm going to instruct the witness not to answer.
BY MS. DEBRIERE:
Q. Were all discussions had in front of counsel about EPSDT?
A. I don't remember.
Q. How about comparability?
MR. PERKO: I'll ask you the same thing.
THE WITNESS: Can you remind me what you're referencing when you say comparability. I think you mentioned that at the very beginning of the day.
MS. DEBRIERE: Comparability is a requirement under the Federal Medicaid Act in the administration of the coverage of the Medicaid services.
THE WITNESS: I don't recall.
BY MS. DEBRIERE:
Q. Were there communications with the Centers for Medicare and Medicaid Services about AHCA's decision to assess whether the services listed in the exclusion were experimental?

A. I don't know. I personally did not have any conversations.

Q. Who communicates with CMS about those kinds of things?

A. Those kinds of things, you mean changes in coverage?

Q. Does CMS ever reach out to AHCA about concerns they have about an action that they're taking related to Medicaid coverage?

A. Yes.

Q. Who would be the point person at AHCA to have those conversations?

A. So if an update to a federal authority were needed, that would be either Catherine Mcgrath or myself.

Q. Okay. You would not have had -- have you had any conversations with CMS about the GAPMS report related to the treatment of gender dysphoria?

A. No.

Q. Has Catherine?

A. Not to my knowledge.

Q. Have you had any conversations with CMS about the exclusion of the treatment for gender dysphoria as contained in Rule 59G-1.050?

A. I have not.

Q. Has Catherine?
A. Not to my knowledge.
Q. Has anybody else at AHCA?
A. I don't know.
Q. Okay. You mentioned a second ago that you weren't sure if you were talking about EPSDTs as it related to the report or the rulemaking. When you make that distinction, are you referring the writing of the report versus the adoption of the rule?
A. Yes.
Q. Okay. How was it decided that the conclusions from the GAPMS report should be adopted into rule?
A. I'm trying to remember the specific conversations. But I do believe those were conversations with counsel as well.
Q. Okay. The expedited GAPMS that you were involved in from start to finish, was that decision adopted into rule?
A. It was just one other GAPMS. And I don't believe any rule update was needed for that one.
Q. Why was a rule update needed for this GAPMS report?
MR. PERKO: If that's discussion with counsel, I will instruct you not to answer.
THE WITNESS: Because there was not any policy

language that clearly explained the coverage, it was determined that developing policy language was the best approach. Anything past that was -- how that process went was conversation with counsel.

BY MS. DEBRIERE:

Q. How often in your day-to-day in making decisions in your job do you have to consult with legal counsel?

A. Often.

Q. Okay. So does that mean -- okay. Like, every day?

A. I would say the majority of days.

Q. Okay.

A. And I'll just specify. I have some sort of contact or interaction with legal counsel.

Q. On most days?

A. Yes. And, again, because the rule promulgation does require review and some other documents we route are managed care contracts also route through legal. Just to give you examples of why it's quite often.

Q. They're all contacts with legal counsel about things related to the doing of your job?

A. The development of policy and -- yes.

Q. Okay. So there was -- you said there was -- the reason that it needed to be adopted into rule is

because there was no clear coverage policy on the services at issue; is that correct?

A. I can't remember all the factors that went into the decision. But I believe that was one of the factors when it was assessed that there was no coverage policy specific to the treatment of gender dysphoria.

Q. Were there existing coverage guidelines?

A. Not to my knowledge.

Q. At the time were you aware of existing pharmacy policies related to the treatment of gender dysphoria?

A. At what time? Can you specify.

Q. It was 2017/2016.

A. I was not with the agency in 2016. So I would not have been part of any development of policy at that time.

Q. But when you were deciding whether to adopt this exclusion into the rule, did you do any review of existing coverage guidelines or past coverage decisions?

A. I believe we did. But I can't recall the specifics.

Q. Did you review past GAPMS reports regarding the treatment of gender dysphoria?

A. I believe we did.

Q. And why weren't they enough to establish the coverage policy?

MR. PERKO: Object to form.

THE WITNESS: I don't know.

BY MS. DEBRIERE:

Q. 59G-1.050, Subpart 7 -- it bans Medicaid coverage for puberty blockers, hormones and surgery if done so to treat gender dysphoria; correct?

A. It covers that Medicaid does not cover those services for the treatment of gender dysphoria; correct.

Q. Does it distinguish between adults and children?

A. No.

Q. So the exclusion applies equally to both children and adults; is that correct?

A. Yes.

Q. Okay. And it excludes Medicaid coverage for puberty blockers and hormones and surgery to treat gender dysphoria, but it does not exclude Medicaid coverage for those services to treat other diagnoses; is that correct?

A. Correct.

Q. And I just forgot you answer; I apologize. Were you involved in the rule hearing held on July 8th regarding the exclusion set forth in 1.050?

A. No.

Q. Were you aware that outside legal counsel

participated in that hearing?

A. I don't know if I was made aware prior to today. I can't remember.

Q. At rule hearings you've been in in the past, do the State agencies have a panel of subject matter experts who respond to public comment during the hearing?

A. I can't cite the specific language, but it's actually required per Chapter 120 that the agency has subject matter experts who can speak to the contents of whatever is being discussed at a public meeting available.

Q. Other than the July 8th hearing, are you aware of any time that any agency has retained outside subject matter experts to participate on that panel?

A. I'm not aware of any.

Q. To your knowledge is this the only time AHCA has created a slogan to advertise the conclusion in its GAPMS memo?

MR. PERKO: Object to form.

BY MS. DEBRIERE:

Q. Are you aware of the slogan "Let kids be kids"?

A. I've seen the website, yes.

Q. In your experience has AHCA ever designed a website page for any other rule adoption?

A. I can't remember if it was specific to rule adoption. But I can think of a couple of examples where we created web pages for policy updates; for example, for home and community based settings rule that was an administrative rule as well as a federal rule. There's a specific external web page for updates regarding that and information on that rule.

When we received the American Rescue Act funding approval, we created a web page with information on that funding and what those funding could be used for. So I feel like it's pretty common for us to update our external website when there's important information to communicate.

Q. In those other examples, did AHCA ever develop a slogan to go along with those web pages?

A. Not in the examples that I used, I don't think.

Q. Did they issue press releases?

A. The American Rescue Act funding may have had one. But I can't remember.

Q. Okay. Just going back quickly. My co-counsel has pointed out to me that in Chapter 120 it says that at the rule hearing agency staff must be available but not an expert. Do you think maybe you were confusing that requirement that an expert needs to be available under 120?

A. I think it says an agency staff with knowledge.

Q. Okay. "Ensure that staff are available to explain the agency's proposal and to respond to questions or comments regarding the rule." Is that the provision you were --

A. Yes.

Q. -- thinking of? Okay.

Typically when AHCA decides not to cover a particular service, where is that information included?

MR. PERKO: Object to form.

THE WITNESS: I think it depends on the policy. Each policy has different exclusions, if there are any, with the service. Or most of the coverage policies include a section specific to exclusions.

MS. DEBRIERE: Most of the policies? Is that what you said? I apologize.

THE WITNESS: Most of the coverage policies.

BY MS. DEBRIERE:

Q. Okay. And those coverage policies are service specific policies?

A. The examples I was thinking of, yes, were service specific coverage policies and include -- I can't remember exactly what section in the example of where to find that in the coverage policy. But, yes, it would include exclusion specific to the coverage that's

being described in the policy.

Q. Okay. The exclusion on the treatment of gender dysphoria, is it in a service specific coverage policy?

A. No. This is a general Medicaid policy. But it does include coverage information including what Florida Medicaid reimburses for and what it does not.

Q. Does it speak to the exclusion of any other services under Florida Medicaid but those services excluded for the treatment of gender dysphoria?

A. Yes.

Q. Which ones?

A. No. 4 is an example. (4)(b), that speaks to that Florida Medicaid does not cover continuous services after the emergency has been alleviated.

Q. Is that a specific service? Or is that the length of time for any service?

A. I apologize. It's emergency service. It's under the section for emergency Medicaid.

Q. But, again, is that speaking to the coverage of any service deemed emergency?

A. It's specific to emergency services provided to aliens who meet all Florida Medicaid eligibility requirements except for citizenship.

Q. It says an exclusion under Subpart 7 speaks specifically to the exclusion of sex reassignment

surgeries; correct?

A. Services for the treatment of gender dysphoria.

Q. But only three services.

A. Four.

Q. What are examples of procedures that alter primary or secondary sexual characteristics that are not related to surgery?

A. I don't know.

Q. Just going back to the surgery, why not include that in service specific policies that discuss surgery?

A. Can you repeat the question.

Q. Looking at the exclusion of sex reassignment surgeries, why was that not included in the coverage policies related to surgeries that we discussed earlier?

A. I don't recall the specific conversation on how it was decided that this was the most appropriate policy. And I do believe that most of that conversation was with counsel.

Q. So same question for puberty blockers. Why wouldn't you include that in a pharmacy coverage policy?

A. I don't know.

Q. And Subpart 7's subject line is "Gender Dysphoria"; correct?

A. Yes.

Q. And that's a diagnosis?

A. I don't know clinically the definition.
Q. We've been talking about the treatment of gender dysphoria; right?
A. Yes.
Q. So in order to exclude treatment of gender dysphoria, it would be the exclusion of a treatment for a diagnosis; correct?
A. Yes. But I can't speak to the specifics of the diagnosis or what that means in clinical terms.
Q. Okay. For the July 8th hearing, do you know how many public comments were submitted?
A. I don't know.
Q. Do you know if it was more than 100?
MR. PERKO: Asked and answered.
THE WITNESS: I know it was a lot.
BY MS. DEBRIERE:
Q. Okay. And do you know how long it took AHCA to review and consider the comments before adopting the final rule?
A. I don't know the length of time. But I know that all the public comments were reviewed.
Q. Who reviewed them?
A. I know Cole Giering did. I don't know if anybody else -- if anybody else did.
Q. Okay. So after the July 8th hearing up until

the final adoption of the rule, other than reviewing and considering public comment, what else did AHCA do before adopting the rule?

A. Can you repeat the question.

Q. So after the July 8th hearing up until the final adoption of the rule, other than reviewing public comment, what other activities did AHCA undertake in deciding to adopt the rule?

A. I don't know. I can't remember specific to this rule. But after it's been determined there's no changes needed to the rule, the filing for adoption would be the next step.

Q. How do you reach that decision that no changes should be made?

MR. PERKO: Object to form.

THE WITNESS: There's various factors involved in that decision. And it really depends on the specific circumstances.

MS. DEBRIERE: Okay. I don't know what it would be labeled, but do you have an exhibit -- it's an email from Ms. McGriff to Magellan.

MS. CHRISS: Yes. The email exchange between Magellan and AHCA.

MS. DEBRIERE: Thank you.

Court Reporter, just for your reference what we

just marked as Exhibit 12 is Bates stamped DEF_00288753 to 000288756.

(Plaintiff's Exhibit No. 12 was marked for identification.)

BY MS. DEBRIERE:

Q. So Magellan is emailing several people at AHCA. And she says, "Attached are the internal criteria not publicly posted."

What are the internal criteria?

A. I don't know.

Q. Does Magellan rely on internal criteria for the coverage of Medicaid services?

A. I don't know.

Q. What does "CCM" mean? It's right after that sentence. "Attached are the internal criteria 'not publicly posted' CCM."

A. I don't know.

Q. What does gender code mean?

A. I don't know.

Q. Do you know hot had significance of "B for both" is?

A. I do not.

Q. Who is Linda Simone Moore?

A. Who?

Q. So there's a sender up top here -- I'm sorry.

Leslie.

A. Moore-Simons.

Q. I need reading glasses. Leslie Moore-Simons. That's exactly right.

A. I don't know.

Q. Okay. Who is Susan Williams?

A. She works for Ashley Peterson in the pharmacy unit in the Bureau of Medicaid Policy.

Q. Okay. And who is Arlene Elliott? I'll just note the date that Arlene's email was sent was 8/21/2017.

A. Currently Arlene Elliott is in a different division at the Agency for Health Care Administration. But at this time, she was the AHCA administrator over the pharmacy policy section of the Bureau of Medicaid Policy.

Q. And what unit is she in now?

A. I don't know. She's no longer in the division of Medicaid.

Q. What division is she in?

A. I believe it's Health Quality Assurance.

Q. Do you know when she left her position in the Bureau of Medicaid Policy?

A. I believe it was spring or summer 2021. I'm not sure the exact date.

Q. Okay. Earlier in the exchange -- and yet dated later -- is the email dated April 20th, 2022, from Elica King-Wilson at Magellan. And she's included some language which she underlined and bolded. And it says, "All requests require vetting by AHCA before a final determination is made."

And it appears this is related to a final determination as to whether -- well, it says -- Leslie noted, "MMA does have an internal gender dysphoria criteria, which is attached."

MMA stands for?

A. I don't know in what context she's using it.

Q. Okay.

A. But to me, MMA would normally stand for managed medical assistance.

Q. I assume you're confused because this is coming from Magellan which is not a managed medical assistance program; is that right?

A. Yes. So I don't know if that's what she's referring to.

Q. And it says, "This internal document serves for GnRH analog use to delay puberty in adolescents with gender dysphoria." This document was provided by AHCA due to a fair hearing request received for Lupron for a recipient with this diagnosis" -- meaning gender

dysphoria. And it goes on with the underlying language that all of those requests -- coverage of Lupron for gender dysphoria -- need to be vetted by AHCA before a final determination is made.

Were you familiar with that process at all?

A. No. I don't know what process they were referring to.

Q. Would Ashley Peterson know?

A. I don't know. But she does work closely with Magellan.

Q. Okay. Did AHCA work with managed care plans to implement the exclusion in 1.050?

A. They were notified. But the specifics of how that communication happened, I can't recall.

MS. DEBRIERE: Okay. Can I have the SMMC Policy Transmittal relating to the Non-Coverage of Gender Dysphoria Treatment.

MS. DUNN: Do you want the policy or the emails?

MS. DEBRIERE: Could you do both.

MS. DUNN: Do you want them together?

MS. DEBRIERE: That would be great. But separate exhibits.

(Plaintiff's Exhibit No. 13 was marked for identification.)

(Plaintiff's Exhibit No. 14 was marked for identification.)

BY MS. DEBRIERE:

Q. So right now we're looking at an email that's Bates stamped DEF_000258835 to 000258838. It's an email from D.D. Pickle CC-ing you. And it's to Jason Weida.

In this -- I'm sorry. Looking specifically at an email dated August 22, 2022, from D.D. to Ashley Peterson and Matt Brackett. It states, "Ashley, Ann wants to include the 60-day language in the alert?"

What alert is D.D. Pickle referring to?

A. I believe it was the provider alert.

Q. And what's a provider alert?

A. It's the main way -- one of the main ways we communicate information to our providers and external stakeholders.

(Plaintiff's Exhibit No. 15 was marked for identification.)

BY MS. DEBRIERE:

Q. I'm handing you a document that's marked as Exhibit 15, called Florida Medicaid Health Care Alert Sign-Off Form, starting at Bates stamp DEF_000258839.

Is this the provider alert you were referring to?

A. Yes. It looks to be a provider alert regarding

the coverage of treatment for gender dysphoria.

MS. DEBRIERE: Okay. And then what was the transmittal?

MS. DUNN: It was 14.

BY MS. DEBRIERE:

Q. No. 14 -- can you look at that document. And that's Bates stamped DEF_000258833.

What is this document?

A. It looks to be a draft -- a policy transmittal.

Q. And who does that go to?

A. This specific one is marked to be sent to the medical assistance and specialty plans.

Q. Is that the final that was sent?

A. It does not appear so, no.

Q. Okay. How do you know that?

A. The policy transmittal number is not completed and it's not signed.

Q. Okay. Going back to the provider alert, was that the final that was sent?

A. I can't tell from this document if this was the final that was sent.

Q. Okay. Would you be able to tell from any of the versions whether it was the final?

A. Seeing the actual email alert would be how I would make sure. My team actually does not send out the

final provider alerts. So that's typically how I would look at the final version.

Q. Okay. And the policy transmittals and the provider alerts -- are those available on the agency's website? The finals?

A. Yes.

Q. Okay. So turning back to that email exchange where D.D. mentions you by name.

What is 60-day language?

A. I believe she's referring to the continuity of care.

Q. What is continuity of care?

A. It's a contract requirement for the plans to provide services for a period of time. I don't know if it's specific to when they change plans. I can't recall the exact contract language, but it's a contract provision.

Q. And are services previously being covered supposed to be continue being covered for 60 days according to the 60-day language?

A. I can't recall the exact parameters of the requirement.

Q. Do you recall why --

MR. PERKO: Counsel, we're getting on seven hours here.

BY MS. DEBRIERE:

Q. Do you recall why the 60-day language -- you wanted the 60-day language included in this alert?

A. I can't remember the conversation around this. And I can't speak for D.D.

Q. Well, D.D. is speaking for you; right?

The subject is "GD Policy Transmittal"; correct?

A. Yes.

Q. And what does "GD" stand for?

A. Based on the attachments, I would conclude that it is for gender dysphoria.

Q. Okay. And this would be discussion had after the rule was adopted excluding coverage of services for the treatment of gender dysphoria; correct?

A. Can you repeat that question.

Q. The date of this email is after the rule was adopted to exclude coverage of services for treatment of gender dysphoria.

A. I believe so.

Q. You don't recall why you thought it was important to have the 60-day language included in the alert?

A. I don't recall the specifics of the conversation. But I believe it was to ensure if there

was any current reimbursement or authorization that would apply.

Q. Current authorization of treatment of gender dysphoria?

A. Of the services listed in Rule 1.050, No. 7.

Q. Did any plans state to AHCA that they would continue coverage of the services excluded in the rule even though that rule had been adopted?

A. I don't know.

Q. Who would know that?

A. I don't know who it would have gone to. If there was a question, the communications typically go through the contract managers.

Q. Okay. Do you know if all plans have implemented the exclusion contained in the rule?

A. I don't know.

Q. Are you familiar with the variance and waiver process under Chapter 120?

A. Yes.

Q. Okay. What is the purpose of that statute?

MR. PERKO: Object to form; calls for a legal conclusion.

BY MS. DEBRIERE:

Q. What it the purpose of the variance and waiver process?

MR. PERKO: Object to form.

THE WITNESS: I don't know.

MR. PERKO: Counsel, we're getting on seven hours here.

MS. DEBRIERE: All right. Let me just consult with my team for just a second.

(Brief recess.)

MS. DEBRIERE: We'll all set with direct.

Thank you for your time, Ms. Dalton.

MR. PERKO: I don't have any questions.

THE COURT REPORTER: Would you like to read or waive?

THE WITNESS: Read.

THE COURT REPORTER: Would you like to order at this time?

MS. DEBRIERE: Yes.

THE COURT REPORTER: Would anybody like to order a copy?

MR. PERKO: Yes.

(This deposition was concluded at 6:05 p.m.)

- - -

CERTIFICATE OF OATH

STATE OF FLORIDA:
COUNTY OF LEON:

I, GREG T. SMITH, Notary Public, State of Florida, do hereby certify that ANN DALTON personally appeared before me on January 24, 2023 and was duly sworn and produced her ID badge as identification.

Signed this 30TH day of JANUARY, 2023.

GREG T. SMITH

Notary Public, State of Florida
My Commission No.: GG933698
Expires: March 21, 2024

CERTIFICATE OF REPORTER

STATE OF FLORIDA:

COUNTY OF LEON:

I, GREG T. SMITH, Notary Public, State of Florida, certify that I was authorized to and did stenographically report the deposition of ANN DALTON; that a review of the transcript was requested; and that the foregoing transcript, pages 6 through 175, is a true and accurate record of my stenographic notes.

I further certify that I am not a relative, employee, or attorney, or counsel of any of the parties, nor am I a relative or employee of any of the parties' attorneys or counsel connected with the action, nor am I financially interested in the action.

DATED this 30TH day of JANUARY, 2023.

Greg T. Smith

GREG T. SMITH

KATHERINE J. DEBRIERE, ESQUIRE
DEBRIERE@FLORIDAHEALTHJUSTICE.ORG

January 30, 2023

RE: Dekker, August v Marstiller, Simone
1-24-23 Ann Dalton, Job# 5662663

The above-referenced transcript is available for review.

(The witness/You) should read the testimony to verify its accuracy. If there are any changes, (the witness/you) should note those with the reason on the attached Errata Sheet.

(The witness/You) should, please, date and sign the Errata Sheet and email to the deposing attorney as well as to Veritext at Transcripts-fl@veritext.com and copies will be emailed to all ordering parties.

It is suggested that the completed errata be returned 30 days from receipt of testimony, as considered reasonable under Federal rules*, however, there is no Florida statute to this regard.

If the witness fails to do so, the transcript may be used as if signed.

Yours,
Veritext Legal Solutions

*Federal Civil Procedure Rule 30(e)/Florida Civil Procedure Rule 1.310(e).

Dekker, August v Marstiller, Simone
1-24-23 Ann Dalton, Job# 5662663

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Under penalties of perjury, I declare that I have read the foregoing document and that the facts stated in it are true.

_____ _____
(WITNESS NAME) DATE

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Federal Rules of Civil Procedure

Rule 30

(e) Review By the Witness; Changes.

(1) Review; Statement of Changes. On request by the deponent or a party before the deposition is completed, the deponent must be allowed 30 days after being notified by the officer that the transcript or recording is available in which:

(A) to review the transcript or recording; and

(B) if there are changes in form or substance, to sign a statement listing the changes and the reasons for making them.

(2) Changes Indicated in the Officer's Certificate. The officer must note in the certificate prescribed by Rule 30(f)(1) whether a review was requested and, if so, must attach any changes the deponent makes during the 30-day period.

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Veritext Legal Solutions represents that the foregoing transcript is a true, correct and complete transcript of the colloquies, questions and answers as submitted by the court reporter. Veritext Legal Solutions further represents that the attached exhibits, if any, are true, correct and complete documents as submitted by the court reporter and/or attorneys in relation to this deposition and that the documents were processed in accordance with our litigation support and production standards.

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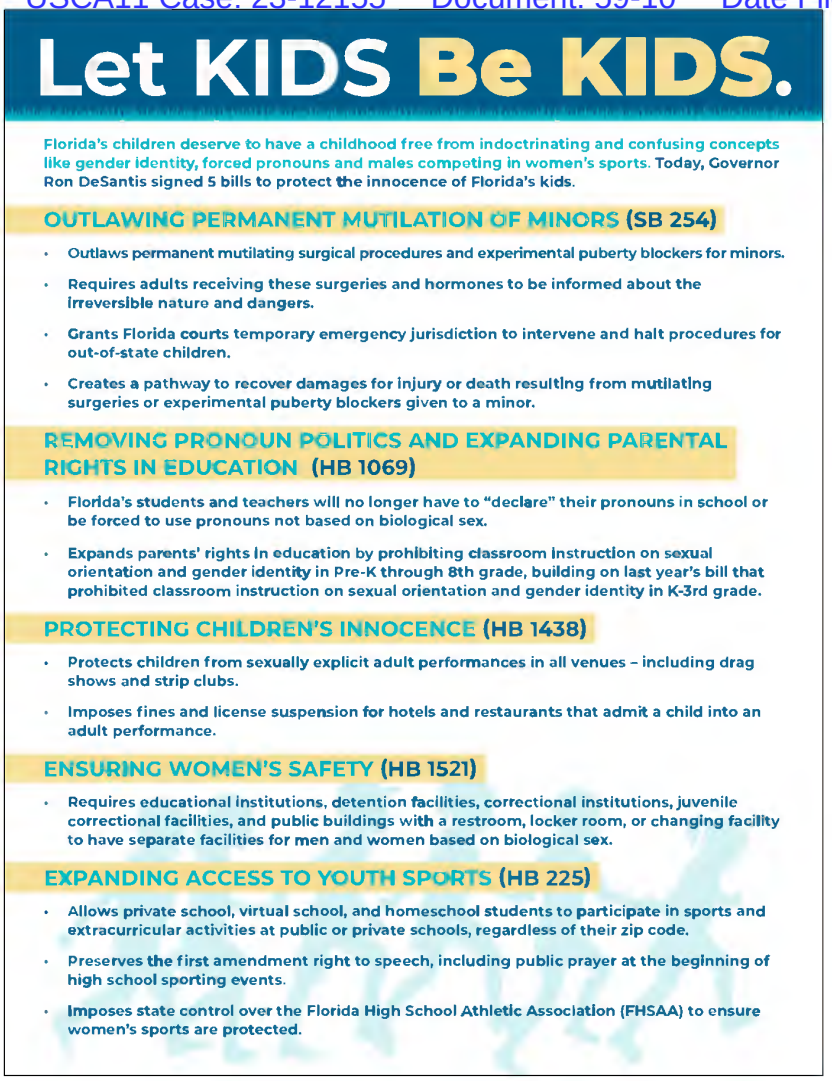
TAB 236-1

Governor Ron DeSantis Signs Sweeping Legislation to Protect the Innocence of Florida's Children

On May 17, 2023, in News Releases, by Staff

TAMPA, Fla. — Today, Governor Ron DeSantis signed the Let Kids Be Kids bill package to protect Florida's children from permanent mutilating surgical procedures, gender identity politics in schools, and attending sexually explicit adult performances. For more information about the bills signed today, click here.

Pl. Trial Ex. 365



Let KIDS Be KIDS.

Florida's children deserve to have a childhood free from indoctrinating and confusing concepts like gender identity, forced pronouns and males competing in women's sports. Today, Governor Ron DeSantis signed 5 bills to protect the innocence of Florida's kids.

OUTLAWING PERMANENT MUTILATION OF MINORS (SB 254)

- Outlaws permanent mutilating surgical procedures and experimental puberty blockers for minors.
- Requires adults receiving these surgeries and hormones to be informed about the irreversible nature and dangers.
- Grants Florida courts temporary emergency jurisdiction to intervene and halt procedures for out-of-state children.
- Creates a pathway to recover damages for injury or death resulting from mutilating surgeries or experimental puberty blockers given to a minor.

REMOVING PRONOUN POLITICS AND EXPANDING PARENTAL RIGHTS IN EDUCATION (HB 1069)

- Florida's students and teachers will no longer have to "declare" their pronouns in school or be forced to use pronouns not based on biological sex.
- Expands parents' rights in education by prohibiting classroom instruction on sexual orientation and gender identity in Pre-K through 8th grade, building on last year's bill that prohibited classroom instruction on sexual orientation and gender identity in K-3rd grade.

PROTECTING CHILDREN'S INNOCENCE (HB 1438)

- Protects children from sexually explicit adult performances in all venues – including drag shows and strip clubs.
- Imposes fines and license suspension for hotels and restaurants that admit a child into an adult performance.

ENSURING WOMEN'S SAFETY (HB 1521)

- Requires educational institutions, detention facilities, correctional institutions, juvenile correctional facilities, and public buildings with a restroom, locker room, or changing facility to have separate facilities for men and women based on biological sex.

EXPANDING ACCESS TO YOUTH SPORTS (HB 225)

- Allows private school, virtual school, and homeschool students to participate in sports and extracurricular activities at public or private schools, regardless of their zip code.
- Preserves the first amendment right to speech, including public prayer at the beginning of high school sporting events.
- Imposes state control over the Florida High School Athletic Association (FHSAA) to ensure women's sports are protected.

"Florida is proud to lead the way in standing up for our children," said **Governor Ron DeSantis**. "As the world goes mad, Florida represents a refuge of sanity and a citadel of normalcy."

"Thank you to Governor Ron DeSantis for continuing to implement legislation to keep our students safe and our schools focused on education, not indoctrination," said **Commissioner of Education Manny Diaz, Jr.** "Today's actions make it clear – educators in Florida are expected to teach our standards, and not interject their own opinions or worldview into the classroom. The Department will remain focused on teaching students core subjects, rather than woke gender ideology or inappropriate topics."

"Thank you Governor DeSantis for signing legislation that protects our children," said **Agency for Health Care Administration Secretary Jason Weida.** "Florida is following the science to elevate our standards of care to protect kids from harmful drugs and surgeries."

SB 254 – Treatments for Sex Reassignment:

- Prohibits sex reassignment surgeries and experimental puberty blockers for children.
- Requires adult patients who are receiving these medications or surgeries to be informed about the dangers and irreversible nature of these procedures and to give written, informed consent.
- Provides courts temporary emergency jurisdiction to step in and halt sex reassignment procedures for out-of-state children present in Florida.
- Creates a pathway for individuals to obtain damages when they were injured or killed after receiving sex reassignment surgeries or medications as minors.

HB 1069 protects students from having to declare their pronouns in school. Additionally, this bill expands parental rights in education by prohibiting classroom instruction on sexual orientation and gender identity in Pre-K through 8th grade.

HB 1438 protects children from sexually explicit performances in all venues. This bill prohibits a person from knowingly admitting a minor to an adult performance. Additionally, this legislation authorizes the Department of Business and Professional Regulation to fine, suspend, or revoke the operating or alcohol licenses of hotels or restaurants if they admit a child into an adult performance.

HB 1521 ensures that Florida's bathrooms, changing rooms, and locker rooms are safe places for women. The bill requires educational institutions, detention facilities, correctional institutions, juvenile correctional facilities, and public buildings with a restroom or changing facility to designate

separate facilities based on biological sex or to provide one-person unisex facilities.

The Governor also signed legislation to protect youth sports in Florida and ensure that all students can play sports without interference from extremist bureaucratic boards. HB 225 allows private school, virtual school, and home school students to participate in sports and other extracurricular activities at other public or private schools, regardless of zip code.

HB 225 also reorganizes the FHSAA Board of Directors to 13 members, instead of the current 16 members. Four members will be elected by school representative members while eight members will be appointed by the governor, and the final member will be the Commissioner of Education or his designee. This bill also allows teams to provide brief opening remarks, including prayers, before high school athletic contests.

###

Comments are closed.

Contact Governor DeSantis

Executive Office of Governor Ron DeSantis
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(850) 488-7146

Email Governor DeSantis

Email First Lady DeSantis

Email Lt. Governor Nuñez

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TAB 241

United States District Court

CIVIL MINUTES - TRIAL

Case No.: 4:22cv325-RH

Dates: May 9-11, 2023
Dates: May 17-19, 2023
Dates: May 22, 2023

AUGUST DEKKER et al. v. JASON WEIDA et al.

PROCEEDINGS: Bench Trial held. Ruling by Court: The Court's ruling will be made in a separate order to follow.

PRESENT: ROBERT L. HINKLE, U.S. DISTRICT JUDGE

Cindy Markley
Deputy Clerk

Megan Hague, Judy Gagnon
Court Reporters

Attorneys for Plaintiffs:
Omar Gonzalez-Pagan
Katherine DeBriere
Jennifer Altman
Carl Charles
Abigail Coursolle
Catherine McKee
Simone Chriss
Chelsea Dunn
Joseph Little
William Miller
Gary Shaw
Shani Rivaux

Attorneys for Defendants:
Mohammad Jazil
Gary Perko
Michael Beato

☐ Case called and continued to _____.
☒ COURT TRIAL
☐ JURY TRIAL. Jury impaneled and sworn in. See separate minutes for jury selection.
☐ Jury retires to deliberate at _____ on _____.
☐ Jury returns at ____ on _____.
☐ JURY VERDICT. See signed verdict.
☐ Jury polled ☐ Polling waived ☐ Mistrial declared
☒ FINDINGS BY COURT: Order to follow.
☐ JUDGMENT BY COURT for ☐ Plaintiff ☐ Defendant for $_____
☐ Findings, Conclusion of Law, Judgment to be prepared by ☐ Plaintiff ☐ Defendant
☐ Briefs to be filed ☐ Plaintiff ☐ Defendant ☐ Reply
☐ Continued to _____ for ☐ setting trial ☐ further trial

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA

CIVIL MINUTES

JUDGE ROBERT L. HINKLE
Cindy Markley, Courtroom Deputy
Megan Hague, Official Court Reporter (May 9-11, May 22)
Judy Gagnon, Contract Court Reporter (May 17-19)

Case: 4:22cv325-RH
Legend: Plaintiff Attys: Omar Gonzalez-Pagan
Katherine DeBriere
Jennifer Altman
Carl Charles
Abigail Coursolle
Catherine McKee
Simone Chriss
Chelsea Dunn
Joseph Little
William Miller
Gary Shaw
Shani Rivaux
Defense Attys: Mohammad Jazil
Gary Perko
Michael Beato

Bench Trial – Day 1
DATE: May 9, 2023

9:00 Court in session
Opening statement by Plaintiffs (Gonzalez-Pagan)
9:18 Opening statement by Defense (Jazil)
9:21 Plaintiff moves to admit all joint exhibits (Gonzalez-Pagan)
9:21 Ruling by Court: Exhibits identified in ECF 219 are admitted.
9:23 Plaintiff Witness:
Dan Karasic – sworn, direct (DeBriere)
Plaintiff Exhibit 359 – previously admitted
Defendant Exhibit 16 – previously admitted
10:51 Court in recess

11:05 Court in session
Continued direct examination (DeBriere)
12:04 Cross examination (Jazil)
Defendant Exhibit 16 – previously admitted
Plaintiff Exhibit 45 – shown to witness
Defendant Exhibit 24 – previously admitted
Plaintiff Exhibit 140 – shown to witness
1:07 Court in recess

2:11 Court in session
Continued cross examination (Jazil)
Defendant Exhibit 24 – previously admitted
Defendant Exhibit 28 – shown to witness
2:42 Redirect (DeBriere)
2:55 Court inquires of witness
3:15 Plaintiff Witness:
Daniel Evan Shumer – sworn, direct (Coursolle)
Plaintiff Exhibit 360 – previously admitted
3:39 Court in recess

3:47 Court in session
Continued direct (Coursolle)
5:05 Parties discuss legislation
5:13 Plaintiff expresses intent to move to amend the complaint (Gonzalez-Pagan)
5:14 Response by Defense (Jazil)
5:18 Court addresses the parties
5:26 Court in recess

Bench Trial – Day 2
DATE: May 10, 2023

9:01 Court in session
Parties discuss housekeeping matters
9:04 Cross examination of Dr. Shumer (Jazil)
Defendant Exhibit 24 – previously admitted
Plaintiff Exhibit 188 – shown to witness
Plaintiff Exhibit 235 – previously admitted (not published)
Plaintiff Exhibit 236B – previously admitted (not published)
9:37 Redirect (Coursolle)
9:52 Court inquires of witness
9:58 Additional cross examination (Jazil)
10:00 Court in recess

10:10 Court in session
Plaintiff Witness:
Loren Sloan Schechter – sworn, direct (McKee)
Plaintiff Exhibit 362 – previously admitted
10:43 Cross examination (Perko)
Plaintiff Exhibit 34 – shown to witness
Defendant Exhibit 24 – previously admitted
Plaintiff Exhibit 234A – previously admitted (not published)
10:56 Redirect (McKee)
10:56 Court inquires of witness
11:00 Plaintiff Witness:
Armand Herbert Matheny Antommaria – sworn, direct (Charles)
Plaintiff Exhibit 157 – shown to witness
Defendant Exhibit 24 – previously admitted
12:14 Court in recess

1:15 Court in session
Continued direct (Charles)
Defendant Exhibit 28 – shown to witness
2:18 Cross examination (Perko)
Plaintiff Exhibit 157 – shown to witness
Plaintiff Exhibit 5 – shown to witness
Defendant Exhibit 8 – shown to witness
2:35 Court inquires of witness
2:41 Plaintiff Witness:
Jeffrey A. English – sworn, direct (Altman)
Plaintiff Exhibit 18 – marked, ID'd, admitted
Defendant Exhibit 6 – marked, ID'd, admitted
Plaintiff Exhibit 30 – marked, ID'd, admitted
Plaintiff Exhibit 23 – previously admitted
Plaintiff Exhibit 238 – previously admitted
Plaintiff Exhibit 302 – shown to witness
3:34 Court in recess

3:50 Court in session
Continued direct (Altman)
3:54 Cross examination (Perko)
Plaintiff Exhibit 23 – previously admitted
4:01 Redirect (Altman)
4:04 Court inquires of witness
4:07 Plaintiff Witness:
Kellan Baker – sworn, direct (Dunn)
Plaintiff Exhibit 363 – previously admitted
Plaintiff Exhibit 142 – shown to witness
Plaintiff Exhibit 71 – marked, ID'd, admitted
5:06 Parties discuss schedule
5:15 Court in recess

Bench Trial – Day 3
DATE: May 11, 2023

9:00 Court in session
Cross examination of Dr. Baker (Beato)
Plaintiff Exhibit 23 – previously admitted
Defendant Exhibit 4 – previously admitted
9:06 Redirect (Dunn)
9:09 Statement to the Court by Plaintiffs regarding schedule (Gonzalez-Pagan)
9:11 Plaintiff Witness:
Johanna Olson-Kennedy – sworn, direct (Gonzalez-Pagan)
Plaintiff Exhibit 361 – previously admitted
Plaintiff Exhibit 141 – shown to witness
10:41 Court in recess

10:55 Court in session
Cross examination (Jazil)
Defendant Exhibit 16 – previously admitted
Plaintiff Exhibit 141 – shown to witness

Plaintiff Exhibit 164 – shown to witness
Plaintiff Exhibit 176 – shown to witness
11:20 Redirect (Gonzalez-Pagan)
11:23 Court inquires of witness
11:30 Additional redirect (Gonzalez-Pagan)
11:34 Plaintiff Witness:
Jane Doe – sworn, direct (Coursolle)
11:57 Cross examination (Jazil)
12:01 Court inquires of witness
12:03 Plaintiff Witness:
Brit Rothstein – sworn, direct (Chriss)
12:43 Cross examination (Jazil)
Plaintiff Exhibit 234 – previously admitted (not published)
12:48 Court in recess

1:50 Court in session
Plaintiff Witness:
August Dekker – sworn, direct (Charles)
2:44 Cross examination (Jazil)
Plaintiff Exhibit 237A – previously admitted (not published)
2:47 Redirect (Charles)
Plaintiff Exhibit 237A – previously admitted (not published)
2:51 Plaintiff Witness:
Jade Ladue – sworn, direct (DeBriere)
3:31 Parties discuss schedule
3:32 Ruling by Court: Trial will continue Wednesday, May 17, at 9:00 a.m.
3:33 Court in recess

Bench Trial – Day 4
DATE: May 17, 2023

9:00 Court in session
Plaintiff Witness:
Elliot Kale Edmiston – sworn, direct (Rivaux)
Plaintiff Exhibit 357 – previously admitted
9:35 Cross examination (Beato)
Defendant Exhibit 16 – previously admitted
Defendant Exhibit 24 – previously admitted
Plaintiff Exhibit 351 – shown to witness
Plaintiff Exhibit 352 – shown to witness
Plaintiff Exhibit 354 – shown to witness
9:57 Court inquires of witness
10:02 Additional cross examination (Beato)
10:04 Plaintiff Witness:
Kim Hutton – sworn, direct (Little)
10:30 Cross examination (Perko)
10:31 Redirect (Little)
10:32 Court in recess

10:50 Court in session
10:51 Plaintiff Witness (by Zoom):
Aron Christopher Janssen – sworn, direct (Gonzalez-Pagan)
Plaintiff Exhibit 364 – previously admitted
11:45 Cross examination (Perko)
11:50 Redirect (Gonzalez-Pagan)
11:51 Court inquires of witness
11:54 Plaintiff addresses the court to clarify a previously admitted exhibit (Gonzalez-Pagan)
11:56 Response by Defense (Jazil)
11:59 Plaintiff moves to admit Plaintiff Exhibits 24, 21, 22, 74, 27, 28, 67, 62, 63, 295, 296, 330, 331, 332, 333, 291, 292, 292A, 313, 313A, 314, 315, 316, 254, 255, 263, 276, 346 (DeBriere)
Ruling by Court: Those exhibits are admitted with the exhibit of Plaintiff Exhibit 330.
12:31 Plaintiff moves to admit Plaintiff Exhibit 302 (Dunn)
12:32 Ruling by Court: Plaintiff Exhibit 302 is admitted.
12:32 Plaintiff moves to enter into evidence deposition designations (Dunn)
12:33 Ruling by Court: Those are admitted (Brackett, Dalton, Donovan). (Plaintiff will post them on the docket.)
12:36 Plaintiffs rest
Parties discuss possibility of amending complaint
12:43 Court in recess

1:45 Court in session
Defense Witness:
Paul William Hruz – sworn, direct (Perko)
Defendant Exhibit 29 – previously admitted
Defendant Exhibit 8 – shown to witness
Defendant Exhibit 9 – shown to witness
Defendant Exhibit 10 – shown to witness
Defendant Exhibit 11 – shown to witness
Defendant Exhibit 12 – shown to witness
Defendant Exhibit 13 – shown to witness
Defendant Exhibit 14 – shown to witness
2:55 Court inquires of witness
2:57 Cross examination (Rivaux)
Plaintiff Exhibit 46 – marked, ID'd, admitted
Plaintiff Exhibit 37 – marked, ID'd, admitted
Plaintiff Exhibit 38 – marked, ID'd, admitted
Plaintiff Exhibit 36 – marked, ID'd, admitted
Plaintiff Exhibit 39 – marked, ID'd, admitted
Plaintiff Exhibit 40 – marked, ID'd, admitted
Plaintiff Exhibit 41 – marked, ID'd, admitted
Plaintiff Exhibit 42 – marked, ID'd, admitted
Plaintiff Exhibit 45 – marked, ID'd, admitted
Plaintiff Exhibit 47 – marked, ID'd, admitted
Plaintiff Exhibit 48 – marked, ID'd, admitted
Plaintiff Exhibit 49 – marked, ID'd, admitted
3:40 Court in recess

3:55 Court in session
Continued cross examination (Rivaux)
Plaintiff Exhibit 43 – marked, ID'd, admitted

Defendant Exhibit 10 – shown to witness
Defendant Exhibit 13 – shown to witness
Plaintiff Exhibit 170 – shown to witness
4:19 Redirect (Perko)
Plaintiff Exhibit 38 – previously admitted
4:27 Defense moves to admit Defendant Exhibits 8-14 (Perko)
Ruling by Court: Those exhibits are admitted.
4:27 Court inquires of witness
4:50 Court in recess

Bench Trial – Day 5
DATE: May 18, 2023

9:01 Court in session
Defense Witness:
Stephen B. Levine – sworn, direct (Perko)
Defendant Exhibit 32 – previously admitted
9:50 Cross examination (Charles)
Defendant Exhibit 16 – previously admitted
10:35 Court in recess

10:50 Court in session
Continued cross examination (Charles)
11:06 Redirect (Perko)
11:15 Court inquires of witness
12:07 Court in recess

1:10 Court in session
Defense Witness:
Patrick Walter Lappert – sworn, direct (Jazil)
Defendant Exhibit 31 – previously admitted
1:27 Voir dire of witness by Plaintiff (Miller)
1:32 Continued direct (Jazil)
Defendant Exhibit 16 – previously admitted
1:52 Cross examination (Miller)
Plaintiff Exhibit 81 – shown to witness
Plaintiff Exhibit 135 – shown to witness
2:01 Defense Witness:
Kristopher Edward Kaliebe – sworn, direct (Perko)
Defendant Exhibit 30 – previously admitted
2:09 Voir dire of witness by Plaintiff (Gonzalez-Pagan)
2:15 Court inquires of witness
2:20 Continued direct (Perko)
2:35 Cross examination (Gonzalez-Pagan)
2:46 Court inquires of witness
2:53 Parties discuss schedule and other housekeeping matters
2:58 Ruling by Court: Motion to amend complaint is granted.
3:01 Parties discuss preliminary injunction in the Doe case
3:09 Ruling by Court: Motion for leave to amend the complaint in the Doe case is granted.
3:10 Court in recess

3:14 Court in session
Parties discuss preliminary injunction and temporary restraining order in the Doe case
3:26 Court in recess

Bench Trial – Day 6
DATE: May 19, 2023

10:20 Court in session
Defense Witness:
Ann Dalton – sworn, direct (Beato)
Plaintiff Exhibit 238 – previously admitted
10:35 Cross examination (Dunn)
Plaintiff Exhibit 29 – shown to witness
Plaintiff Exhibit 291 – previously admitted
Plaintiff Exhibit 321 – previously admitted
Plaintiff Exhibit 320 – previously admitted
Plaintiff Exhibit 292A – previously admitted
Plaintiff Exhibit 294 – previously admitted
Plaintiff Exhibit 295 – previously admitted
Plaintiff Exhibit 296 – previously admitted
Plaintiff Exhibit 297A – previously admitted
11:07 Court inquires of witness
11:14 Additional cross examination (Dunn)
11:15 Court in recess

11:20 Court in session
11:21 Defense Witness:
John Matthew Brackett – sworn, direct (Jazil)
Plaintiff Exhibit 23 – previously admitted
Defendant Exhibit 6 – previously admitted
Plaintiff Exhibit 329 – previously admitted
Plaintiff Exhibit 297A – previously admitted
Defendant Exhibits 1, 2, 3 – previously admitted
Plaintiff Exhibits 240, 242, 244 – previously admitted
Plaintiff Exhibit 326 – previously admitted
12:08 Cross examination (DeBriere)
Plaintiff Exhibit 141 – shown to witness
Plaintiff Exhibit 18 – previously admitted
Plaintiff Exhibit 166 – shown to witness
Plaintiff Exhibit 176 – shown to witness
Plaintiff Exhibit 151 – shown to witness
Plaintiff Exhibit 154 – shown to witness
Plaintiff Exhibit 155 – shown to witness
Plaintiff Exhibit 192 – shown to witness
Plaintiff Exhibit 23 – previously admitted
Plaintiff Exhibit 331 – previously admitted
Plaintiff Exhibit 284 – previously admitted
Plaintiff Exhibit 285 – previously admitted
Plaintiff Exhibit 303 – previously admitted
Plaintiff Exhibit 286A – previously admitted
Plaintiff Exhibit 291 – previously admitted

Plaintiff Exhibit 365 – marked, ID'd, admitted
12:57 Redirect (Jazil)
Defendant Exhibit 6 – previously admitted
Plaintiff Exhibit 176 – shown to witness
1:01 Court inquires of witness
1:09 Additional redirect (Jazil)
1:10 Additional cross examination (DeBriere)
1:11 Court in recess

Bench Trial – Day 7
DATE: May 22, 2023

9:00 Court in session
Defense Witness (by Zoom):
Sophie Kerttu Scott – sworn, direct (Jazil)
Defendant Exhibit 33 – previously admitted
9:13 Voir dire by Defense (Shaw)
9:18 Plaintiff moves to exclude witness testimony
9:21 Ruling by Court: The motion to exclude testimony in its entirety is denied.
9:25 Continued direct (Jazil)
9:57 Cross examination (Shaw)
10:15 Redirect (Jazil)
10:18 Court inquires of the witness
10:25 Defense rests
10:25 Court in recess

10:40 Court in session
10:43 Closing argument by Plaintiffs (Gonzalez-Pagan)
11:30 Closing argument by Defense (Jazil)
12:31 Rebuttal by Plaintiffs (Gonzalez-Pagan)
12:37 Ruling by Court: An order will follow.
12:40 Court adjourned

TAB 241-1

AO 187 (Rev. 7/87) Exhibit and Witness List

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF FLORIDA

AUGUST DEKKER et al.

v.

JASON WEIDA et al.

EXHIBIT LIST

Case Number: 4:22cv325-RH

PRESIDING JUDGE	PLAINTIFF ATTORNEYS	DEFENSE ATTORNEYS
Robert L. Hinkle	Omar Gonzalez-Pagan, Katherine DeBriere, et al.	Mohammad Jazil, Gary Perko, Michael Beato
HEARING DATE	**COURT REPORTERS**	**COURTROOM DEPUTY**
May 9-11, 2023 May 17-19, 2023 May 22, 2023	Megan Hague (May 9-11, May 22) Judy Gagnon (May 17-19)	Cindy Markley

PLTF. NO.	DFT. NO.	MARKED	ADMITTED	DESCRIPTION OF EXHIBITS
				All exhibits were pre-filed on the docket
1		5/9/23	5/9/23	Defendants' Response to Pls' First Set of Request for Admissions
2		5/9/23	5/9/23	Defendants' Response to Pls' First Set of Interrogatories
3		5/9/23	5/9/23	Defendants' Response to Pls' Second Set of Interrogatories
4		5/9/23	5/9/23	Pls' First Set of Request for Admissions
18		5/10/23	5/10/23	AHCA GAPMS June 2022
19		5/9/23	5/9/23	Marstiller Letter to Wallace re AHCA June 2022 GAPMS
20		5/9/23	5/9/23	Fla. Admin. Code R. 59G-1.050
21		5/17/23	5/17/23	Fla. Admin. Code R. 59G-1.010
22		5/17/23	5/17/23	Florida Medicaid Definitions Policy (Aug. 2017)
23		5/9/23	5/9/23	Fla. Admin. Code R. 59G-1.035
		5/9/23	5/9/23	AHCA's Preferred Drug List, accessible at: https://ahca.myflorida.com/content/download/8681/file/PDL.pdf (online only); including but not limited to the criteria for testosterone: https://ahca.myflorida.com/content/download/6451/file/Testosterone_Criteria.pdf
		5/9/23	5/9/23	AHCA's Drug Criteria, accessible at: https://ahca.myflorida.com/medicaid/prescribed-drugs/drug-criteria (online only)
24		5/17/23	5/17/23	AHCA's Automated Prior Authorizations and Bypass Lists 01-2023
25		5/9/23	5/9/23	DRUGDEX listing for Testosterone
26		5/9/23	5/9/23	DRUGDEX listing for Estradiol
27		5/17/23	5/17/23	Prior Authorization Criteria - Testosterone
28		5/17/23	5/17/23	Agency Responses to Plaintiffs' Questions: March 1, 2023
30		5/10/23	5/10/23	Email communication between Jeffrey English and Devona Pickle – 3/22/22

33		5/9/23	5/9/23	DSM 5 Gender Dysphoria
36		5/17/23	5/17/23	AACAP Statement Responding to Efforts to Ban Care (Nov. 8, 2019)
37		5/17/23	5/17/23	AAFP – Care for Transgender Patients
38		5/17/23	5/17/23	AAP – Ensuring Comprehensive Care and Support
39		5/17/23	5/17/23	ACOG Committee Opinion on Health Care for Transgender Individuals (March 2021)
40		5/17/12	5/17/23	ACP – Attacks on Gender-Affirming and Transgender Health Care (May 3, 2022)
41		5/17/23	5/17/23	LGBT Health Disparities Policy, ACOP
42		5/17/23	5/17/23	AMA Letter to Nat'l Gov. Assoc. (April 26, 2021)
43		5/17/23	5/17/23	AMA/GLMA Issue Brief on health insurance coverage for gender-affirming care
45		5/17/23	5/17/23	APA, Guidelines for Psychological Practice with Transgender and Gender Non-conforming People
46		5/17/23	5/17/23	APA Resolution on Gender Identity Change Efforts (Feb. 2021)
47		5/17/23	5/17/23	APA Position Statement Trans and Gender Diverse Youth (July 2020)
48		5/17/23	5/17/23	APA Position Statement on Access to Care (July 2018)
49		5/17/23	5/17/23	Endocrine Society Transgender Health Position Statement
62		5/17/23	5/17/23	Ctrs. for Medicare & Medicaid Servs., EPSDT – A Guide for States: Coverage in the Medicaid Benefit for Children and Adolescents
63		5/17/23	5/17/23	Ctrs. for Medicare & Medicaid Servs., CMCS Informational Bulletin (July 21, 2022), https://www.medicaid.gov/federal-policy-guidance/downloads/cib07212022.pdf
64		5/9/23	5/9/23	Ctrs. for Medicare & Medicaid Servs., Decision Memo for Gender Dysphoria and Surgery (Aug. 20, 2016)
67		5/17/23	5/17/23	FDA, Understanding Unapproved Use of Approved Drugs "Off Label," (2018), https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label
71		5/10/23	5/10/23	Dep't of Health & Human Servs., Departmental Appeals Bd., Appellate Div., Decision No. 2576 (May 30, 2014), hhs.gov/sites/default/files/static/dab/decisions/boarddecisions/2014/dab2576.pdf
72		5/9/23	5/9/23	OASH, Gender-Affirming Care and Young People
74		5/17/23	5/17/23	SAMHSA, Moving Beyond Change Efforts (2023)
229		5/9/23	5/9/23	Template Notice of Adverse Benefit Determination
230		5/9/23	5/9/23	Template Notice of Plan Appeal Resolution
231		5/9/23	5/9/23	Sample AHCA Final Order – 20-FH0855
232		5/9/23	5/9/23	Medical records of August Dekker
234		5/9/23	5/9/23	Medical records of Brit Rothstein
234A		5/9/23	5/9/23	Medical records of Brit Rothstein
235		5/9/23	5/9/23	Medical records of K.F.
235A		5/9/23	5/9/23	Medical records of K.F.
236		5/9/23	5/9/23	Medical records of S.D.

236A		5/9/23	5/9/23	Medical records of S.D.
236B		5/9/23	5/9/23	Medical records of S.D.
236C		5/9/23	5/9/23	Medical records of S.D.
237		5/9/23	5/9/23	Dekker medical records
237A		5/9/23	5/9/23	Dekker medical records
238		5/9/23	5/9/23	GAPMS Decision Tree Checklist
239		5/9/23	5/9/23	GAPMS – GnRH for treatment of gender dysphoria
240		5/9/23	5/9/23	GAPMS – GnRH for treatment of gender dysphoria
241		5/9/23	5/9/23	GAPMS – Cross Sex Hormone Therapy – 5/20/2022
242		5/9/23	5/9/23	GAPMS – Cross Sex Hormone Therapy Report (edited) - 5/20/2022
243		5/9/23	5/9/23	GAPMS – Cross Sex Hormone Therapy – 11/2/2016
244		5/9/23	5/9/23	GAPMS – Gender Confirmation Surgery (incomplete) – 7/19/2017
250		5/9/23	5/9/23	AHCA review of research – 7/25/2016
254		5/17/23	5/17/23	Arlene Elliot email re GnRH coverage – 8/29/2016
255		5/17/23	5/17/23	Rebecca Borgert email regarding Endocrine Society guidelines – 8/29/2016
256		5/9/23	5/9/23	AHCA GAPMS routing and tracking form for puberty suppression therapy – 8/31/2016
257		5/9/23	5/9/23	Special services criteria re GnRH coverage – 9/20/2016 (updated 11/17/17)
260		5/9/23	5/9/23	AHCA GAPMS routing and tracking form for cross-sex hormone therapy – 11/2/2016
263		5/17/23	5/17/23	Draft GAPMS re gender-affirming surgery – 7/19/2017
264		5/9/23	5/9/23	Email exchange re Medicaid coverage of gender affirming surgery – June 2018
264A		5/9/23	5/9/23	Email exchange re Medicaid coverage of gender affirming surgery – June 2018
265		5/9/23	5/9/23	AHCA routing form tracking response to MCO question about Medicaid coverage of surgery – June 2018
266		5/9/23	5/9/23	AHCA document closing the project re responding to MCO question about Medicaid coverage of surgery – June 2018
272		5/9/23	5/9/23	Email from Andy Bardos to Andrew Sheeran re Cantor and legal research – 4/11/2022
273		5/9/23	5/9/23	Email forwarded by Andrew Sheeran from Ashley Lukis scheduling a call with James Cantor – 4/13/2022
274		5/9/23	5/9/23	Email from Andrew Sheeran to Miriam Grossman – 4/14/2022
275		5/9/23	5/9/23	Email exchange between Andrew Sheeran and Romina Brignardello Petersen – 4/18/2022
276		5/17/23	5/17/23	Email from Susan Williams to Shantrice Green re GAPMS on cross-sex hormone therapy – 4/20/2022
277		5/9/23	5/9/23	Email from Amy Zitiello to Vern Hamilton regarding FDOH guidance – 4/20/2022
277A		5/9/23	5/9/23	Email from Amy Zitiello to Vern Hamilton regarding FDOH guidance – 4/20/2022
279		5/9/23	5/9/23	Communication between Jason Weida and Dr. Michelle Cretella – 4/21/2025

280		5/9/23	5/9/23	Communication between Romina Brignardello-Petersen and Jason Weida regarding types of surgeries on which to focus – 4/25/2022
281		5/9/23	5/9/23	Communication between Jason Weida and Vern Hamilton regarding planned response to Dr. Zitiello's question about FDOH guidance – 4/29/2022
282		5/9/23	5/9/23	Draft GAPMS on gender affirming surgery (with handwritten notes) - May 2022
283		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
283A		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
283B		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
283C		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
283D		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
283E		5/9/23	5/9/23	Jason Weida communication regarding report from Romina Brignardello-Petersen – 5/5/2022
284		5/9/23	5/9/23	Jason Weida communication regarding articles provided to him by Dr. Van Mol – 5/6/2022
285		5/9/23	5/9/23	Dr. Van Mol communication with Jason Weida and Matthew Brackett about gender affirming care – 5/7/022
286		5/9/23	5/9/23	Dr. Van Mol's edits to June 2022 GAPMS memo – 5/13/2022
286A		5/9/23	5/9/23	Dr. Van Mol's edits to June 2022 GAPMS memo – 5/13/2022
286B		5/9/23	5/9/23	Dr. Van Mol's edits to June 2022 GAPMS memo – 5/13/2022
287		5/9/23	5/9/23	Text message from Jason Weida regarding Eknes-Tucker and James Cantor – 5/17/2022
288		5/9/23	5/9/23	Email from Shantrice Green to Susan Williams and Kelly Rubin regarding the GAPMS memo on cross-sex hormone therapy – 5/20/2022
289		5/9/23	5/9/23	Draft of GAPMS cross-sex hormone therapy memo – 5/20/2022
291		5/17/23	5/17/23	Email between Dr. Van Mol and Jason Weida regarding reimbursement – 5/21/2022
292		5/17/23	5/17/23	Invoices from Romina Brignardello-Petersen – 5/24/2022
292A		5/17/23	5/17/23	Invoices from Romina Brignardello-Petersen – 5/24/2022
294		5/9/23	5/9/23	Projected Rulemaking Timeline – June 2022
295		5/17/23	5/17/23	Gender Dysphoria/Transgender Health Care Non-Legislative Pathway – June 2022
296		5/17/23	5/17/23	Gender Dysphoria/Transgender Health Care Policy Pathway – June 2022
297		5/9/23	5/9/23	AHCA GAPMS routing and tracking form for June 2022 GAPMS – 6/1/2022
297A		5/9/23	5/9/23	AHCA GAPMS routing and tracking form for June 2022 GAPMS – 6/1/2022
298		5/9/23	5/9/23	Communication between Ashley Peterson and Jason Weida regarding an inventory of gender affirming care – 6/3/2022
298A		5/9/23	5/9/23	Communication between Ashley Peterson and Jason Weida regarding an inventory of gender affirming care – 6/3/2022
299		5/9/23	5/9/23	Email communication between AHCA and Magellan regarding coverage of GnRH to treat gender dysphoria

300		5/9/23	5/9/23	AHCA communication regarding the Special Services Criteria for puberty blockers – 6/10/2022
301		5/9/23	5/9/23	Communication between Jason Weida and Dr. Van Mol about a witness for the July 8th hearing – 6/14/2022
302		5/17/23	5/17/23	Email communication between Dr. Christopher Cogle and Jeffrey English – 6/27/2022
303		5/9/23	5/9/23	Communication regarding meeting between Miriam Grossman, Dr. Van Mol, Jason Weida, Andrew Sheeran, and Holtzman Vogel regarding July 8th hearing – 6/30/2022
304		5/9/23	5/9/23	Communication between Dr. Van Mol and AHCA - 7/2/2022
305		5/9/23	5/9/23	Brief of the July 8th rule hearing – 7/8/2022
306		5/9/23	5/9/23	Transcript from July 8th rule hearing – 7/8/2022
307		5/9/23	5/9/23	Email from Miriam Grossman – 7/10/2022
308		5/9/23	5/9/23	Email communications with Jason Weida and Dr. Van Mol – 7/14/2022
309		5/9/23	5/9/23	Communications regarding AHCA's development of public comment binder provided to the consultants – 7/19/2022
310		5/9/23	5/9/23	Invoice from Dr. Van Meter – 8/4/2022
311		5/9/23	5/9/23	Communication to Jason Weida regarding witnesses for a hearing – 8/10/2022
312		5/9/23	5/9/23	Invoices from Dr. Van Mol – 8/11/2022
313		5/17/23	5/17/23	Email communications regarding implementation of 59G-1.050(7) - 8/22/2022
313A		5/17/23	5/17/23	Email communications regarding implementation of 59G-1.050(7) - 8/22/2022
314		5/17/23	5/17/23	Communication between AHCA and EOG regarding planned communications about June 2022 GAPMS and 59G-1.050(7) - 8/22/2022
315		5/17/23	5/17/23	SMMC Policy Transmittal draft regarding non-coverage of gender dysphoria treatments – August 22, 2022
316		5/17/23	5/17/23	AHCA Medicaid Health Care Alert regarding prohibition on coverage for gender affirming care
317		5/9/23	5/9/23	AHCA draft response to media regarding gender affirming care – 9/1/2022
318		5/9/23	5/9/23	List of appeals for denials of hormone therapy – 12/19/2022
319		5/9/23	5/9/23	List of requests for surgery to treat gender dysphoria – 12/19/2022
320		5/9/23	5/9/23	AHCA After the Fact Request form for Quentin Van Meter – 6/13/2022
321		5/9/23	5/9/23	AHCA After the Fact Request form for Andre Van Mol – 5/26/2022
322		5/9/23	5/9/23	Draft of welcome/opening remarks for July 8th rule hearing
323		5/9/23	5/9/23	Endocrine Society public comment
324		5/9/23	5/9/23	Yale public comment
325		5/9/23	5/9/23	American Academy of Pediatrics public comment
326		5/9/23	5/9/23	Florida Medicaid, Comment Summary for Rule 59G-1.050 (20 pages)
327		5/9/23	5/9/23	Florida Medicaid, Comment Summary for Rule 59G-1.050 (17 pages)
328		5/9/23	5/9/23	Email communication between Van Mol and Weida and attachment
328A		5/9/23	5/9/23	Email communication between Van Mol and Weida and attachment

329		5/9/23	5/9/23	Florida Medicaid & G/TAT, Andrea Van Mol – May 2022
331		5/17/23	5/17/23	GAPMS – Scleral Contact Lenses
332		5/17/23	5/17/23	GAPMS – Fractional Exhaled Nitric Oxide
333		5/17/23	5/17/23	GAPMS – Breast Pump
334		5/9/23	5/9/23	Email from Miriam Grossman – July 7, 2022
335		5/9/23	5/9/23	Proposed media response from Brock Juarez to Taryn Fenske – 8/29/2022
337		5/9/23	5/9/23	Email communication between Van Meter and AHCA Counsel
338		5/9/23	5/9/23	AHCA Microsoft Teams Meeting Invite
340		5/9/23	5/9/23	AHCA Van Meter Invoice
341		5/9/23	5/9/23	HCA Hearing on General Medicaid Policy
342		5/9/23	5/9/23	Email communication between Devona Pickle and Van Meter
343		5/9/23	5/9/23	Email communication between consultants, counsel, and Van Meter
344		5/9/23	5/9/23	AHCA Teams Meeting Invites
344A		5/9/23	5/9/23	AHCA Teams Meeting Invites
345		5/9/23	5/9/23	Email communication between AHCA and consultants
346		5/17/23	5/17/23	Email communication between Sheeran and Brignardello-Petersen
347		5/9/23	5/9/23	Email communication between Van Mol and Weida
348		5/9/23	5/9/23	Van Mol comments to Alstott letter
350		5/9/23	5/9/23	Email communication between Cantor and Weida
355		5/9/23	5/9/23	Spreadsheet summarizing Florida Medicaid coverage
356		5/9/23	5/9/23	DOJ, Dear State Attorneys General Letter re Transgender Youth (March 31, 2022)
357		5/9/23	5/9/23	Curriculum Vitae of Dr. Kale Edmiston
358		5/9/23	5/9/23	Curriculum Vitae of Dr. Armand Antommaria
359		5/9/23	5/9/23	Curriculum Vitae of Dr. Dan H. Karasic
360		5/9/23	5/9/23	Curriculum Vitae of Dr. Daniel Shumer
361		5/9/23	5/9/23	Curriculum Vitae of Dr. Johanna Olson-Kennedy
362		5/9/23	5/9/23	Curriculum Vitae of Dr. Loren S. Schechter
363		5/9/23	5/9/23	Curriculum Vitae of Kellan E. Baker, Ph.D.
364		5/9/23	5/9/23	Curriculum Vitae of Dr. Aron Janssen
365		5/19/23	5/19/23	Press Release
	1	5/9/23	5/9/23	U.S. Health and Human Services Notice and Guidance on Care
	2	5/9/23	5/9/23	U.S. Health and Human Services Fact Sheet on Gender-Affirming Care

	3	5/9/23	5/9/23	U.S. Department of Justice Letter to State Attorneys General
	4	5/9/23	5/9/23	Centers for Medicare and Medicaid Services Decision Memo for Gender Dysphoria and Gender Reassignment Surgery
	5	5/9/23	5/9/23	Florida Department of Health Fact Sheet on Treatments for Gender Dysphoria
	6	5/10/23	5/10/23	Florida Medicaid Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria (with attachments)
	8	5/17/23	5/17/23	Sweden's Care of Children and Adolescents with Gender Dysphoria, Summary of National Guidelines
	9	5/17/23	5/17/23	Finland's Recommendation of the Council for Choices in Health Care in Finland
	10	5/17/23	5/17/23	The Cass Review, Independent Review of Gender Identity Services for Children and Young People
	11	5/17/23	5/17/23	National Institute for Health and Care Excellence, Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria
	12	5/17/23	5/17/23	National Institute for Health and Care Excellence, Evidence Review: Gender-Affirming Hormones for Children and Adolescents with Gender Dysphoria
	13	5/17/23	5/17/23	France's Academie Nationale de Medecine Press Release
	14	5/17/23	5/17/23	The Royal Australian and New Zealand College of Psychiatrists' Position Statement on Gender-Affirming Care
	16	5/9/23	5/9/23	WPATH Standards of Care, Version 8
	17	5/9/23	5/9/23	WPATH Standards-of-Care-Revision Team Criteria
	18	5/9/23	5/9/23	WPATH's Press Release Regarding Florida Department of Health
	19	5/9/23	5/9/23	WPATH's Statement of Opposition to Florida Draft Rule Banning Gender Affirming Care for Adolescents
	20	5/9/23	5/9/23	WPATH's Press Release on National and International Issues
	21	5/9/23	5/9/23	WPATH's Letter to Japanese Officials
	22	5/9/23	5/9/23	WPATH's Press Release Regarding New York Times Article
	23	5/9/23	5/9/23	WPATH Press Release on United Kingdom Matter
	24	5/9/23	5/9/23	Endocrine Society Guidelines on Treatments for Gender Dysphoria
	26	5/9/23	5/9/23	American Academy of Pediatrics, Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents
	29	5/9/23	5/9/23	Curriculum Vitae of Dr. Paul Hruz
	30	5/9/23	5/9/23	Curriculum Vitae of Dr. Kristopher Kaliebe
	31	5/9/23	5/9/23	Curriculum Vitae of Dr. Patrick Lappert
	32	5/9/23	5/9/23	Curriculum Vitae of Dr. Stephen Levine
	33	5/9/23	5/9/23	Curriculum Vitae of Dr. Sophie Scott
	34	5/9/23	5/9/23	Curriculum Vitae of Dr. Quentin Van Meter
	35	5/9/23	5/9/23	Curriculum Vitae of Dr. Joseph Zanga
	36	5/9/23	5/9/23	Curriculum Vitae of Dr. Michael Laidlaw

TAB A

CERTIFICATE OF SERVICE

I hereby certify that on November 28, 2023, I filed a true and correct copy of the foregoing with the Clerk of the United States Court of Appeals for the Eleventh Circuit by using the appellate case filing CM/ECF system. Participants in the case are registered CM/ECF users, and service will be accomplished by the appellate CM/ECF system.

/s/ Omar Gonzalez-Pagan
Omar Gonzalez-Pagan