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

---

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 Kadel*, 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).

* * *

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

---

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.

---

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

---

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

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

PILLSBURY WINTHROP SHAW PITTMAN, LLP

Jennifer Altman (Fl. Bar No. 881384)
Shani Rivaux (Fl. Bar No. 42095)
600 Brickell Avenue, Suite 3100
Miami, FL 33131
(786) 913-4900
jennifer.altman@pillsbury.com
shani.rivaux@pillsbury.com

William C. Miller*
Gary J. Shaw*
1200 17th Street N.W.
Washington, D.C. 20036
(202) 663-8000
william.c.miller@pillsburylaw.com

Joe Little*
500 Capitol Mall, Suite 1800
Sacramento, CA 95814

LAMBDA LEGAL DEFENSE AND EDUCATION FUND, INC.

Omar Gonzalez-Pagan*
120 Wall Street, 19th Floor
New York, NY 10005
(212) 809-8585
ogonzalez-pagan@lambdalegal.org

Carl S. Charles*
1 West Court Square, Suite 105
Decatur, GA 30030
(404) 897-1880
ccharles@lambdalegal.org

SOUTHERN LEGAL COUNSEL, INC.

Simone Chriss (Fl. Bar No. 124062)
Chelsea Dunn (Fl. Bar No. 1013541)
1229 NW 12th Avenue

(916) 329-4700
joe.little@pillsburylaw.com

NATIONAL HEALTH LAW PROGRAM

Abigail Coursolle*
3701 Wilshire Boulevard, Suite 315
Los Angeles, CA 90010
(310) 736-1652
coursolle@healthlaw.org

Catherine McKee*
1512 E. Franklin Street, Suite 110
Chapel Hill, NC 27541
(919) 968-6308
mckee@healthlaw.org

Gainesville, FL 32601
(352) 271-8890
Simone.Chriss@southernlegal.org
Chelsea.Dunn@southernlegal.org

FLORIDA HEALTH JUSTICE PROJECT

Katy DeBriere (Fl. Bar No. 58506)
3900 Richmond Street
Jacksonville, FL 32205
(352) 278-6059
debriere@floridahealthjustice.org

* *Admitted pro hac vice*
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.

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

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 ABIGAIL COURSOLLE

Pursuant to 28 U.S.C.§ 1746, I, Abigail Coursolle, do hereby declare as follows:

1. I am over 18 years of age.

2. I am a Senior Attorney at the law firm of the National Health Law Program, 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' Motion to Exclude Expert Testimony of Dr. Michael K. Laidlaw.

5. Attached as **Exhibit 1** is a true and correct copy of the amended expert witness report of Dr. Michael K. Laidlaw, M.D. (including a copy of his references and curriculum vitae) in the above- captioned matter, which is dated February 17, 2023; the original version was served upon plaintiffs that same date, and the amended version (which added highlighting of portions designated by the parties as confidential), was served upon plaintiffs on February 21, 2023.

6. Attached as **Exhibit 2** is a true and correct copy of the expert witness rebuttal report of Dr. Michael K. Laidlaw, M.D. (including a copy of his references) in the above- captioned matter, which is dated March 10, 2023, and was served upon plaintiffs that same date.

7. Attached as **Exhibit 3** is a true and correct copy of an excerpt of the declaration of Dr. Michael K. Laidlaw, M.D. in the above- captioned matter, which is dated October 2, 2022, which was attached as Appendix Attachment 11 to Defendant's Opposition to Plaintiffs' Motion for Preliminary Injunction in the above-captioned matter, and was filed in this case on October 3, 2022.

8. Attached as **Exhibit 4** is a true and correct copy of excerpts of the transcript of the hearing on Plaintiffs' Motion for Preliminary Injunction in the above-captioned matter, which was held on October 12, 2022, and the transcript of which was provided to plaintiffs by Court Reporter Megan A. Hague that same date.

9. Attached as **Exhibit 5** is what I understand, upon information and belief, to be a true and correct copy of excerpts of the transcript of the deposition of Dr. Michael K. Laidlaw on September 2, 2022 taken in relation to *C.P. v. Blue Cross*, No. 3:20-cv-06145-RJB (W.D. Wa.).

10. Attached as **Exhibit 6** is a true and correct copy of the article "Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden Gender nonconforming youth: current perspectives," by Cecilia Dhejne et al., published in the scientific journal *PLoS ONE* on February 22, 2011.

11. Attached as **Exhibit 7** is a true and correct copy of the article "Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study" by Richard Bränström and John E. Pachankis, published in the scientific journal *American Journal of Psychiatry* in August, 2020.

12. Attached as **Exhibit 8** is a true and correct copy of the article "Most trans adults say transitioning made them more satisfied with their lives" by Casey Parks et al., published in the newspaper, *The Washington Post* on March 23, 2023.

13. Attached as **Exhibit 9** is a true and correct copy of the Center for Medicare & Medicaid Services August, 30 2016 "Decision Memo" on "Gender Dysphoria and Gender Reassignment Surgery."

14. Attached as **Exhibit 10** is a true and correct copy of the U.S. Department of Health & Human Services' Departmental Appeals Board May 30, 2014 Decision to remove the national exclusion of "Transsexual Surgery" from coverage in Medicare.

15. Attached as **Exhibit 11** is a true and correct copy of the article "Long-term outcomes of the treatment of central precocious puberty" by Federica Guaraldi et al., published in the scientific journal *European Journal of Endocrinology* in March, 2016.

16. Attached as **Exhibit 12** is a true and correct copy of the article "Fertility of Women Treated during Childhood with Triptorelin (Depot Formulation) for Central Precocious Puberty: The PREFER Study" by Laetitia Martinerie et al., published in the scientific journal *Hormone Research in Paediatrics* on March 26, 2021.

17. Attached as **Exhibit 13** is a true and correct copy of the article "Gender dysphoria in childhood" by Jiska Ristoria and Thomas D. Steensmab, published in the scientific journal *International Review of Psychology*, on January 7, 2016.

18. Attached as **Exhibit 14** is a true and correct copy of the article "Gender Identity 5 Years After Social Transition" by Kristina R. Olson et al., published in the scientific journal *Pediatrics*, in August, 2022.

19. Attached as **Exhibit 15** is a true and correct copy of the article "Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study" by Annelou L.C. de Vries et al., published in the scientific journal *Journal of Sexual Medicine*, in August, 2011.

20. Attached as **Exhibit 16** is a true and correct copy of excerpts of *Understanding the Well-Being of LGBTQI+ Populations*, a Consensus Study Report of the National Academies of Sciences, Engineering, and Medicine published in 2020.

21. Attached as **Exhibit 17** is a true and correct copy of the article "The Right to Best Care for Children Does Not Include the Right to Medical Transition" by Michael K. Laidlaw et al., published in the scientific journal, *The American Journal of Bioethics* on February 20, 2019.

22. Attached as **Exhibit 18** is a true and correct copy of a printout of the webpage "SAHM Response to Dr. Michelle Cretella," published by the Society for Adolescent Health & Medicine.

23. Attached as **Exhibit 19** is a true and correct copy of the article "Strangers in a Strange Land: How Our Founding Principles and a Bitter Pill Undo the Assimilation of US Catholics," by G. Kevin Donovan and Claudia Sotomayor, published in the academic journal, *The Linacre Quarterly*, in May, 2020.

24. Attached as **Exhibit 20** is a true and correct copy of Section 2.1.1 of

the American Medical Association's Code of Medical Ethics.

25. Attached as **Exhibit 21** is a true and correct copy of the article "Effect of antidepressant medications on semen parameters and male fertility," by Lauren A Beeder and Mary K Samplaski, published in the scientific journal, *International Journal of Urology*, on September 21, 2019.

26. Attached as **Exhibit 22** is a true and correct copy of the article "The effect of antidepressants on fertility," by Marianne M. Casilla-Lennon et al., published in the scientific journal, *American Journal of Obstetrics & Gynecology*, in September, 2016.

I declare under penalty of perjury that the foregoing is true and correct.

Dated this 7th day of April, 2023.

/s/ Abigail Coursolle
Abigail Coursolle

EXHIBIT 1

(REDACTED)

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

EXPERT REPORT OF MICHAEL K. LAIDLAW, M.D.

Confidential Un-Redacted Copy

ONLY for Court, Counsel, and Experts who have agreed to abide by the Protective Order in this case.

Highlighted text to be redacted in any public filing.

I, Michael K. Laidlaw, M.D., hereby declare as follows:

1. I am over the age of eighteen and submit this expert declaration based on my personal knowledge and experience.

2. I am a board-certified endocrinologist. I received my medical degree from the University of Southern California in 2001. I completed my residency in internal medicine at Los Angeles County/University of Southern California Medical Center in 2004. I also completed a fellowship in endocrinology, diabetes and metabolism at Los Angeles County/University of Southern California Medical Center in 2006.

3. The information provided regarding my professional background are detailed in my curriculum vitae. A true and correct copy of my curriculum vitae is attached as Exhibit A.

4. In my clinical practice as an endocrinologist, I evaluate and treat patients with hormonal and/or gland disorders. Hormone and gland disorders can cause or be associated with psychiatric symptoms, such as depression, anxiety, and other psychiatric symptoms. Therefore, I frequently assess and treat patients demonstrating psychiatric symptoms and determine whether their psychiatric symptoms are being caused by a hormonal issue, gland issue, or something else.

5. I have been retained by Defendants in the above-captioned lawsuit to provide an expert opinion on the efficacy and safety of sex reassignment treatment.

6. If called to testify in this matter, I would testify truthfully and based on my expert opinion. The opinions and conclusions I express herein are based on a reasonable degree of scientific certainty.

7. I have testified as an expert witness either at trial or in deposition in the following in the past four years:

a. 2022 Testified in Court. *August Dekker, et at. V Simone Marstiller, et al.*, Case No. 4:22-cv-00325 (N.D. Fla.). Report October 2, 2022.

b. 2022 Testified at Deposition. *C.P., by and through his parents, Patricia Pritchard and Nolle Pritchard, and Patricia Pritchard v. Blue Cross Blue Shield of Illnois*, Case No. 3:20-cv-06145 (W.D. Wash.)

c. 2021 Testified in Court and Deposition. *Juliana Paoli v. Joseph Hudson, et al.,* Case No. VCU279126 (CA Superior, Tulare County)

8. A list of my publications is contained in my curriculum vitae, which is attached as Attachment A.

9. I am being compensated at an hourly rate of $450 per hour plus expenses for my time spent preparing this declaration, and to prepare for and provide testimony in this matter. I am being compensated at an hourly rate of $650 for testimony at depositions or trial. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I may provide.

10. My opinions contained in this report are based on: (1) my clinical experience as an endocrinologist; (2) my clinical experience evaluating individuals who have or have had gender incongruence including a detransitioner; (3) my knowledge of research and studies regarding the treatment of gender dysphoria, including for minors and adults; and (4) my review of the various declarations submitted by Plaintiffs.

11. I was provided with and reviewed the following case-specific materials: The Florida Medicaid's "Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria"; the expert declaration of Johanna Olson-Kennedy; the expert declaration of Loren Schechter; the expert declaration of Dan H. Karasic; the expert declaration of Armand H. Matheny Antommaria; the declaration of Brit Rothstein; the declaration of August Dekker; the declaration of Jane Doe; the declaration of Jade Ladue; files from Florida Medicaid.

12. In my professional opinion, treatment interventions on behalf of children and adults diagnosed with gender dysphoria must be held to the same scientific standards as other medical treatments. These interventions must be optimal, efficacious, and safe. Any treatment which alters biological development in children should be used with extreme caution. Except in the case of a fatal injury or disease, the minor will become an adult and present to the adult physician. The adult

physician must be able to have a thorough understanding of any condition which alters the biological development of children and, in the case of the endocrinologist, be knowledgeable about the long term effects of hormones on the human body, particularly when the hormones are being used in ways that alter development.

13. The following expresses my expert opinion regarding minors and adults who present with a disparity between their biological sex and internal feeling about their gender, specifically with regard to the use of social transition, medications which block normal pubertal development, the applications of hormones of the opposite sex, and surgical procedures that alter the genitalia and/or breasts for those individuals.

I. Background

A. Endocrine Disorders

14. Before discussing gender dysphoria and gender affirmative therapy from the perspective of an endocrinologist, it is helpful to discuss the background of endocrine diseases. This background demonstrates the difference in gender dysphoria, which is a psychological diagnosis, and other conditions treated by endocrinologists, which are physical diagnoses.

15. Endocrinology is the study of glands and hormones. Endocrine disorders can be divided into three main types: those that involve hormone excess,

those that involve hormone deficiency, and those that involve structural abnormalities of the glands such as cancers.

16. It is important for the endocrinologist to determine the cause of hormone gland excess or deficiency in order to devise an appropriate treatment plan. The plan will generally be to help bring the hormones back into balance and thus bring the patient back to health.

17. To give an example of hormone excess, hyperthyroidism is a term which means overactivity of the thyroid gland. In this condition excess thyroid hormone is produced by the thyroid gland. This results in various physical and psychological changes for the afflicted patient. Examples of physical changes can include tachycardia or fast heart rate, hand tremors, and weight loss. Examples of psychological symptoms include anxiety, panic attacks, and sometimes even psychosis.

18. An endocrinologist can recognize thyroid hormone excess in part by signs and symptoms, but can also confirm the diagnosis with laboratory testing that shows the thyroid hormones to be out of balance. Once this is determined and the degree of excess is known, then treatments can be given to bring these levels back into balance to benefit the patient's health and to prevent other disease effects caused by excess hormone.

19. To give another example, consider a deficiency of insulin. Insulin is a hormone which regulates blood glucose levels. If there is damage to the pancreas such that insulin levels are very low, then blood glucose levels will rise. If the glucose levels rise to a certain abnormally high level, then this is considered diabetes. In the case of type 1 diabetes, insulin levels are abnormally low and therefore blood glucose levels are abnormally high leading to a variety of signs and symptoms. For example, the patient may have extreme thirst, frequent urination, muscle wasting, and weight loss. They may often experience lethargy and weakness.

20. In this case laboratory tests of glucose and insulin levels can confirm the diagnosis. Once diabetes is confirmed, the patient is then treated with insulin to help restore glucose balance in the body and prevent long-term complications of diabetes.

21. To give an example of a structural abnormality, a patient may have a lump on the thyroid gland in the neck. This may be further examined by an imaging test such as an ultrasound. A needle biopsy can be performed so that the cells can be examined under a microscope. A trained medical professional such as a pathologist can then examine the cells to determine if they are benign or cancerous. In the case of a thyroid cancer, a surgical procedure known as a thyroidectomy may be performed to remove the diseased thyroid gland in order to treat the cancer.

22. Noteworthy in the preceding three examples is that all three disease conditions are diagnosed by physical observations. In other words, a laboratory test of a hormone, an imaging test of an organ, an examination of cells under a microscope, or all three may be employed in the diagnosis of endocrine disease.

B. Gender Dysphoria is a Psychological Diagnosis

23. Gender dysphoria, on the other hand, is not an endocrine diagnosis, it is in fact a psychological diagnosis. It is diagnosed purely by psychological methods of behavioral observation and questioning.

24. Likewise what is termed gender identity is a psychological concept. It has no correlate in the human body. In the letter to the editor I wrote with my colleagues, discussed above, we wrote in our critique of the Endocrine Society Guidelines that "There are no laboratory, imaging, or other objective tests to diagnose a 'true transgender' child" (Laidlaw et al., 2019).

25. For example, one cannot do imaging of the human brain to find the gender identity. Likewise, there is no other imaging, laboratory tests, biopsy of tissue, autopsy of the brain, genetic testing, or other biological markers that can identify the gender identity. There is no known gene that maps to gender identity or to gender dysphoria. In other words, there is no objective physical measure to identify either gender identity or gender dysphoria.

26. This is in contrast to all other endocrine disorders which have a measurable physical change in either hormone levels or gland structure which can be confirmed by physical testing. Therefore, gender dysphoria is a purely psychological phenomenon and not an endocrine disorder. But as my colleagues and I wrote in our letter to the editor, it becomes an endocrine condition through gender affirmative therapy: "Childhood gender dysphoria (GD) is not an endocrine condition, but it becomes one through iatrogenic puberty blockade (PB) and high-dose cross-sex (HDCS) hormones. The consequences of this gender-affirmative therapy (GAT) are not trivial and include potential sterility, sexual dysfunction, thromboembolic and cardiovascular disease, and malignancy" (Laidlaw et al. 2019).

27. As a practicing endocrinologist and scientist, I have made a study of GD and its treatment for two reasons: 1) I want to be sure that my colleagues and I understand the science before we treat any patients with GD; and 2) I am concerned that the medical society that claims to speak for me and other endocrinologists has abandoned scientific principles in endorsing treatments for GD that have questionable scientific support. The opinions expressed in this report are the result of my own experience, studies, education, and review of the scientific literature related to GD.

C. Gender Dysphoria and Desistance

28. GD is a persistent state of distress that stems from the feeling that one's gender identity does not align with their physical sex (American Psychiatric Association, 2013). It has been a relatively rare condition in children and adolescents. However there have been very significant increases in referrals for this condition noted around the globe.

29. For example, in the UK, "The number of referrals to GIDS [Gender Identity Development Service] has increased very significantly in recent years. In 2009, 97 children and young people were referred. In 2018 that number was 2519" (Bell v Tavistock Judgment, 2020). There is evidence that this increase may be in part due to social contagion and fueled by social media/internet use (Littman, 2018).

30. The French National Academy of Medicine wrote recently: "Parents addressing their children's questions about transgender identity or associated distress should remain vigilant regarding the addictive role of excessive engagement with social media, which is both harmful to the psychological development of young people and is responsible for a very significant part of the growing sense of gender incongruence" (SEGM, 2022).

31. In "a study of the Finnish gender identity service, '75% of adolescents [assessed] had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria' (Kaltiala-Heino, 2015). In fact,

'68% had their first contact with psychiatric services due to other reasons than gender identity issues.' The same study also showed that 26% percent had an autistic spectrum disorder and that a disproportionate number of females (87%) were presenting to the gender clinics compared to the past" (Laidlaw in gdworkinggroup.org, 2018).

32. Desistance is a term indicating that the child, adolescent, or adult who initially presented with gender incongruence has come to experience a realignment of their internal sense of gender and their physical body. "Children with [gender dysphoria] will outgrow this condition in 61% to 98% of cases by adulthood. There is currently no way to predict who will desist and who will remain dysphoric" (Laidlaw et al., 2019; Ristori & Steensma, 2016).

33. Because there is no physical marker to diagnose gender identity, and because it is not possible to predict which child or adolescent will desist, it is not possible to know which young person will remain transgender identified as adults. Also, because the 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.

34. Dr. Olson-Kennedy states that "[t]he studies pertaining to desistance upon which the GAPMS Memo relies pertain to prepubertal youth, not adolescents. In fact, contrary to the GAPMS Memo's assertion, studies show that if gender

dysphoria is present in adolescence, it usually persists (DeVries, et al., 2011)." (Oslon-Kennedy decl, p. 22).

35. Dr. Olson-Kennedy confuses prepubertal (a medical term) with preadolescence (a psychological designation). Puberty which pertains to the phsyical development of the reproductive tract, breasts and associated secondary sex characterestics can begin as early as age 8 in girls and age 9 in boys. The studies which have examined desistance involved children aged twelve and under. For example table 1 in Ristori and Steensma 2016 shows multiple studies involving children. For the three most recent - Singh (2012), Wallien & Cohen-Kettenis (2008), and Drummond et al. (2008) - these involved age ranges from 3 to nearly 13 years old.[1] The desistance rate varied from 61 to 88%. Since the upper age was twelve (or slightly higher), this would include children in the age range of 8-12 years old many of whom were going through puberty based on their age and were therefore not Tanner stage 1 (pre-pubertal).[2] Therefore Dr. Olson-Kennedy's statement that

1 "This study provided information on the natural histories of 25 girls with gender identity disorder (GID). Standardized assessment data in childhood (mean age, 8.88 years; range, 3-12 years)" (Drummond et al., 2008).
"The mean age of the participating gender-referred children was 10.47 years (SD = 1.27; range, 8.11–12.77)" (Wallien et al., 2009).
" Standardized assessment data in childhood (mean age, 7.49 years; range, 3–12 years) and at follow-up (mean age, 20.58 years; range, 13–39 years) were used to evaluate gender identity and sexual orientation outcome. At follow-up, 17 participants (12.2%) were judged to have persistent gender dysphoria." (Singh, 2012).

2 To my knowledge the desistance literature does not examine Tanner stages of puberty as part of their studies. However one can infer based on the ages that many children had at least begun puberty (Tanner stage 2) or were at a more advanced stage of puberty.

"[t]he studies pertaining to desistance upon which the GAPMS Memo relies pertain to prepubertal youth" is incorrect.

D. Biological Sex in Contrast to Gender Identity

36. A recognition and understanding of biological sex is critical to my practice as an endocrinologist because the endocrine physiology of men and women, boys and girls, differ.

37. Biological sex is the objective physical condition of having organs and body parts which correspond to a binary sex. There are only two physical sexes, male and female. The male is identified as having organs and tissues such as the penis, testicles and scrotum. The female sex is identified by having organs and tissues such as the labia, vagina, uterus, and ovaries. Biological sex is easily identified by physical observation such that adults and even young children can identify the biological sex of a newborn baby.

38. This is in contrast to gender identity, which does not exist in any physical sense. It is a subjective identification known only once a patient makes it known. It cannot be identified by any physical means, cannot be confirmed by any outside observer, and can change over time.

39. It is also noteworthy that the physical organs described above as representing biological sex have a physical genetic correlate. In other words, it is a

2. Pubertal Development

46. As mentioned previously, at the time of birth an infant's sex is easily identified through observation of the genitalia. Corresponding internal structures could also be confirmed through imaging if needed.

47. In early childhood, some low level of sex hormones are produced by the sex glands. The male testes produce testosterone. The female ovaries produce primarily the hormone estrogen. These sex glands remain quiescent for the most part, producing low levels of sex hormones until the time of pubertal development.

48. Puberty is a time of development of the sex organs, body, brain and mind. There are well known changes in physical characteristics of the male such as growth of facial hair, deepening of the voice, and increasing size of the testicles and penis. Importantly the testicles will develop sperm under the influence of testosterone and become capable of ejaculation. Because of these changes, the male will become capable of fertilizing an egg. The inability to produce sperm sufficient to fertilize an egg is termed infertility.

49. For the female, pubertal development includes changes such as breast development, widening of the pelvis, and menstruation. The female will also begin the process of ovulation which is a part of the menstrual cycle and involves the release of an egg or eggs from the ovary. Once the eggs are released in a manner in which they can become fertilized by human sperm then the female is termed fertile.

The inability to release ovum that can be fertilized is infertility (Kuohong and Hornstein, 2021).

3. Tanner stages of development

50. From a medical perspective it is important to know the stage of pubertal development of the developing adolescent. This can be determined through a physical examination of the body. The female will have changes in breast characteristics and pubic hair development.

Similarly, the male will have changes in testicular size and pubic hair development. These findings can be compared to the Tanner staging system which will allow the stage of puberty to be known.

51. Tanner stages are divided into five. Stage 1 is the pre-pubertal state before pubertal development of the child begins. Stage 5 is full adult sexual maturity. Stages 2 through 4 are various phases of pubertal development (Greenspan and Gardner, 2004).

52. Awareness of the Tanner stage of the developing adolescent is also useful to assess for maturation of sex organ development leading to fertility. For girls, the first menstruation (menarche) occurs about two years after Tanner stage 2 and will typically be at Tanner stage 4 or possibly 3 (Emmanuel and Boker, 2022). The first appearance of sperm (spermarche) will typically be Tanner stages 4 (Id.).

If puberty is blocked or disrupted before reaching these critical stages, the sex glands will be locked in a premature state and incapable of fertility.

4. Biological Sex Cannot Be Changed

53. It is not possible for a person to change from one biological sex to the other, and there is no technology that allows a biological male to become a biological female or vice-versa. It is not technologically possible at this time to change sex chromosomes; these will remain in every cell throughout life. It is not technologically possible to transform sex glands from one to the other. In other words, there are no hormones or other means currently known to change an ovary into a testicle or a testicle into an ovary.

54. Furthermore, as noted earlier, several of the sex specific structures (such as the epidymis of the male or uterus of the female) are produced early in embryological development from around weeks 8 to 12. The primitive ducts which lead to these organs of the opposite sex are obliterated. There is no known way to resuscitate these ducts and continue development of opposite sex structures.

55. It is also not possible to produce gametes of the opposite sex. In other words, there is not any known way to induce the testicles to produce eggs. Nor is there any known way to induce the ovaries to produce sperm. Therefore, creating conditions for a biological female to create sperm capable of fertilizing another ovum is impossible. The induction of opposite sex fertility is impossible.

56. In fact, as I will discuss, gender affirming therapy actually leads to infertility and potential sterilization.

F. Iatrogenic Harms

57. The term iatrogenic is used in medicine to describe harms or newly created medical conditions that are the result of medications, surgeries, or even psychological treatments. In this section I will discuss the iatrogenic harms of "gender affirmative treatment," for females. Each of the four interventions which I will describe (social transition, blocking normal puberty, opposite sex hormones, and surgery) lead to iatrogenic harms to the patient. These harms will be described in detail below. I speak of these harms because it is important to understand that once a patient begins GAT it is more likely the patient will continue on to surgery (de Vries et al., 2014). Thus, GAT interrupts the natural desistence process and instead places the patient on a lifetime regimen of hormonal and surgical care. A good understanding of these harms is also critical to my practice as an endocrinologist, because if I did not understand these harms, I could not advise patients of the risks associated with GAT.

G. Gender Affirmative Therapy

58. The approaches to gender dysphoria in minors may be divided into three main types. (Zucker, 2020). One is psychosocial treatment that helps the young person align their internal sense of gender with their physical sex. Another would be

to "watch and wait" and allow time and maturity to help the young person align sex and gender through natural desistance. The third option, which is the focus of that which follows, is referred to as gender affirmative therapy.

59. Gender affirmative therapy (GAT) of adults and minors consists of psychosocial, medical, and surgical interventions that attempt to psychologically and medically alter the patient so that they come to believe they may become similar to the physical sex which aligns with their gender identity (but not their biological sex) and thereby reduce gender dysphoria. GAT consists of four main parts: 1) social transition, 2) blocking normal puberty or menstruation, 3) high dose opposite sex hormones, and 4) surgery of the genitalia and breasts.

60. The application of this medical therapy to minors[3] is a fairly new intervention and is associated with a number of harms both known and unknown. GAT suffers from a lack of a quality evidence-base, poorly performed studies, and ongoing unethical human experimentation.

3. "[T]he US Department of Health and the Food and Drug Administration reference approximate age ranges for these phases of life, which consist of the following: (1) infancy, between birth and 2 years of age; (2) childhood, from 2 to 12 years of age; and (3) adolescence, from 12 to 21 years of age.1 Additionally, *Bright Futures* guidelines from the American Academy of Pediatrics identify adolescence as 11 to 21 years of age,2 dividing the group into early (ages 11–14 years), middle (ages 15–17 years), and late (ages 18–21 years) adolescence. The American Academy of Pediatrics has previously published a statement on the age limit of pediatrics in 1988,3 which was reaffirmed in 2012 and identified the upper age limit as 21 years with a note that exceptions could be made when the pediatrician and family agree to an older age, particularly in the case of a child with special health care needs.
Recent research has begun to shed more light on the progression of mental and emotional development as children progress through the adolescent years into young adulthood. It is increasingly clear that the age of 21 years is an arbitrary demarcation line for adolescence because there is increasing evidence that brain development has not reliably reached adult levels of functioning until well into the third decade of life" (Hardin, 2017).

1. Social transition

61. The first stage of gender affirmative therapy is termed social transition. Social transition is a psychological intervention. The child may be encouraged to adopt the type of clothing and mannerisms or behaviors which are stereotypical of the opposite sex within a culture. For example, in the United States a boy might wear his hair long and wear dresses in order to socially transition. A girl may cut her hair short and wear clothes from the boys' section of a department store.

62. Social transition of the child has been noted by expert researcher in the field of child gender dysphoria, Ken Zucker, to itself be a form of iatrogenic harm (Zucker, 2020). This is because the social transition process may solidify the young person's belief that they are in fact the sex opposite of their biological sex.

63. From an endocrine point of view, it is understandable that a child having the outward appearance of the opposite sex, would believe that he or she is destined to go through puberty of the opposite sex as they have only a poor understanding of the internal structures of the body, the function of the sex glands, the role of the sex glands in fertility and so forth.

64. Therefore, it would be quite frightening for a boy who believes he is a girl to be turning into a man with all of the adult features that accompany manhood. Vice versa, the girl who has become convinced that she is a boy will be frightened by the physical changes brought on by womanhood.

65. In fact, it would appear that in the minds of the children and adolescents that they are anticipating a sort of disease state in the future by the hormone changes that will occur as a normal and natural part of human development. Until relatively recently in human history, it has not been possible to interfere with puberty through pharmaceutical means.

2. Medications which Block Pubertal Development

a. Background

66. A second stage of gender affirmative therapy may involve blocking normal pubertal development. This may be done with puberty blocking medications (PB) that act directly on the pituitary to cause the endocrine condition known as hypogonadotropic hypogonadism (HH).

67. In order to understand what is occurring in this process, it is helpful to be aware of normal hormone function during pubertal development.

There is a small pea-sized gland in the brain called the pituitary. It is sometimes referred to as the "master gland" as it controls the function of several other glands. One key function for our purposes is the control of the sex glands. There are two specific hormones produced by the pituitary referred to as luteinizing hormone (LH) and follicle stimulating hormone (FSH). These are responsible for sex hormone

production and fertility. The LH and FSH act as signals to tell the sex glands begin or continue their function.

68. In the adult male, the production of LH will cause adult levels of testosterone to be produced by the testicles. In the adult female, the production of LH will cause adult levels of estrogen to be produced by the ovaries.

69. In early childhood, prior to the beginning of puberty, the pituitary function with respect to the sex glands is quiescent. However, during pubertal development LH will signal the testicle to increase testosterone production and this carries the boy through the stages of pubertal development into manhood. Likewise for the female, the interaction of LH with the ovaries increases estrogen production and carries the girl through the stages of development into womanhood.

70. Hypogonadotropic hypogonadism is a medical condition in which the pituitary does not send the hormonal signals (LH and FSH) to the sex glands. Therefore the sex glands are unable to make their sex specific hormones of testosterone or estrogen.

71. If this condition occurs during puberty, the effect will be to stop pubertal development. This is a disease state which is diagnosed and treated by the endocrinologist.

72. Medications such as GnRH anologues (sometimes called puberty blockers) act on the pituitary gland to lower the pituitary release of LH and FSH

levels dramatically. The result is a blockage of the signaling of the pituitary to the testicles or ovaries and therefore underproduction of the sex hormones. This will stop normal menstrual function for the female and halt further pubertal development. For the male this will halt further pubertal development. If the male had already reached spermarche, then production of new sperm will stop.

b. GnRH Agonist Medication Effects Vary by Use Case

73. There are a variety of uses for GnRH agonists. The use and outcome can be very different for different applications.

74. For example, the initial development of the medication called Lupron was for the treatment of prostate cancer. The idea being that blocking pituitary hormones will block the adult male's release of testosterone from the testicles. Since testosterone will promote the growth of prostate cancer, the idea is to lower testosterone levels to a very low amount and therefore prevent the growth and spread of prostate cancer. This is a labeled use of the medication. In other words, there is FDA approval for this use.

75. Another labeled use of GnRH agonist medication is for the treatment of central precocious puberty. In the disease state of central precocious puberty, pituitary signaling is activated at an abnormally young age, say age four, to begin pubertal development. In order to halt puberty which has begun at an abnormally early time, a GnRH agonist may be used. Here the action of the medication on the

pituitary will disrupt the signaling to the sex glands, stop early sex hormone production, and therefore stop abnormal pubertal development.

76. Then, at a more normal time of pubertal development, say age 11, the medication is stopped and puberty is allowed to proceed. The end result is to restore normal sex gland function and timing of puberty. This is a labeled use for a GnRH agonist medication.

77. What about the use of GnRH anologue medications such as Lupron in gender affirmative therapy? In these cases, we have physiologically normal children who are just beginning puberty or are somewhere in the process of pubertal development. They have healthy pituitary glands and sex organs. However, a puberty blocking medication is administered to stop normal pubertal development.

78. In this case the condition of hypogonadotropic hypogonadism described above (a medical disease) is induced by medication and is an iatrogenic effect of treating the psychological condition of gender dysphoria. GnRH anologue medications have not been FDA approved for this use. The use of GnRH anolgue medication for this purpose in adolescents is experimental as there have been no randomized controlled trials for this specific use case.

c. Hypogonadotropic Hypogonadism

i. Description and Diagnosis

79. As described above, hypogonadotropic hypogonadism is a condition in which the pituitary fails to send signals to the gonads thereby preventing the testicle of the male from making testosterone or the ovary of the female from making estrogen.

80. As an endocrinologist I frequently evaluate patients to ascertain if they have the condition of hypogonadotropic hypogonadism. This is done by a laboratory evaluation. If the patient has this condition, I then determine the cause and the proper treatment.

81. The primary hormone of the pituitary which is abnormal in this condition is called luteinizing hormone or LH. In order to diagnose the condition, a laboratory test with reference ranges based on the person's sex and age is used to evaluate the blood sample.

82. For example, figure 1 shows the normal laboratory reference range for LH over the course of a month in an adult pre-menopausal female (0.5-76.3 mIU/mL) (Quest LH, 2023). A very low level of LH (red) with low estrogen levels indicates hypogonadotropic hypogonadism[4].

4 Levels will be similarly low for adolescents, though the normal reference range is different.

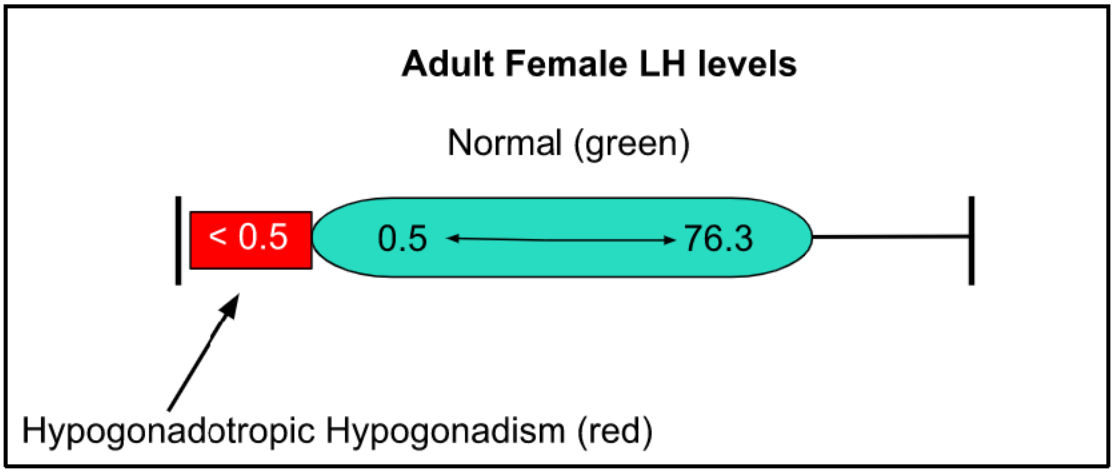


Figure 1.

83. As one can see, in hypogonadotropic hypogonadism the level of LH is below the reference range. In the female, this causes the cessation of estrogen production, and in the male it causes cessation of testosterone production. In adolescents of either sex, this will stop further pubertal development. For females in mid-puberty or beyond, this condition will also stop normal menstrual cycles and ovulation. For the male in mid-puberty or beyond, it will cause the cessation of normal sperm production.

84. As an endocrinologist, I would confirm the condition of hypogonadotropic hypogonadism based on laboratory results and then treat this medical condition.

85. What occurs to pituitary hormones and the sex hormones[5] when administering a GnRH analogue medication such as Lupron? The effect is identical

5 The primary sex hormones being estrogen for females and testosterone for males.

CONFIDENTIAL

to figure 1. Over time, the result of the medication is to cause very low LH levels (red) leading to low sex hormone levels thereby medically inducing the condition of hypogonadotropic hypogonadism.

86. In gender affirmative therapy, the medical condition of hypogonadotropic hypogonadism is being deliberately created by the use of medications called GnRH analogues, one of which is called Lupron.

ii. [redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

CONFIDENTIAL

CONFIDENTIAL

[redacted]

[redacted]

[redacted]

6 The implant is continuously effective for one year. If one were to remove the implant after one year it can take 6-18 months or longer for HH to resolve. It's also possible that HH will not resolve.

CONFIDENTIAL

CONFIDENTIAL

[redacted]

c. Adverse Health Consequences of Blocking Normal Puberty

i. Infertility

92. [redacted]

93. Dr. Antommaria writes that "The [Endocrine Society] guideline recommends that informed consent for pubertal blockers and gender-affirming hormones include a discussion of the implications for fertility and options for fertility preservation (Antommaria decl, p.23). However, even though procedures to preserve fertility are available, studies show that less than 5% of adolescents receiving GAT even attempt fertility preservation (FP) (Nahata, 2017). Moreover, "ovarian tissue cryopreservation is still considered experimental in most centers and testicular tissue cryopreservation remains entirely experimental. These experimental

CONFIDENTIAL

CONFIDENTIAL

forms of FP would be the only options in children [with puberty] blocked prior to spermarche and menarche and are high in cost and limited to specialized centers. Even with FP there is no guarantee of having a child" (Laidlaw, Cretella, et al., 2019).

94. [redacted]

95. Dr. Antommaria states that "Florida Medicaid provides coverage for the use of puberty blockers to treat central precocious puberty, but now prohibits coverage for the use of puberty blockers to treat gender dysphoria, even though the use of puberty blockers to treat both conditions has comparable risks and is supported by comparable types of evidence" (Antommaria decl, p. 24). These statements fail to recognize the very different effects of PB medication in early childhood versus during adolescence.

CONFIDENTIAL

CONFIDENTIAL

96. Giving puberty blockers to a four year old with central precocious puberty will obviously not impair fertility, as the four year old has not yet become fertile. The child will at a later time have the puberty blocker discontinued and then normal pubertal development can proceed. Therefore when they are no longer taking the medication, they will gain natural fertility.

97. [redacted]

ii. Sexual Dysfunction

98. [redacted]

CONFIDENTIAL

CONFIDENTIAL

[redacted]

iii. Negative Effects of Hypogonadotropic Hypogonadism on Bone Density

100. Puberty is a time of rapid bone development. This time period is critical in attaining what we call peak bone density or the maximum bone density that one will acquire in their lifetime (Elhakeem, 2019).

101. [redacted]

7 Jazz's age is somewhere in the mid-teens during this episode.

CONFIDENTIAL

CONFIDENTIAL

[redacted]

102. DEXA scans are used to evaluate changes in bone density and to help evaluate risk for future fractures. In my practice I order and interpret DEXA scans for this purpose.

103. The Z-score of a DEXA scan is used to compare a patient's bone density to the same population based on age and sex. For example a person who has a bone density similar to the average of the population would be at the 50th percentile. Those who have greater relative bone density would be above the 50th percentile. Those who have lower bone density would have a Z score below the 50th percentile.

104. Puberty blockers used in adolescence to cause HH will inhibit the normal accrual of bone density. This can be evaluated by DEXA scan. In a study in the UK, 44 patients aged 12-15 with gender dysphoria were given puberty blockers and tests of bone density were done at baseline, 12 months, 24 months and 36 months (Carmichael, 2021).

105. Figure 2 shows the Z-scores of the average age matched population percentile which is 50%. It shows the average baseline (before puberty blockers) Z-score percentile for the study participants. It also shows the bone density percentile at 12, 24, and 36 months. One can see that the average baseline z score was about

CONFIDENTIAL

CONFIDENTIAL

32% compared to peers of similar age and sex. At 12 months this had decreased to about 15%, and by 24 months it had declined further to about 5% compared to their peers and remained at this low level.

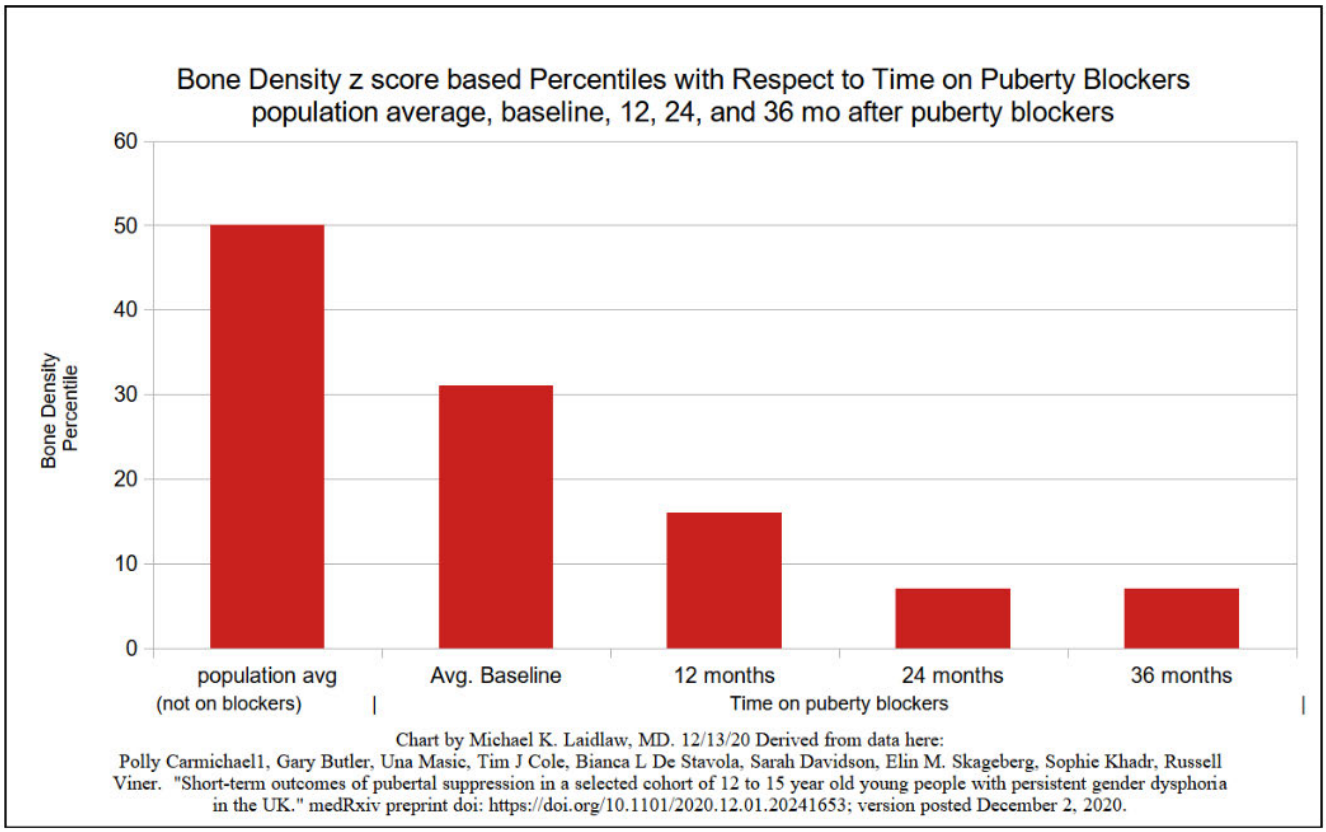


Figure 2

106. [redacted]

CONFIDENTIAL

CONFIDENTIAL

107. [redacted]

8 "This" refers to cardiovascular disease: "Diagnosis and treatment of amenorrheic states is of increasing clinical importance because lifetime menstrual irregularities are known to be predictive of subsequent CVD in women."

CONFIDENTIAL

CONFIDENTIAL

[redacted]

d. The Effect of Puberty Blockers on Desistance

111. As stated earlier a very high proportion of minors diagnosed with gender dysphoria will eventually desist or come to accept their physical sex. Puberty blockers have been shown to dramatically alter natural desistance.

112. In a Dutch study that included seventy adolescents who took puberty blockers, all seventy decided to go on to hormones of the opposite sex (de Vries, et al. 2011). In a follow-up study, the overwhelming majority went on to have sex reassignment surgery by either vaginoplasty for males or hysterectomy with ovariectomy for females (de Vries, et al. 2014). These surgeries resulted in

CONFIDENTIAL

sterilization. This is why puberty blockers, rather than being a "pause" to consider aspects of mental health, are instead a pathway towards future sterilizing surgeries[9].

3. Opposite Sex Hormones

113. The third stage of gender affirmative therapy involves using hormones of the opposite sex (also called cross sex hormones) at high doses to attempt to create secondary sex characteristics in the person's body.

a. Testosterone

114. Testosterone is an anabolic steroid of high potency. It is classified as a Schedule 3 controlled substance by the DEA: "Substances in this schedule have a potential for abuse less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2022). A licensed physician with a valid DEA registration is required to prescribe testosterone.

115. I prescribe testosterone to men for testosterone deficiency. The state of testosterone deficiency can cause various problems including problems of mood, sexual function, libido, and bone density. Prescription testosterone is given to correct the abnormally low levels and bring them back into balance. The dose of testosterone must be carefully considered and monitored to avoid excess levels in the male as

9 The surgeries were consequential in another important way. One person who had a vaginoplasty died of post-surgical complications of necrotizing fasciitis which is a rapidly progressive and very severe infection of the soft tissues beneath the skin and which has a high mortality (Id.).

there are a number of serious concerns when prescribing testosterone. The use of high dose testosterone in females is experimental.

116. Regarding the potential for abuse, the labeling reads "Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication...Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions...Abuse and misuse of testosterone are seen in male and female adults and adolescents...There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice." (Actavis Pharma, 2018)

117. Adverse events with respect to the nervous system include: "Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia." (Actavis Pharm, 2018)

118. With regard to ultimate height, "[t]he following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth" (Actavis Pharma, Inc., 2018). What this means is that testosterone applied to the adolescent will cause premature closure of the growth plates, stopping further gains in height in the growing individual, and ultimately making the person shorter than they otherwise would have been.

119. With respect to the cardiovascular system of men using ordinary doses, "Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men" (Actavis Pharma, 2018). No clinical safety trials have been performed for women or adolescent girls to my knowledge.

120. "There have been postmarketing reports of venous thromboembolic events [blood clots], including deep vein thrombosis (DVT) [blood clot of the extremity such as the lef] and pulmonary embolism (PE) [blood clot of the lung which may be deadly], in patients using testosterone products, such as testosterone cypionate" (Actavis Pharma, 2018).

121. A very recently published study of adverse drug reactions (ADRs) as part of gender affirming hormone therapies in France states that "[o]ur data show a previously unreported, non-negligible proportion of cases indicating cardiovascular ADRs in transgender men younger than 40 years… In transgender men taking testosterone enanthate, all reported ADRs were cardiovascular events, with pulmonary embolism in 50% of cases" (Yelehe et al., 2022).

122. There are also serious concerns regarding liver dysfunction: "Prolonged use of high doses of androgens ... has been associated with development of hepatic adenomas [benign tumors], hepatocellular carcinoma [cancer], and peliosis hepatis

[generation of blood-filled cavities in the liver that may rupture] —all potentially life-threatening complications" (Actavis Pharma, 2018).

123. In GAT, what is termed "cross sex hormones" is the use of hormones of the opposite sex to attempt to create secondary sex characteristics. To do so, very high doses of these hormones are administered. When hormone levels climb above normal levels they are termed supraphysiologic.

i. Hyperandrogenism

124. Hyperandrogenism is a medical condition of elevated blood androgens such as testosterone. As an endocrinologist I frequently evaluate patients to determine if they have the condition of hyperandrogenism. Hyperandrogenism in the female or male is harmful and can lead to various maladies.

125. In order to diagnose hyperandrogenism, a laboratory blood test of testosterone is done. In hyperandrogenism, one will find testosterone levels elevated above the reference range.

126. For example for females aged 18 or older, the normal reference range is 2-45 ng/dL (Quest testosterone, 2023).[10] However, in female disease conditions these levels can be much higher. Levels above this normal reference range are considered hyperandrogenism (figure 3).

10 For females aged 11-17 the reference range is <= 40 and below this age group, the range is even lower.

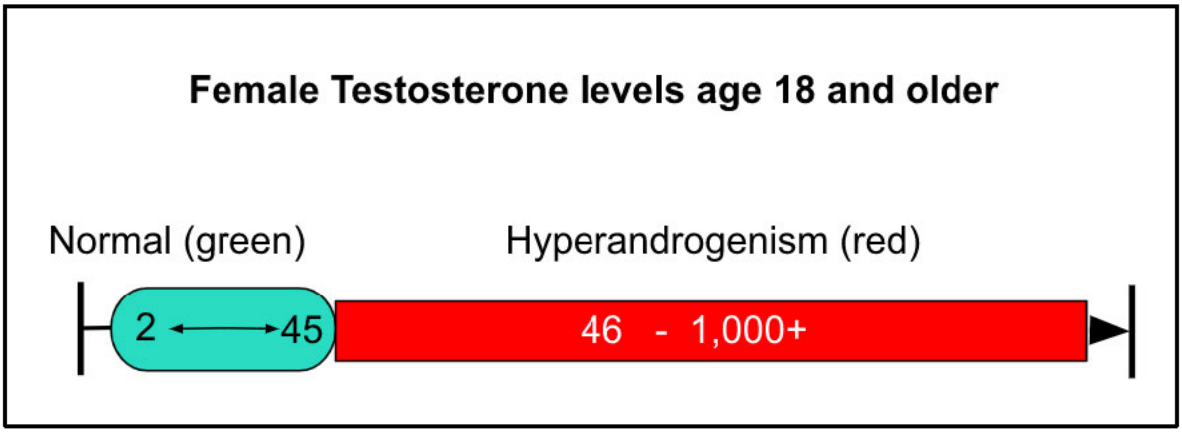


Figure 3

127. For example, in polycystic ovarian syndrome levels may range from 50 to 150 ng/dL.

128. I frequently diagnose and treat the hyperandrogen condition called polycystic ovarian syndrome (PCOS). These patients have elevated testosterone levels. These levels are mildly to moderately elevated and may range from 50-150. Hyperandrogenism found in PCOS has been associated with insulin resistance (Dunaif, 1989), metabolic syndrome (Apridonidze, 2005) and diabetes (Joham, 2014).

129. I also evaluate patients to rule out rare androgen producing tumors that generate very high levels of testosterone. These rare endocrine tumors can cause severely elevated testosterone levels in the 300-1000 range. Once the cause of a hyperandrogen condition is identified, treatments may be put in place to help bring the testosterone levels down to the normal reference range.

130. Recommendations from the Endocrine Society's clinical guidelines related to GAT are to ultimately raise female levels of testosterone to 320 to 1000 ng/dL[11] which is on the same order as dangerous endocrine tumors for women as described above (Hembree, 2017). A simple calculation shows this level for the adult may be anywhere from 6 to 100 times higher than native female testosterone levels. In doing so they are inducing severe hyperandrogenism. These extraordinarily high levels of testosterone are associated with multiple risks to the physical and mental health of the patient.

131. The following chart shows testosterone levels in the normal adult female range (blue), PCOS (graycrine tumors, and gender affirmative therapy as part of female to male (FtM) transition (figure 4).

11 In the Endocrine Society's Guidelines there is no grading of evidence for the rationale of using such high supraphysiologic doses of opposite sex hormones for the female or male. There seems to be an underlying assumption that because the person believes to be the opposite sex then they acquire the sex specific laboratory ranges of the opposite sex. "The root cause of this flaw in thinking about diagnostic ranges was exemplified in a response letter by Rosenthal et al claiming that gender identity determines the ideal physiologic range of cross-sex hormone levels (5). Thus, a psychological construct, the 'gender identity', is imagined to affect physical reality and change a person's sex-specific laboratory reference ranges. This is clearly not the case, otherwise there would be no serious complications of high-dose androgen treatment in transgender males" (Laidlaw et al., 2021).

CONFIDENTIAL

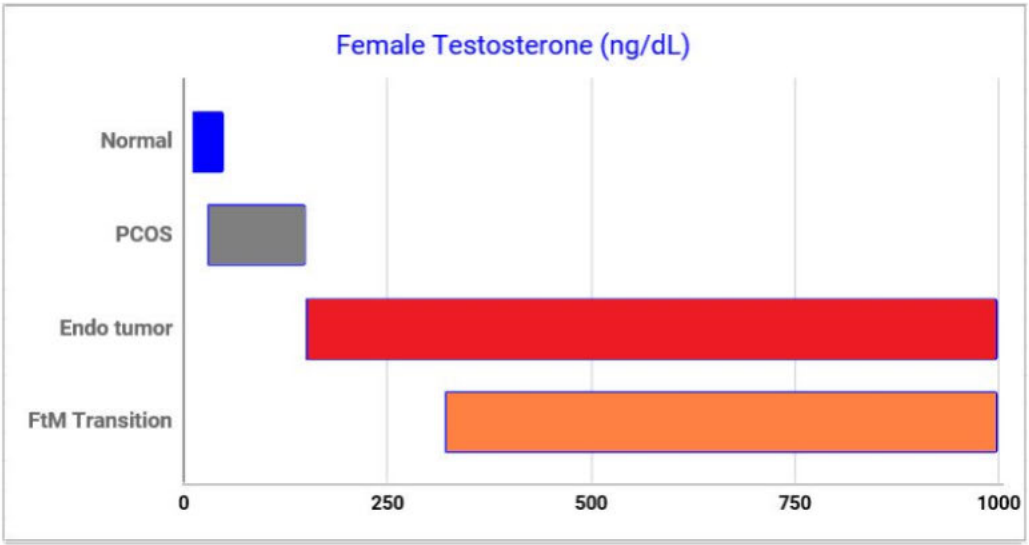


Image by Michael K Laidlaw. MD. Approximate total testosterone in ng/dL based on laboratory, etc. FtM transition from 2017 Endo Society Guidelines on Gender Dysphoria. With PCOS testosterone levels may be as high as 150. With endocrine tumors testosterone may be in the 150-1000 range. The recommendations of the Endocrine Society/WPATH are to bring levels into the 300-1000 range which is 6-100 times higher than normal endogenous adult female levels.

Figure 4.

ii. [redacted]

132. [redacted]

133. [redacted]

12 See II.B. Medical Concerns Regarding Brit Rothstein

CONFIDENTIAL

CONFIDENTIAL

Table 2

134. [redacted]

135. [redacted]

136. [redacted]

13 See II.D. Medical Concerns Regarding August Dekker
14See II.A. Medical Concerns Regarding K.F.

CONFIDENTIAL

CONFIDENTIAL

iii. Medical Problems Related to Hyperandrogenism

137. With respect to cardiovascular risk "Studies of transgender males taking testosterone have shown up to a nearly 5-fold increased risk of myocardial infarction relative to females not receiving testosterone" (Laidlaw et al.,2021; Alzahrani et al., 2019). I would expect Brit Rothstein and August Dekker to be at increased risk of cardiovascular disease due to hyperandrogenism.

138. Permanent physical effects of testosterone therapy involve irreversible changes to the vocal cords. Abnormal amounts of hair growth which may occur on the face, chest, abdomen, back and other areas is known as hirsutism. Should the female eventually regret her decision to take testosterone, this body hair can be very difficult to remove. Male pattern balding of the scalp may also occur. I would expect these changes to occur to the plaintiffs taking testosterone to induce hyperandrogenism. Common sense suggests that changes of voice and hair growth could be psychologically troubling should a patient decide to detranstition and attempt to reintegrate into society as female.

139. Changes to the genitourinary system due to hyperandrogenism include polycystic ovaries, clitoromegaly and atrophy of the lining of the uterus and vagina (Hembree, 2017). The breasts have been shown to have an increase in fibrous breast tissue and a decrease in normal glandular tissue (Grynberg et al., 2010). Potential cancer risks from high dose testosterone include ovarian and breast cancer

CONFIDENTIAL

CONFIDENTIAL

(Hembree, 2017). I would expect some or all of these effects and risks to occur to the plaintiffs taking testosterone to induce hyperandrogenism.

140. According to research anabolic steroid abuse[15] has been shown to predispose individuals towards mood disorders, psychosis, and psychiatric disorders. The "most prominent psychiatric features associated with AAS [anabolic androgenic steroids, i.e. testosterone] abuse are manic-like presentations defined by irritability, aggressiveness, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior. Other psychiatric presentations include the development of acute psychoses, exacerbation of tics and depression, and the development of acute confusional/delirious states" (Hall, 2005). Moreover, "[s]tudies... of medium steroid use (between 300 and 1000 mg/week of any AAS) and high use (more than 1000 mg/week of any AAS) have demonstrated that 23% of subjects using these doses of steroids met the DSM-III-R criteria for a major mood syndrome (mania, hypomania, and major depression) and that 3.4% — 12% developed psychotic symptoms" (Hall, 2005).

141. [redacted]

15Anabolic steroid abuse involves the deliberate creation of hyperandrogenism in the body as a result of high doses of testosterone or other androgens.

CONFIDENTIAL

CONFIDENTIAL

[redacted]

iv. Erythrocytosis as a Result of Hyperandrogenism

142. I regularly monitor patients who are receiving testosterone to evaluate for erythrocytosis. Erythrocytosis is a condition of high red blood cell counts. Prolonged hyperandrogenism such as occurs with the use of testosterone at supraphysiologic levels can cause erythrocytosis.

143. Males and females have different reference ranges for red blood cells (measured as hematocrit). For example the normal range of hematocrit for females over age 18 is 35.0-45.0% and males 38.5-50.0% (Quest Hematocrit, 2023). Levels above this range signify erythrocytosis (see figure 5).

16 See II.A. Medical Concerns Regarding K.F.
17 See II.B. Medical Concerns Regarding Brit Rothstein

CONFIDENTIAL

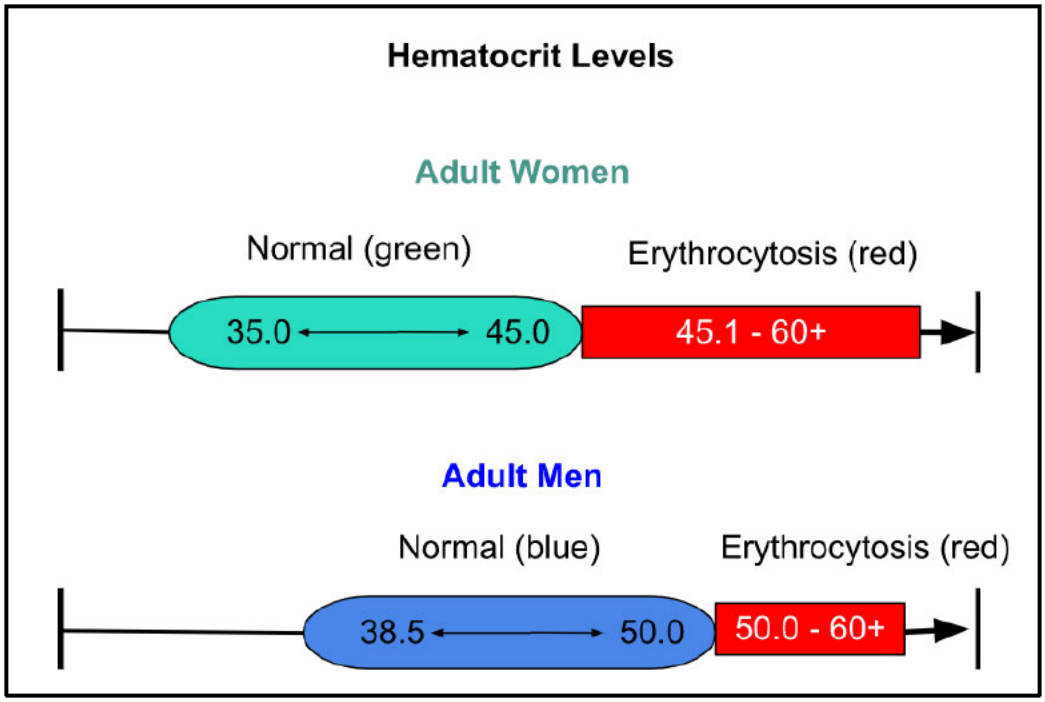


Figure 5.

144. As one can see, there is an overlap in the ranges of males and females such that levels between 45.1 and 50 are considered normal for the male. However for the female these levels are considered erythroctotic. Levels above 50 for the male are considered erythrocytosis and for the female severe erythrocytosis.

145. The Madsen study was a "20-year follow-up study in [1,073] adult trans men who started testosterone therapy and had monitoring of hematocrit at our center" (Madsen, 2021). In this study, 24% of trans men had hematocrit levels 50% at some time which would be considered severe erythrocytosis. Unfortunately, they did not examine the hematocrit range of 45-50. However one would presume that this would occur in at least the same percentage or higher as those who had developed severe erythrocytosis.

CONFIDENTIAL

146. Any level of erythrocytosis in young women has been shown to be an independent risk factor for cardiovascular disease, coronary heart disease and death due to both (Gagnon, 1994).

147. [redacted]

148. [redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 3

[redacted]

CONFIDENTIAL

b. Estrogen

149. Estrogen is the primary sex hormone of the female. Prescription estrogen may be used if a woman has low estrogen levels due to premature failure of her ovaries. Estrogen is prescribed to bring these levels back into a normal range for the patient's age. Another labeled use of estrogen is to treat menopausal symptoms. The use of estrogen to treat pediatric age males is experimental.

i. Hyperestrogenism

150. Hyperestogenemia is a condition of elevated blood estrogens such as estradiol. I regularly evaluate patients for hyperestrogenemia in my practice. Hyperestrogenemia in the male is harmful and can lead to various maladies.

151. In order to diagnose hyperestrogenemia, a laboratory blood test of estrogen is performed. In hyperestrogenemia, one will find estrogen levels elevated above the reference range.

152. For example, in an adult male the normal estrogen reference range is 60-190 pg/mL (Quest Estrogen, 2023). Levels above this range are consistent with hyperestrogenemia. See figure 6.

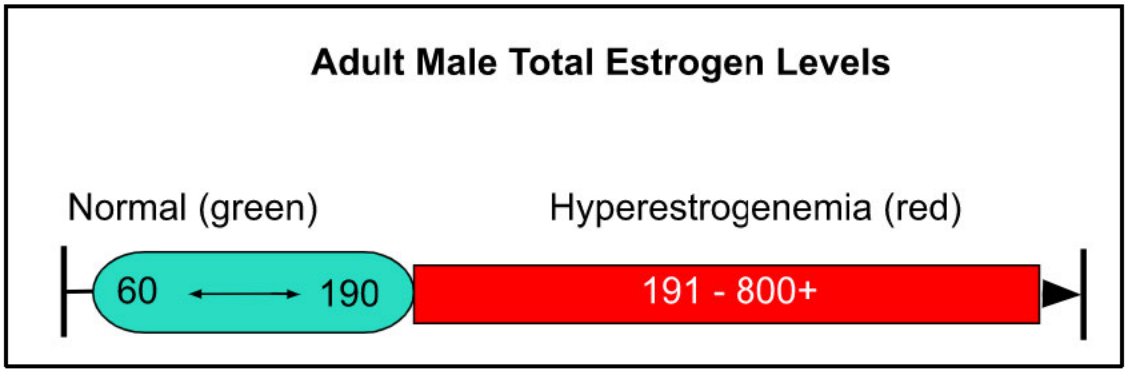


Figure 6.

153. There are medical conditions which can result in hyperestrogenemia. For example, "[t]he concentration of estrogen in cirrhotic patients is thought to increase by fourfold compared to individuals without cirrhosis" (Pagadala, 2023). Certain rare tumors for example of the adrenal gland can result in estrogen levels 3 to 10 fold higher than normal (Cavlan, 2010).

154. In gender affirmative therapy, the medical condition of hyperestrogenemia is being deliberately, medically induced by the off-label use of high doses of estrogen. Endocrine Society guidelines recommend raising estradiol levels to 2 to 43 times above the normal range.[18] The high doses are used in an attempt to primarily affect an increase of male breast tissue development known as gynecomastia. Gynecomastia is the abnormal growth of breast tissue in the male. I evaluate and treat patients with gynceomastia. I have prescribed medication and have referred patients for surgery for this condition.

18 Estradiol is a type of estrogen. Endocrine Society Guidelines recommend raising estradiol levels to 100-200 pg/mL (Hembree, 2017). The normal adult male estradiol range is 7.7-42.6 pg/mL (Labcorp Estadiol, 2023).

CONFIDENTIAL

155. Other changes of secondary sex characteristics may develop because of hyperestrogenemia such as softening of the skin and changes in fat deposition and muscle development.

156. Long-term consequences of hyperestrogenemia include increased risk of myocardial infarction and death due to cardiovascular disease (Irwig, 2018). Also "[t]here is strong evidence that estrogen therapy for trans women increases their risk for venous thromboembolism[19] over 5 fold" (Irwig, 2018).

157. Breast cancer is a relatively uncommon problem of the male. However the risk of a male developing breast cancer has been shown to be 46 times higher with high dose estrogen (Christel et al., 2019).

158. Sexual dysfunction, including decreased sexual desire and decreased spontaneous erections, is another adverse effect of hyperestrogenemia (Hembree, 2017).

159. [redacted]

19 Venous thromboembolism is a blood clot that develops in a deep vein and "can cause serious illness, disability, and in some cases, death" (CDC, 2022).

CONFIDENTIAL

4. Surgeries

160. The fourth stage of gender affirmative therapy is surgical alterations of the body of various kinds in an attempt to somehow mimic features of the opposite sex.

161. As an endocrinologist, I refer patients for surgeries for endocrine conditions. I have to be aware of the indications for surgery, the risks and benefits of surgery, and long term comorbidities that may arise from surgeries.

162. Individual surgical procedures can be a complex topic. It is helpful to first step back and consider conceptually what any surgery can and cannot accomplish.

163. In its basic form surgery is subtractive. In other words, a portion of tissue, an organ or organs are removed in order to restore health. For example, a diseased gallbladder may be surgically removed to help the patient get back to wellness. An infected appendix may be surgically removed to prevent worsening infection or even death. In both of these cases an unhealthy body part is surgically removed in order to restore health.

164. In some cases a diseased tissue or organ is removed so that a foreign replacement part may be substituted for an unhealthy organ or tissue. For example, a diseased heart valve may be replaced with a pig valve or a prosthetic heart valve. Another example is a failed liver may be replaced by liver transplant.

165. Though modern surgical techniques and procedures are astounding, there are very noteworthy limitations. Importantly, surgery cannot de novo create new organs. If a person's kidneys fail, the surgeon has no scientific method for creating a new set of kidneys that can be implanted or grown within the patient. This conceptual background is helpful when considering various gender affirming surgeries.

166. There are a variety of gender affirming surgeries for females. These may include mastectomies, metoidioplasty, and phalloplasty.

a. Mastectomy

167. Mastectomies are the surgical removal of the breasts. The procedure is used in GAT in an attempt to make the chest appear more masculine. The surgery results in a permanent loss of the ability to breastfeed and significant scarring of 7 to 10 inches. The scars are prone to widening and thickening due to the stresses of breathing and arm movement. Other potential complications include the loss of normal nipple sensation and difficulties with wound healing (American Cancer Society, 2022).

168. It is important to note that this operation cannot be reversed. The female will never regain healthy breasts capable of producing milk to feed a child (Mayo Clinic, Top Surgery, 2022).

169. Another important consideration is that compared to the removal of an unhealthy gallbladder or appendix, in the case of gender dysphoria the breasts are perfectly healthy and there is no organic disease process such as a cancer warranting their removal. The future woman who later desists is left with regret about what happened to her at an age before she could provide true informed consent. Functioning breasts cannot be created by a surgeon and restored to a patient in case of regret. She is left with permanent injury and loss of function with respect to her breasts.

b. GAT Surgeries on the Male

170. GAT surgeries for the male include removal of the testicles alone to permanently lower testosterone levels. This is by nature a sterilizing procedure. Further surgeries may be done in an attempt to create a pseudo-vagina which is called vaginoplasty. In this procedure, the penis is surgically opened and the erectile tissue is removed. The skin is then closed and inverted into a newly created cavity in order to simulate a vagina. A dilator must be placed in the new cavity for some time so that it does not naturally close.

171. Potential surgical complications may include urethral strictures, infection, prolapse, fistulas and injury to the sensory nerves with partial or complete loss of erotic sensation (Mayo Clinic, Feminizing Surgery, 2022).

c. GAT Surgeries of the Female Pelvis and Genitalia

172. Other types of surgery for females include those of the genitalia and reproductive tract. For example, the ovaries, uterus, fallopian tubes, cervix and the vagina may be surgically removed. Removal of the ovaries results in sterilization.

173. Importantly, removing female body parts does not produce a male. Rather, the female has had sex specific organs permanently destroyed with no hope of replacement, while remaining biologically female.

174. There have also been attempts to create a pseudo-penis. This procedure is known as phalloplasty. It is not possible to de novo create a new human penis. Instead, a roll of skin and subcutaneous tissue is removed from one area of the body, say the thigh or the forearm, and transplanted to the pelvis. An attempt is made to extend the urethra or urinary tract for urination through the structure. This transplanted tissue lacks the structures inherent in the male penis which allow for erection, therefore erectile devices such as rods or inflatable devices are placed within the tube of transplanted tissue in order to simulate erection (Hembree, 2017). The labia may also be expanded to create a simulated scrotum containing prosthetic objects to provide the appearance of testicles.

175. Complications may include urinary stricture, problems with blood supply to the transplanted roll of tissue, large scarring to the forearm or thigh, infections including peritonitis, and possible injury to the sensory nerve of the

clitoris (Mayo Clinic, Masculinizing Surgery, 2022). A recent systematic review and meta-analysis of 1731 patients who underwent phalloplasty found very high rates of complications (76.5%) including a urethral fistula rate of 34.1% and urethral stricture rate of 25.4% (Wang, 2022).

H. Life Threatening Physical Medical Conditions Versus Suicidal Ideation

176. Any child or adolescent who has suicidal ideation or has attempted suicide should receive immediate, appropriate psychiatric care. Psychologists and psychiatrists are trained in the recognition and treatment of suicidal ideation and prevention of suicide. A child or adolescent with gender dysphoria who also has suicidal ideation should not be treated any differently. They require compassionate care and a full psychological evaluation of comorbidities such as depression, anxiety, and self-harming behaviors.

177. However, suicidal ideation or attempts are categorically different than other life-threatening situations, such as a rapidly expanding brain tumor or a severe infection. In these situations, a medication or a surgery is used to stop the progression of an organic physical condition. In contrast, the danger to the self with suicidal ideation relates to a condition of the mind.

178. Gender affirmative therapy does not treat any life-threatening physical condition. In fact, it creates a number of new medical conditions as described above. It is also not an appropriate treatment for suicidal ideation. Neither puberty blocking

medications, nor testosterone, nor estrogen have been FDA approved for suicide prevention. Moreover, as noted above, the hormone imbalances generated by the medications used in GAT actually increase psychological conditions that lead to suicidal ideation and completed suicide.

I. Informed Consent

179. Any person who is to take a medication, undergo a surgical procedure, or have a psychological intervention should understand the risks and benefits before proceeding. A discussion of these risks and benefits should be provided by medical professionals and then the person of sufficient intellectual capacity and maturity can consent to the treatment.

180. Naturally difficulties arise when a minor is involved in the process of medical decision-making. Their intellect, emotions, and judgment are not fully developed and they are not capable of fully appreciating permanent, life altering changes such as described above. Therefore, they cannot provide informed consent. They may sometimes "assent" to a procedure or medication with a parent or guardian making the final decision.

181. With respect to GAT, in my opinion, it 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 long-term 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.

182. Because this age group is still undergoing brain development and they are immature with respect to intellect, emotion, judgment, and self-control, in my professional opinion there is a significant chance a young person may later regret the irreversible bodily changes that result from hormones or from removing an organ or organs that will no longer function and cannot be replaced.

183. I would also note that adolescents are more prone to high-risk behavior and less likely to fathom the risks and consequences of these decisions (Steinberg, 2008).

J. The WPATH and The Endocrine Society

184. According to their declarations, the experts Dr. Johanna Olson-Kennedy, Dr. Loren Schechter, and Dr. Dan H. Karasic are members of WPATH. Dr. Schechter was "co-lead author of the surgical and postoperative care chapter" for SOC 8 (Schechter decl, p 4). Dr. Karasic was a lead author of the Mental Health chapter for SOC 8 (Karasic decl, p. 3).

185. WPATH's Standards of Care 7 were produced over a decade ago in 2011. They were prepared within their advocacy organization and are purported to be a "professional consensus about the psychiatric, psychological, medical, and

surgical management of gender dysphoria" (WPATH, 2022). However, the "professional consensus" exists only within the confines of its organization. Furthermore, their Standards of Care 7, unlike the Endocrine Society's guidelines, do not have a grading system for either the strength of their recommendations or the quality of the evidence presented.

186. While the Endocrine Society has issued "Endocrine Treatment of Gender-Dysphoric / Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," these are only "guidelines." The Endocrine Society's guidelines (ESG) specifically state that their "guidelines cannot guarantee any specific outcome, nor do they establish a standard of care" (Hembree at al, 2017, p. 3895).

187. With respect to the makeup of authors of the ESG, nine out of ten authors were members of WPATH or worked on WPATH's scientific committees. Seven of those nine had at some time been in WPATH leadership including the WPATH presidency and board of directors (File: WPATH - Endocrine Society 2017 guidelines.pdf).

188. In the Endocrine Society's guidelines, the quality of evidence for the treatment of adolescents is rated "very low-quality evidence" and "low quality evidence". "The quality of evidence for [puberty blocking agents] is noted to be low. In fact, all of the evidence in the guidelines with regard to treating

children/adolescents by [gender affirmative therapy] is low to very low because of the absence of proper studies" (Laidlaw et al., 2019).

189. Unlike some other recommendations for adolescent GAT, the Endocrine Society's guidelines do not include any grading of the quality of evidence specifically for their justification of laboratory ranges of testosterone or estrogen or for adolescent mastectomy or other surgeries.

190. Endocrinologists W. Malone and P. Hruz and colleagues have written critically of the Endocrine Society's (ES) guidelines: "Unlike standards of care, which should be authoritative, unbiased consensus positions designed to produce optimal outcomes, practice guidelines are suggestions or recommendations to improve care that, depending on their sponsor, may be biased. In addition, the ES claim of effectiveness of these interventions is at odds with several systematic reviews, including a recent Cochrane review of evidence (5), and a now corrected population-based study that found no evidence that hormones or surgery improve long-term psychological well-being (6). Lastly, the claim of relative safety of these interventions ignores the growing body of evidence of adverse effects on bone growth, cardiovascular health, and fertility, as well as transition regret" (Malone et al., 2021).

191. In June of 2022, the Endocrine Society published "Enhancing the Trustworthiness of the Endocrine Society's Clinical Practice Guidelines"

(McCartney et al., 2022). They wrote "In an effort to enhance the trustworthiness of its clinical practice guidelines, the Endocrine Society has recently adopted new policies and more rigorous methodologies for its guideline program." (Id.) They relate that in 2019, the ECRI Guidelines Trust "asked the Society for permission to include its guidelines in the ECRI Guidelines Trust database". However, after an evaluation by ECRI, the guideline related to osteoporosis "was the only guideline for which all recommendations were based on verifiable systematic evidence review with explicit descriptions of search strategy, study selection, and evidence summaries" (Id.). Therefore we can conclude that with regard to the recommendations from the ESG 2017 on Gender Dysphoria/Gender Incongruence not all recommendations were "based on verifiable systematic evidence review with explicit descriptions of search strategy, study selection, and evidence summaries". Furthermore, these ESG 2017 were highly subject to conflicts of interest. As related earlier, nine out of the 10 authors were members or worked on the scientific committees of the advocacy group WPATH. Additionally, the ESG 2017 document was endorsed by WPATH. The "Enhancing Trustworthiness" article recommends the opposite composition of authors for guidelines: "A majority (>50%) of non-Chair GDP members must be free of relevant C/DOI [conflict/duality of interest]" (McCartney et al., 2022).

192. WPATH Standards of Care 8 (SOC 8) were just published Sep. 6, 2022 (Coleman et al., 2022) . In a correction to the SOC 8, all guidelines for minimum age of surgery were removed, meaning a minor of any age could be referred for any of the GAT surgeries listed previously (Correction IJTH, 2022). All guidelines for minimum age of oppposite sex hormones were also removed.

193. The correction reads: "On page S258, the following text was removed: 'The following are suggested minimal ages when considering the factors unique to the adolescent treatment time frame for gender-affirming medical and surgical treatment for adolescents, who fulfil all of the other criteria listed above.

– Hormonal treatment: 14 years
– Chest masculinization: 15 years
– Breast augmentation, Facial Surgery: 16 years
– Metoidioplasty, Orchiectomy, Vaginoplasty,
– Hysterectomy, Fronto-orbital remodeling: 17 years
– Phalloplasty: 18 years'" (WPATH SOC 8 Correction, p. S261).

194. Of great concern is that the minimum age recommendations were retracted, it appears, in contradiction to the recommendation of their own expert consensus:

"On page S66, the following text was removed:
'Age recommendations for irreversible surgical procedures were determined by a review of existing literature and the expert consensus of mental health providers, medical providers, and surgeons highly experienced in providing care to TGD adolescents.'" (WPATH SOC 8 Correction, p. S260).

195. Additionally, a chapter regarding eunuchs was inserted into SOC 8 that gives recommendations for how to induce hypogonadism in men who have the

eunuch "gender identity"[20] by either orchiectomy [testicle removal] or chemical castration such as with GnRH analogues (Coleman et al., 2022)[21].

196. The SOC8 also used an aberrant form of the GRADE approach for systematic reviews that removed the grading of quality of evidence (which should be categorized as very low, low, moderate, and high quality).[22] Instead any recommendation of "recommend" is automatically assigned as high quality of evidence. SOC 8 also failed to provide evidence profile tables which should include "an explicit judgment of each factor that determines the quality of evidence for each outcome" (Guyatt et al., 2021).

20 The notion that there is a "eunuch gender identity" further invalidates the gender identity as a serious biological property of human beings: "Many eunuch individuals see their status as eunuch as their distinct gender identity with no other gender or transgender affiliation" (Coleman et al., 2022, p. S88).

21 "Treatment options for eunuchs to consider include:
• Hormone suppression to explore the effects of androgen deficiency for eunuch individuals wishing to become asexual, nonsexual,
or androgynous;
• Orchiectomy [testicle removal] to stop testicular production
of testosterone;
• Orchiectomy with or without penectomy to
alter their body to match their self-image;
• Orchiectomy followed by hormone replacement with testosterone or estrogen. " (Id.)

22 From SOC 8 "The [recommendation] statements were classified as:
• Strong recommendations ("we recommend") are for
those interventions/therapy/strategies where:
• the evidence is of high quality" (Id., p. S250).

197. Such a modification of GRADE is explicitly recommended against in the referenced GRADE document[23] and in so doing, in my opinion, invalidates all of the SOC 8 recommendations as being evidence-based.

198. For at least the reasons above, in my 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.

K. Harms of off-label treatments in GAT

199. Dr. Antommaria makes a faulty comparison between migraine headaches and gender dysphoria (Antommaria decl, p. 7). First, migraine headaches are a neurological condition with a potential vascular component and not a condition of the mind, nor found as a psychological diagnosis in the DSM-5. Second the treament of migraine headaches with a medication such as sumitriptan or similar are labled indications for the condition unlike GnRH agonists and opposite sex hormones in GAT (FDA.gov sumitriptan). Third, the side effects of medications like sumitriptan do not alter or block normal human development such as the case with puberty blocking medication, or cause permanent alterations of the body such as

23From the GRADE guidelines: "Some organizations have used modified versions of the GRADE approach. We recommend against such modifications because the elements of the GRADE process are interlinked because modifications may confuse some users of evidence summaries and guidelines, and because such changes compromise the goal of a single system with which clinicians, policy makers, and patients can become familiar" (Guyatt et al., 2011).

with sex hormones, or lead to the permanent loss of healthy functioning organs such as occurs with surgeries which alter sex as a part of GAT.

200. Dr. Olson-Kennedy also draws a faulty comparison when she compares the off-label use of antibiotics or anti-histamines to blocking normal puberty, administering high-dose opposite sex hormones, or the permanent removal of healthy organs as part of GAT (Olson-Kennedy decl, p. 38). The health consequences are categorically different and the lifelong potential for permanent injury are extremely high in GAT.

L. The Lack of Evidence of Effectiveness of GAT

201. There is much additional evidence that questions the long-term benefits of opposite sex hormones and gender reassignment surgery and in fact suggests serious harms.

1. Sweden's Long-term study of 30 years of data by Dhejne

202. The most comprehensive study of its kind is from Sweden in 2011. The authors examined data over a 30-year time period (Dhejne, 2011). The Dhejne team made extensive use of numerous Swedish database registries and examined data from 324 patients in Sweden over 30 years who had taken opposite sex hormones and had undergone sex reassignment surgery. They used population controls matched by birth year, birth sex, and reassigned sex. When followed out beyond ten years, the sex-reassigned group had nineteen times the rate of completed suicides

and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to the general population of Sweden.

2. The Branstrom and Pachankis Retraction

203. Other published studies of GAT have been shown to have serious errors. For example, a major correction was issued by the American Journal of Psychiatry. The authors and editors of a 2020 study, titled "Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study" (Bränström study, 2020) retracted their original primary conclusion. Letters to the editor by twelve authors including myself led to a reanalysis of the data and a corrected conclusion stating that in fact the data showed no improvement in mental health for transgender identified individuals after surgical treatment nor was there improvement with opposite sex hormones ("Correction", 2020; Van Mol et al., 2020).

204. The initial reports of this study claimed that the authors found treatment benefits with surgery, and this was shared widely in the media. For example, ABC News posted an article titled "Transgender surgery linked with better long-term mental health, study shows" (Weitzer, 2019). An NBC news/Reuters headline reads "Sex-reassignment surgery yields long-term mental health benefits, study finds" (Reuters, 2019).

205. However, after twelve authors from around the world including our team investigated the study in detail, a number of serious errors were exposed leading to a retraction (Kalin, 2020; Anckarsäter et al., 2020).

206. In our letter to the editor which I co-wrote with former Chairman of Psychiatry at Johns Hopkins Medical School, Paul McHugh, MD, we noted key missing evidence in the original Branstrom report when compared to the previous body of knowledge yielded from the Swedish Dhejne study. We wrote that "[t]he study supports only weak conclusions about psychiatric medication usage and nothing decisive about suicidality. In overlooking so much available data, this study lacks the evidence to support its pro gender-affirmation surgery conclusion" (Van Mol, Laidlaw, et al., 2020).

207. In another letter, Professor Mikael Landen writes that "the authors miss the one conclusion that can be drawn: that the perioperative transition period seems to be associated with high risk for suicide attempt. Future research should use properly designed observational studies to answer the important question as to whether gender-affirming treatment affects psychiatric outcomes" (Landen, 2020).

208. In another letter to the editor, psychiatrist David Curtis noted that "[t]he study confirms the strong association between psychiatric morbidity and the experience of incongruity between gender identity and biological sex. However, the Branstrom study does not demonstrate that either hormonal treatment or surgery has

any effect on this morbidity. It seems that the main message of this article is that the incidence of mental health problems and suicide attempts is especially high in the year after the completion of gender-affirming surgery" (Curtis, 2020).

209. In yet another critical letter, Dr. Agnes Wold states that "[w]hether these factors involve a causal relationship (i.e., that surgery actually worsens the poor mental health in individuals with gender dysphoria) cannot be determined from such a study. Nevertheless, the data presented in the article do not support the conclusion that such surgery is beneficial to mental health in individuals with gender dysphoria" (Wold, 2020).

3. Flawed studies based on the problematic 2015 US Transgender Survey

210. A 2021 study by Almazan and Keurghlian attempted to address mental health outcomes in relation to surgery as a part of GAT (Almazan & Keurghlian, 2021). This was not a randomized controlled study nor a prospective observational study. Rather the study relied upon the 2015 US Transgender Survey (USTS), which has been severely criticized for its serious limitations and weaknesses.

211. D'Angelo et al. have written about the 2015 USTS survey as part of the criticism of another flawed study in the journal Pediatrics by Jack Turban in 2020 titled "Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation" (Turban, 2020). They write in their critique of the USTS that it is "a convenience

sampling, a methodology which generates low-quality, unreliable data." (Bornstein, Jager, & Putnick, 2013). Specifically, the participants were recruited through transgender advocacy organizations and subjects were asked to 'pledge' to promote the survey among friends and family. This recruiting method yielded a large but highly skewed sample...Their analysis is compromised by serious methodological flaws, including the use of a biased data sample, reliance on survey questions with poor validity, and the omission of a key control variable, namely subjects' baseline mental health status." They also state that "[s]tigmatizing non-'affirmative' psychotherapy for GD [gender dysphoria] as 'conversion' will reduce access to treatment alternatives for patients seeking non-biomedical solutions to their distress" (D'Angelo et al., 2021).

4. Mastectomy Surgery for Minors

212. Any serious look at long-term effects at surgical treatment would follow subjects out at least ten years. For example, an article was published recently examining patients who had mild calcium disorders due to a gland called the parathyroid. They compared a group of patients who had surgical removal of the parathyroid to a control group who had not. They examined data ten years after surgery was completed and concluded that parathyroid surgery in this group "did not appear to reduce morbidity or mortality" in that patient group (Pretorius, 2022).

213. To my knowledge there exists no comparable studies of minors with gender dysphoria comparing those who had mastectomy surgery to a control group who had not. There are also no known studies of minors followed for 10 years or more to determine the long-term risks and benefits of mastectomy for gender dysphoria.

214. Good quality studies specifically showing that mastectomy surgery is safe, effective, and optimal for treating minors with gender dysphoria do not exist. For example, there is a study titled "Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults Comparisons of Nonsurgical and Postsurgical Cohorts" (Olson-Kennedy, 2018). The study authors conclude that "[c]hest dysphoria was high among presurgical transmasculine youth, and surgical intervention positively affected both minors and young adults." However, there are a number of problems with this study. First, the term "chest dysphoria" is a creation of the study authors and is not found as a diagnosis or even referenced in the DSM-5. Second the "chest dysphoria scale" is a measuring tool created by the authors, but which the authors state "is not yet validated." (*Id*., p. 435) Third, the mastectomies were performed on girls as young as 13 and 14 years old and who thereby lacked the maturity and capacity of good judgment for truly informed consent for this life altering procedure. For this reason, in my professional opinion, the research and surgeries performed were flawed and unethical.

215. There exists another poorly designed study which suffers from similar methodological and ethical problems as the Olson-Kennedy study. A 2021 study published in Pediatrics examined females aged 13-21 recruited from a gender clinic. Thirty young females had mastectomy procedures and sixteen had not. The average age at surgery was 16.4 years (Mehringer, 2021). The follow up time after surgery was only 19 months and no data is provided or analyzed about key psychiatric information such as comorbid psychological illnesses, self-harming behaviors, psychiatric hospitalizations, psychiatric medication use, or suicide attempts.

216. Information returned from the study surveys were all qualitative and included responses such as "[My chest dysphoria] made me feel like shit, honestly. It made me suicidal. I would have breakdowns". Another respondent stated, "I've been suicidal quite a few times over just looking at myself in the mirror and seeing [my chest]. That's not something that I should have been born with" (Mehringer, 2021). The omission of psychiatric data is a major flaw in the study and also irresponsible given the obviously dangerous psychological states that some of these young people were in.

217. Since such a high proportion of subjects were using testosterone (83%), some of the responses could be attributed to adverse effects of testosterone. For example, as related earlier, high dose testosterone can manifest in irritability and

aggressiveness. One study subject responded, “I get tingly and stuff and it kind of makes me want to punch something" (Mehringer, 2022).

218. The testosterone labeling also indicates nausea and depression as adverse reactions which are described by another study subject “There’s a feeling of hopelessness, of desperation, of—almost makes me feel physically sick" (Actavis Pharma, Inc., 2018; Mehringer, 2022).

219. The study appears to have been designed, at least in part, to justify insurance companies paying for mastectomy procedure for minors with GD, even though they have provided no long-term statistical evidence of benefit: "These findings...underscore the importance of insurance coverage not being restricted by age" (Mehrniger, 2021). This also appears to be part of the aim of the flawed Olson-Kennedy study which stated “changes in clinical practice and in insurance plans’ requirements for youth with gender dysphoria who are seeking surgery seem essential” (Olson-Kennedy, 2018). So these two studies, rather than being a thorough examination of the psychological and physical risks and benefits of mastectomy surgery over the long-term appear instead to exist, at least in part, to validate the need for insurance companies to insure the costs of these dubious procedures for minors.

5. Centers for Medicare and Medicaid Services

220. The Centers for Medicare and Medicaid Services ("CMS") has found "inconclusive" clinical evidence regarding gender reassignment surgery. Specifically, the CMS Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N) (June 19, 2019) states: "The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population."

221. Dr. Schecter states: "The result of CMS's review of the evidence is not applicable to other population groups" (Schecter decl, p. 39). However it does not make the converse true as Dr. Schecter seems to imply. In other words, the CMS review does not therefore mean that there is conclusive evidence of benefit and lack of harm for the under 65 population. On the contrary, evidence of benefit is lacking and the risks and harms due to GAT are very high as I have described.

6. Nations and States Question and Reverse Course on GAT

222. Also noteworthy is that other nations are questioning and reversing course regarding gender affirmative therapy. For example in the *Bell v. Tavistock* Judgment in the UK, regarding puberty blockers in GAT, they concluded that "there is real uncertainty over the short and long-term consequences of the treatment with

very limited evidence as to its efficacy, or indeed quite what it is seeking to achieve. This means it is, in our view, properly described as experimental treatment" (*Bell v. Tavistock* Judgment, 2020).

223. The case was appealed and although the medical decision making was returned to clinicians (rather than the courts), it was noted that great pains should be taken to ensure that the child and parents are properly informed before embarking on such treatments. In its conclusion the appeals court stated that "[c]linicians will inevitably take great care before recommending treatment to a child and be astute to ensure that the consent obtained from both child and parents is properly informed by the advantages and disadvantages of the proposed course of treatment and in the light of evolving research and understanding of the implications and long-term consequences of such treatment. Great care is needed to ensure that the necessary consents are properly obtained " (*Bell v. Tavistock* Appeal, Judgment, 2021).

224. In the bulletin of the Royal College of Psychiatrists in 2021, in a reevaluation of the evidence, Griffin and co-authors write, "As there is evidence that many psychiatric disorders persist despite positive affirmation and medical transition, it is puzzling why transition would come to be seen as a key goal rather than other outcomes, such as improved quality of life and reduced morbidity. When the phenomena related to identity disorders and the evidence base are uncertain, it might be wiser for the profession to admit the uncertainties. Taking a supportive,

exploratory approach with gender-questioning patients should not be considered conversion therapy" (Griffin et al., 2021).

225. In 2020, Finland recognized that "[r]esearch data on the treatment of dysphoria due to gender identity conflicts in minors is limited," and recommended prioritizing psychotherapy for gender dysphoria and mental health comorbidities over medical gender affirmation (Council for Choices in Healthcare in Finland, 2020). Additionally, "[s]urgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors".

226. In 2021, Sweden's largest adolescent gender clinic announced that it would no longer prescribe puberty blockers or cross-sex hormones to youth under 18 years outside clinical trials (SEGM, 2021). "In December 2019, the SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) published an overview of the knowledge base which <u>showed a lack of evidence for both the long-term consequences of the treatments, and the reasons for the large influx of patients in recent years.</u> <u>These treatments are potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis.</u> This makes it challenging to assess the risk / benefit for the individual patient, and even more challenging for the minors or their guardians to be in a position of an informed stance regarding these treatments" (Gauffen and Norgren, 2021).

227. Dr Hilary Cass "was appointed by NHS England and NHS Improvement to chair the Independent Review of Gender Identity Services for children and young people in late 2020" (The Cass Review website, 2022). In her interim report dated February 2022, it states that "[e]vidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally" (Cass, 2022).

M. Assessment of the patient with gender dysphoria

228. In light of the very serious medical concerns and potential harms of gender affirmative therapy, there are several criteria that I believe would be important to fulfill before applying the GAT model to a patient.

a. Minors should be evaluated to determine if they will follow the natural pattern of desistance which 50 to 98% of pediatric age children will follow[24].

b. Patients, parents and guardians should be made aware of other options for treatment of gender dysphoria including active psychosocial treatment or watching and waiting with support in order to help with natural desistance.

c. The patient should be provided an assessment by a qualified psychologist or psychiatrist who does not follow the WPATH GAT model. If

24 From the DSM-5: "Rates of persistence of gender dysphoria from childhood into adolescence or adulthood vary…In natal males, persistence has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%" (American Psychiatric Association, 2013).

underlying psychological conditions are diagnosed then these should be adequately evaluated and treated before proceeding to hormones and surgery.

d. If a medicalized approach with hormones such as testosterone or medications to stop menstruation is being considered then a clear description of the risks and benefits needs to be conveyed to the patient and if a minor also the parent or guardian. It needs to be verified that they fully understand these risks.

e. If surgical procedures such as mastectomy, hysterectomy, ovariectomy, orchiectomy, or vaginoplasty are being considered then clear descriptions of the risks and benefits need to be conveyed to the patient, and if a minor, the parent or guardian.

229. However, even if a minor and their parents or guardian are made fully aware of the risks and benefits of hormones and surgeries, in my opinion, the minor does not have adequate maturity and judgment to make permanent changes to their body that may result in infertility/sterility and the permanent loss of organs such as breasts whose functions will not be fully utilized (such as breastfeeding) until adulthood.

II. Medical Concerns Regarding Plaintiffs

A. [redacted]

230. [redacted]

[redacted]

231. [redacted]

232. [redacted]

233. [redacted]

[redacted]

234. [redacted]

235. [redacted]

[redacted].

236. [redacted]

237. [redacted]

238. [redacted]

239. [redacted]

240. [redacted]

[redacted]

241. [redacted]

242. [redacted]

243. [redacted]

244. [redacted]

245.

246.

247.

[redacted]

248. [redacted]

249. [redacted]

250. [redacted]

B. [redacted]

251. [redacted]

252. [redacted]

[redacted]

253. [redacted]

254. [redacted]

255. [redacted]

256. [redacted]

257. [redacted]

258. [redacted]

259. [redacted]

260. [redacted]

261. [redacted]

262. [redacted]

263.

264.

25 "Studies of transgender males taking testosterone have shown up to a nearly 5-fold increased risk of myocardial infarction relative to females not receiving testosterone" (Laidlaw et al.,2021; Alzahrani et al., 2019).

265. [redacted]

266. [redacted]

[redacted]

267. [redacted]

268. [redacted]

269. [redacted]

270. [redacted]

[redacted]

C. [redacted]

271. [redacted]

272. [redacted]

273. [redacted]

[redacted]

274. [redacted]

275. [redacted]

276. [redacted]

26 The ESG state that "the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/ gender incongruent in adolescence " (Hembree, 2017.)

[redacted]

277. [redacted]

278. [redacted]

279. [redacted]

27 The ESG state that "social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence" (Hembree, 2017).

28 With respect to estrogen, the ESG state that it is essential that "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" (Id.).

[redacted]

280. [redacted]

281. [redacted]

[redacted]

282. [redacted]

283. [redacted]

284. [redacted]

[redacted]

285. [redacted]

286. [redacted]

287. [redacted]

288. [redacted]

289. [redacted]

290. [redacted]

291. [redacted]

292. [redacted]

293. [redacted]

D. [redacted]

294. [redacted]

295.

296.

[redacted]

297. [redacted]

298. [redacted]

299. [redacted]

[redacted]

300. [redacted]

301. [redacted]

[redacted]

302. [redacted]

303. [redacted]

[redacted]

304. [redacted]

305. [redacted]

III. Conclusion

306. The gender affirmative therapy model suffers from serious deficiencies in logic and lacks scientific foundation. The deep error hidden in this model is that one cannot in fact change sex. One cannot acquire the deep characteristics of

29 There are serious concerns regarding liver dysfunction with testosterone: "Prolonged use of high doses of androgens ... has been associated with development of hepatic adenomas [benign tumors], hepatocellular carcinoma [cancer], and peliosis hepatis [generation of blood-filled cavities in the liver that may rupture] —all potentially life-threatening complications" (Actavis Pharma, 2018).

biological sex in order to gain the complete sexual and reproductive functions of the opposite sex. This is not technologically possible.

307. Children and adolescents are of such immature minds that they are likely to believe that it is possible. In fact they may come to believe that their inherent, biologically necessary puberty is "terrifying" or needs to be stopped. Social transition serves to convince the child or adolescent that they can be the opposite sex. Puberty blockers sustain this state of mind by retaining a childlike state with respect to the genitalia and body habitus. High dose opposite sex hormones then cause medical conditions such as hirsutism and irreversible damage to the vocal cords in females and gynecomastia in males. These conditions serve to convince the young person that they are going through puberty of the opposite sex when in fact they are not developing sexually and are infertile.

308. There are known risks for both adults and minors, some of which I have described above, including cardiovascular disease, cancer, deficiencies in ultimate bone density, harms to sexual function, infertility, and for some permanent sterility. The child or adolescent cannot consent to these harms when they are not mature enough to fully comprehend what they mean. Long-term studies regarding the treatment effects specifically for minors with hormones and surgeries, using randomized controlled studies or even proper observational studies do not exist. The

two adult plaintiffs and the two plaintiffs' children have comorbidities which make GAT particularly dangerous.

309. WPATH's newly released 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.

310. For the reasons set forth above, in my professional opinion as an endocrinologist, no child or adolescent should receive puberty blockers to block normal puberty, nor should they receive supraphysiologic doses of opposite sex hormones to attempt to alter secondary sex characteristics, nor should they have surgeries to remove or alter the breasts, genitalia or reproductive tracts as part of GAT. The child cannot consent or assent to these procedures. The parent or guardian also cannot consent to the life altering changes resulting from GAT. There exists insufficient evidence of benefit for adults, but serious concerns for risk of harm.

311. Finally, the June 2022 AHCA GAPMS report states: "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" (FL Medicaid GAPMS, 2022). I strongly agree with that statement.

I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury that the foregoing is true and correct. Executed this 17th day of February, 2023.

/s/ Michael K. Laidlaw

Michael K. Laidlaw, M.D.

References

Actavis Pharma, Inc. Testosterone Cypionate injection. Actavis Pharma, Inc., 2018. Accessed May 8, 2022 via https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7b57b68-dca6-4df2-b3f2-7017d7b69f17&msclkid=4ed2db18cd5411ecba911bd6e4bded62

Alberts B, Johnson A, Lewis J, et al. "Sperm" in Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.

Almazan AN, Keuroghlian AS. "Association Between Gender-Affirming Surgeries and Mental Health Outcomes". JAMA Surgery 2021; 156(7): 611–618.

Alzahrani T, Nguyen T, Ryan A, et al. "Cardiovascular disease risk factors and myocardial infarction in the transgender population". Circ Cardiovasc Qual Outcomes. 2019;12(4):e005597

The American Cancer Society medical and editorial team. "Mastectomy". American Cancer Society. https://www.cancer.org/cancer/breast-cancer/treatment/surgery-for-breast-cancer/mastectomy.html accessed 06/24/22

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5). Arlington, VA, American Psychiatric Association, 2013.

Anckarsäter, H., (MD, Ph.D.) and Gillberg, C., (M.D., Ph.D.) "Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery". Am J Psychiatry 2020; 177:764– 765; doi: 10.1176/appi.ajp.2020.19111117.

Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. "Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome". J Clin Endocrinol Metab. 2005;90(4):1929. Epub 2004 Dec 28.

Arain, et al. Neuropsychiatric Disease and Treatment. "Maturation of the adolescent brain". Neuropsychiatric Disease and Treatment. 2013:9 449–461

Banikarim, C. “Primary Dysmneorrhea in Adolescents”. UpToDate. Feb 10, 2021.

Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Wallace RB, Ohsfeldt RL, Jones MP, Rosenthal GE, Wolinsky FD "The aftermath of hip fracture: discharge placement, functional status change, and mortality." Am J Epidemiol. 2009;170(10):1290. Epub 2009 Oct 4.

Bell & Mrs A v The Tavistock And Portman NHS Foundation Trust. Approved Judgment.[2020] EWHC 3274 (Admin) (01 December 2020). https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Judgment.pdf

Bell & Mrs A v The Tavistock And Portman NHS Foundation Trust. Appeal No. C1/2020/2142 (17 September 2021).

Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Wallace RB, Ohsfeldt RL, Jones MP, Rosenthal GE, Wolinsky FD "The aftermath of hip fracture: discharge placement, functional status change, and mortality." Am J Epidemiol. 2009;170(10):1290. Epub 2009 Oct 4.

Bouraïma H, Lireux B, Mittre H, Benhaim A, Herrou M, Mahoudeau J, Guillon-Metz F, Kottler ML, Reznik Y. Major hyperestrogenism in a feminizing adrenocortical adenoma despite a moderate overexpression of the aromatase enzyme. Eur J Endocrinol. 2003 Apr;148(4):457-61. doi: 10.1530/eje.0.1480457. PMID: 12656667.

Bränström R, Pachankis JE. “Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study”. Am J Psychiatry 2020; 177:727–734

Bränström R, Pachankis JE. “Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals’ Mental Health: Response to Letters”. Am J Psychiatry 2020; 177:769–772; doi: 10.1176/appi.ajp.2020.20050599.

Brown BB & Larson J. Handbook of Adolescent Psychology. 3 Peer Relationships in Adolescence. John Wiley & Sons, Inc. 2009.

Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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. PLoS One. 2021 Feb 2;16(2):e0243894. doi: 10.1371/journal.pone.0243894. PMID: 33529227; PMCID: PMC7853497.

Cass, Hillary. The Cass Review Interim Report. Feb, 2022. https://cass.independent-review.uk/publications/interim-report/

The Cass Review. Website. The Chair. Accessed on-line April 29, 2022. https://cass.independent-review.uk/about-the-review/the-chair/

Cavlan D, Bharwani N, Grossman A. Androgen- and estrogen-secreting adrenal cancers. Semin Oncol. 2010 Dec;37(6):638-48. doi: 10.1053/j.seminoncol.2010.10.016. PMID: 21167382.

CDC. "What is Venous Thromboembolism?" Accessed online 04/27/2022. https://www.cdc.gov/ncbddd/dvt/facts.html?msclkid=7406875bc6a411ecb67829f71b182f45

Chan Y, et al. "Evaluation of the infant with atypical genital appearance (difference of sex development)" UpToDate. Feb 18, 2021.

Christel J M de Blok, et al. "Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands" BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l1652 (Published 14 May 2019)

Coleman E, et al. "Standards of Care for the Health of Transgender and Gender Diverse People, Version 8". International Journal of Transgender Health. 06 Sep

2022. International Journal of Transgender Health.
https://doi.org/10.1080/26895269.2022.2100644.
https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2100644

Collet S, Gieles NC, Wiepjes CM, Heijboer AC, Reyns T, Fiers T, Lapauw B, den Heijer M, T'Sjoen G. Changes in Serum Testosterone and Adrenal Androgen Levels in Transgender Women With and Without Gonadectomy. J Clin Endocrinol Metab. 2023 Jan 17;108(2):331-338. doi: 10.1210/clinem/dgac576. PMID: 36201493; PMCID: PMC9844963.

"Correction to Bränström and Pachankis," Am J Psychiatry, 177:8 (Aug. 2020).

Correction, International Journal of Transgender Health, 23:sup1, S259- S261, DOI: 10.1080/26895269.2022.2125695

Council for Choices in Healthcare in Finland, Medical treatment methods for dysphoria associated with variations in gender identity in minors—recommendation, June 11, 2020, https://bit.ly/Cohere_Finland_ GDAinMinorsRx.

Curtis, D. "Study of Transgender Patients: Conclusions Are Not Supported by Findings". Am J Psychiatry 2020; 177:766; doi: 10.1176/appi.ajp.2020.19111131 ;

de Vries AL, Steensma T, Doreleijers TA, Cohen-Kettenis PT. "Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study". J Sex Med. 2011 Aug;8(8):2276-83.

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 (2014) 134 (4): 696–704.

DEA. Diversion Control Division. Controlled Substance Schedules. Accessed May 1, 2022. https://www.deadiversion.usdoj.gov/schedules/

D'Angelo R, et al. "One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria". Archives of sexual behavior 2021; 50(1): 7–16.

Dhejne, et al., "Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden," PLoS One, vol. 6, issue 2 (Feb. 22, 2011)

Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. Dev Psychol. 2008 Jan;44(1):34-45. doi: 10.1037/0012-1649.44.1.34. PMID: 18194003.

Dunaif A, Segal KR, Futterweit W, Dobrjansky A. "Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome". Diabetes. 1989;38(9):1165.

Elhakeem A, et al. "Association Between Age at Puberty and Bone Accrual From 10 to 25 Years of Age". JAMA Network Open. 2019;2(8):e198918. doi:10.1001/jamanetworkopen.2019.8918

Emmanuel M & Bokor B. Tanner Stages. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK470280/

FDA.gov, regarding celecoxib https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020998s026lbl.pdf accessed 10/01/22

FDA.gov sumatriptan. "HIGHLIGHTS OF PRESCRIBING INFORMATION..IMITREX (sumatriptan)". https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020080s054lbl.pdf accessed 10/01/2022.

Florida Department of Health website. https://mqa-internet.doh.state.fl.us/MQASearchServices/HealthCareProviders accessed 09/29/22-10/01/22.

Gagnon DR, Zhang T, Brand FN, Kannel WB. “Hematocrit and the risk of cardiovascular disease—The Framingham Study: a 34-year follow-up”. Am Heart J. 1994;127(3):674-682.

Gaufen D and Norgren S. "Policy Change Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children’s Hospital". 2021. https://segm.org/sites/default/files/Karolinska%20Guideline%20K2021-4144%20April%202021%20%28English%2C%20unofficial%20translation%29.pdf

Greenpsan FS & Gardner DG. Basic & Clinical Endocrinology, 7th edition. Puberty. Lange Medical Books/McGraw-Hill. 2004.

Griffin, L., Clyde, K., Byng, R., & Bewley, S. (2021). “Sex, gender and gender identity: A re-evaluation of the evidence”. BJPsych Bulletin, 45(5), 291-299. doi:10.1192/bjb.2020.73

Grynberg M, Fanchin R, Dubost G, Colau J, Brémont-Weil C, Frydman R, Ayoubi J. “Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population”. Reprod Biomed Online. 2010 Apr;20(4):553-8.

Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011 Apr;64(4):380-2. doi: 10.1016/j.jclinepi.2010.09.011. Epub 2010 Dec 24. PMID: 21185693. https://www.jclinepi.com/article/S0895-4356(10)00330-6/fulltext

Hall Ryan CW, Hall Richard CW, Chapman MJ. "Psychiatric Complications of Anabolic Steroid Abuse". Psychosomatics 46:4, July-August 2005.

Hardin AP, Hackell JM; COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE. Age Limit of Pediatrics. Pediatrics. 2017 Sep;140(3):e20172151. doi: 10.1542/peds.2017-2151. Epub 2017 Aug 21. PMID: 28827380.

Hembree WC, et al., "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," The Journal of Clinical Endocrinology & Metabolism, Volume 102, Issue 11 (Nov. 1, 2017).

Irwig MS. "Cardiovascular health in transgender people." Rev Endocr Metab Disord. 2018;19(3):243–251.

Joham AE, Ranasinha S, Zoungas S, Moran L, Teede HJ. "Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome". J Clin Endocrinol Metab. 2014 Mar;99(3):E447-52.

Kalin, N.H. "Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process by the Editor-in-Chief The American Journal of Psychiatry". Am J Psychiatry 2020; 177:7 64; doi: 10.1176/appi.ajp.2020.20060803

Kaltiala-Heino R, Sumia M, Työläjärvi M, Lindberg N. "Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development". Child and Adolescent Psychiatry and Mental Health (2015) 9:9.

Kuohong W and Hornstein MD. "Causes of female infertility". UpToDate. Jul 22, 2021.

Labcorp. Estradiol. https://www.labcorp.com/tests/004515/estradiol Accessed 02/04/23.

Laidlaw MK. "Gender Dysphoria and Children: An Endocrinologist's Evaluation of 'I am Jazz'". Public Discourse, 5 Apr 2018. https://www.thepublicdiscourse.com/2018/04/21220/

Laidlaw MK. "The Gender Identity Phantom", gdworkinggroup.org, Oct. 24, 2018. http://gdworkinggroup.org/2018/10/24/the-gender-identity-phantom/

Laidlaw MK, Cretella M, Donovan K. "The Right to Best Care for Children Does Not Include the Right to Medical Transition". The American Journal of Bioethics. 19(2), Feb 2019.

Laidlaw MK, Van Meter Q, Hruz P, Van Mol W, & Malone W, "Letter to the Editor: Endocrine Treatment of Gender-Dsyphoria/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," J Clin Endocrinol Metab, 104(3) (March 2019).

Laidlaw MK, Van Mol A, Van Meter Q, Hansen JE. Letter to the Editor from M Laidlaw et al.: "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years." The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 12, December 2021, Pages e5275–e5276, https://doi.org/10.1210/clinem/dgab514

Landén, M. "The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided". Am J Psychiatry 2020; 177:767–768; doi: 10.1176/appi.ajp.2020.19111165.

Larsen PR, et al. Williams Textbook of Endocrinology, 10th edition. Philadelphia, W.B. Saunders Company, 2003.

Littman L. "Rapid-onset gender dysphoria in adolescents and young adults: a study of parental reports". PLoS One. 2018;13(8): e0202330

Lupron Depot-Ped. Highlights of Prescribing Information. AbbVie Inc. Accessed May 1, 2022. https://www.rxabbvie.com/pdf/lupronpediatric.pdf

Madsen MC, van Dijk D, Wiepjes CM, Conemans EB, Thijs A, den Heijer M. "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term

Follow-Up Study on Prevalence, Determinants, and Exposure Years". J Clin Endocrinol Metab. 2021 May 13;106(6):1710-1717. doi: 10.1210/clinem/dgab089.

Malone, W. and Roman, S. "Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress". Am J Psychiatry 2020; 177:766–767; doi: 10.1176/appi.ajp.2020.19111149

Mayo Clinic. "Feminizing Surgery".
https://www.mayoclinic.org/tests-procedures/feminizing-surgery/about/pac-20385102
Accessed 07/01/2022

Mayo Clinic. "Masculinizing Surgery". https://www.mayoclinic.org/tests-procedures/masculinizing-surgery/about/pac-20385105 accessed 06/24/2022

Mayo Clinic. "Top surgery for transgender men and nonbinary people". https://www.mayoclinic.org/tests-procedures/top-surgery-for-transgender-men/about/pac-20469462 accessed 06/24/2022.

McCartney CR, Corrigan MD, Drake MT, El-Hajj Fuleihan G, Korytkowski MT, Lash RW, Lieb DC, McCall AL, Muniyappa R, Piggott T, Santesso N, Schünemann HJ, Wiercioch W, McDonnell ME, Murad MH. Enhancing the Trustworthiness of the Endocrine Society's Clinical Practice Guidelines. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2129-2138. doi: 10.1210/clinem/dgac290. PMID: 35690966.

Mehringer JE, et al. "Experience of Chest Dysphoria and Masculinizing Chest Surgery in Transmasculine Youth". Pediatrics (2021) 147 (3): e2020013300.

Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. "Low fertility preservation utilization among transgender youth". J Adolesc Health. 2017;61(1):40–44.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP)

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17;106(25):3143-421. PMID: 12485966.

Olson-Kennedy J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. JAMA Pediatr. 2018 May 1;172(5):431-436.

Pagadala M. "Comparison of the Concentration of Estrogen and Testosterone Ratio in Male Patients With Cirrhosis and Hypotension". ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05051293
Accessed 02/05/23

Palko. Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland). 2020. https://genderreport.ca/wp-content/uploads/2021/04/Finland_Guidelines_Gender_Variance_In_Minors.pdf

Pretorius M, et al. "Mortality and Morbidity in Mild Primary Hyperparathyroidism: Results From a 10-Year Prospective Randomized Controlled Trial of Parathyroidectomy Versus Observation". Ann Intern Med. 2022 Apr 19. doi: 10.7326/M21-4416. Online ahead of print.

Quest Diagnositics. Estrogen, Total, Serum.
https://testdirectory.questdiagnostics.com/test/test-detail/439/estrogen-total-serum?cc=MASTER
accessed on-line 02/05/23

Quest Diagnostics. Hematocrit.
https://testdirectory.questdiagnostics.com/test/test-detail/509/hematocrit?cc=MASTER
accessed on-line 02/05/23

Quest Diagnostics. Testosterone, Total, MS.

https://testdirectory.questdiagnostics.com/test/test-detail/15983/testosterone-total-ms?cc=MASTER
accessed on-line 01/12/23

Reuters. "Sex-reassignment surgery yields long-term mental health benefits, study finds". NBC News. Nov 8, 2019. https://www.nbcnews.com/feature/nbc-out/sex-reassignment-surgery-yields-long-term-mental-health-benefits-study-n1079911

Ristori J, Steensma TD. Gender dysphoria in childhood. Int Rev Psychiatry. 2016;28(1):13-20. doi: 10.3109/09540261.2015.1115754. Epub 2016 Jan 12. PMID: 26754056.

Santoro N. Update in hyper- and hypogonadotropic amenorrhea. J Clin Endocrinol Metab. 2011 Nov;96(11):3281-8. doi: 10.1210/jc.2011-1419. PMID: 22058375.

Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. "Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention." Circulation. 2003;108(17):2154.

Sax L. “How Common is Intersex? A Response to Anne Fausto-Sterling,” Journal of Sex Research 39:3 (August 2002), pp. 174-178.

Singh, D. (2012). A follow-up study of boys with gender identity disorder. Unpublished doctoral dissertation, University of Toronto.

Society for Evidence Based Gender Medicine (SEGM). Sweden’s Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies (May 5, 2021), https://bit.ly/SEGM_SwedenStops Hormones.

Society for Evidence Based Gender Medicine (SEGM). National Academy of Medicine in France Advises Caution in Pediatric Gender Transition. (Mar 3, 2022), https://segm.org/France-cautions-regarding-puberty-blockers-and-cross-sex-hormones-for-youth

Statement of Removal, International Journal of Transgender Health, 23:sup1, S259-S259. 2022. DOI: 10.1080/26895269.2022.2125695 https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2125695

Steinberg L. "A social neuroscience perspective on adolescent risk-taking". Dev Rev. 2008;28(1):78-106.

TLC UK. Bottom Surgery | I am Jazz. Youtube. Accessed May 1, 2022. https://www.youtube.com/watch?v=lG-U8oFpa8o

Turban JL, King D, Carswell JM, et al. "Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation". Pediatrics 2020, 145 (2) e20191725.

Van Mol, A., Laidlaw, M. K., Grossman, M., McHugh, P. "Gender-Affirmation Surgery Conclusion Lacks Evidence" Am J Psychiatry 177:8, August 2020 ajp.psychiatryonline.org 765.

Wang AMQ, Tsang V, Mankowski P, Demsey D, Kavanagh A, Genoway K. Outcomes Following Gender Affirming Phalloplasty: A Systematic Review and Meta-Analysis. Sex Med Rev. 2022 Aug 25:S2050-0521(22)00012-9. doi: 10.1016/j.sxmr.2022.03.002. Epub ahead of print. PMID: 36031521.

Wallien, M.S.C., Veenstra, R., Kreukels, B.P.C. et al. Peer Group Status of Gender Dysphoric Children: A Sociometric Study. Arch Sex Behav 39, 553–560 (2010). https://doi.org/10.1007/s10508-009-9517-3

Weitzer, D. "Transgender surgery linked with better long-term mental health, study shows". ABC News. Oct 8, 2019. https://abcnews.go.com/Health/transgender-surgery-linked-long-term-mental-health-study/story?id=66125676

Wilson D and Bruno B. Embryology, Mullerian Ducts (Paramesonephric Ducts). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK557727/

Wold, A. (M.D., Ph.D.) Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, Am J Psychiatry 2020; 177:768; doi: 10.1176/appi.ajp.2020.19111170

WPATH member search. https://www.wpath.org/member/search accessed 09/29/2022 and 10/01/2022.

Yelehe M. et al. "Adverse effects of gender-affirming hormonal therapy in transgender persons: Assessing reports in the French pharmacovigilance database." Fundamental and Clinical Pharmacology. June 2, 2022.

Zucker KJ. “Debate: Different strokes for different folks”. Child and Adolescent Mental Health, Volume 25, Issue 1 (Feb 2020).

Attachment A

Michael K. Laidlaw, M.D.
Endocrinology, Diabetes, and Metabolism
5180 Grove St.
Rocklin, CA 95677
Office: (916) 315-9100
Fax: (916) 315-0141
docdrlaidlaw@gmail.com

EMPLOYMENT

2006-Present Michael K Laidlaw, MD Inc. Private Practice – Endocrinology, Diabetes, and Metabolism. Rocklin, CA

EDUCATION

2004-2006 Endocrinology and Metabolism Fellowship - Los Angeles County/University of Southern California Keck School of Medicine

2001-2004 Internal Medicine Residency - Los Angeles County/University of Southern California Keck School of Medicine

1997-2001 University of Southern California Keck School of Medicine
Doctor of Medicine Degree May 2001

1990-1997 San Jose State University
Bachelor of Science Degree in Biology with a concentration in Molecular Biology, Cum Laude

LICENSURE

California Medical License – Physician and Surgeon: # A81060: Nov 6, 2002. Exp 5/31/2024.

PROFESSIONAL AFFILIATIONS

Endocrine Society 2006-2022
American Board of Internal Medicine - Endocrinology, Diabetes, and Metabolism – 2006
American Board of Internal Medicine - Internal Medicine - 2005
National Board of Physicians and Surgeons - Endocrinology, Diabetes, & Metabolism 2018-2024
National Board of Physicians and Surgeons - Internal Medicine 2018-2024

HONORS AND RECOGNITION

2010 Endocrine Society Harold Vigersky Practicing Physician Travel Award
2004-2005 Vice President - Joint Council of Interns and Residents
2002-2004 Council Member – Joint Council of Interns and Residents
1996, 1997 Dean's Scholar, San Jose State University
1995 Golden Key National Honor Society

RESEARCH AND PUBLICATIONS

2021 Publication – Michael K Laidlaw, Andre Van Mol, Quentin Van Meter, Jeffrey E Hansen. Letter to the Editor from M Laidlaw et al.: "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years." The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 12, December 2021, Pages e5275–e5276, https://doi.org/10.1210/clinem/dgab514

2020 Publication – Van Mol A, Laidlaw MK, Grossman M, McHugh P. "Correction: Transgender Surgery Provides No Mental Health Benefit." Public Discourse, 13 Sep 2020. https://www.thepublicdiscourse.com/2020/09/71296/

2020 Publication – VanMol A, Laidlaw MK, Grossman M, McHugh P.. "Gender-affirmation surgery conclusion lacks evidence (letter)". Am J Psychiatry 2020; 177:765–766.

2020 Publication – Laidlaw MK. "The Pediatric Endocrine Society's Statement on Puberty Blockers Isn't Just Deceptive. It's Dangerous." Public Discourse. 13 Jan 2020. https://www.thepublicdiscourse.com/2020/01/59422/

2019 Speech to the U.K. House of Lords – Laidlaw MK. "Medical Harms Associated with the Hormonal and Surgical Therapy of Child and Adolescent Gender Dysphoria". Parliament, London, U.K. 15 May 2019.

2019 Publication – Laidlaw MK, Cretella M, Donovan K. "The Right to Best Care for Children Does Not Include the Right to Medical Transition". The American Journal of Bioethics. Volume 19. Published online 20 Feb 2019. 75-77. https://doi.org/10.1080/15265161.2018.1557288

2018 Publication – Laidlaw MK, Van Meter QL, Hruz PW, Van Mol A, Malone WJ. Letter to the Editor: "Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline." The Journal of Clinical Endocrinology & Metabolism, Volume 104, Issue 3, 1 March 2019, Pages 686–687, https://doi.org/10.1210/jc.2018-01925 (first published on-line 11/2018)

2018 Publication – Laidlaw MK. "The Gender Identity Phantom". gdworkinggroup.org, 24 Oct 2018. http://gdworkinggroup.org/2018/10/24/the-gender-identity-phantom/

2018 Publication – Laidlaw MK. "Gender Dysphoria and Children: An Endocrinologist's Evaluation of 'I am Jazz'". Public Discourse, 5 Apr 2018. https://www.thepublicdiscourse.com/2018/04/21220/

2013 Abstract – Poster presentation Jun 2013. Endocrine Society Annual Meeting. A 12 Step Program for the Treatment of Type 2 Diabetes and Obesity.

2011 Abstract – Poster presentation Nov 2011. Journal of Diabetes Science and Technology. A Video Game Teaching Tool for the Prevention of Type 2 Diabetes and Obesity in Children and Young Adults.

2011 Abstract – Journal of Diabetes Science and Technology. A Web-Based Clinical Software Tool to Assist in Meeting Diabetes Guidelines and Documenting Patient Encounters.

2008 Abstract - Accepted to Endocrine Society Annual Meeting 2008. Hypercalcemia with an elevated 1,25 dihydroxy-Vitamin D level and low PTH due to granulomatous disease.

2005-2006 Clinical Research - University of Southern California – Utility of Thyroid Ultrasound in the Detection of Thyroid Cancer. Study involving the use of color flow/power doppler ultrasound and ultrasound guided biopsy to detect the recurrence of thyroid cancer in patients with total thyroidectomies.

2005 Certification - Certification in Diagnostic Thyroid Ultrasound and Biopsy – AACE 2005

2003 Certification - Understanding the Fundamentals: Responsibilities and Requirements for the Protection of Human Subjects in Research. University of Southern California. 29 Sep 2003 - 29 Sep 2006

2002-2005 Clinical Research - University of Southern California - Determining the Role of Magnesium in Osteoporosis. Study involved collecting and analyzing patient data related to patient characteristics, laboratory results, bone mineral density exams, nutrition analysis, and genetic analysis in order to determine a link between magnesium deficiency and osteoporosis.

1996 Research Assistant - San Jose State University - Role of the suprachiasmatic nucleus pacemaker in antelope ground squirrels.

1995-1996 Research Assistant - San Jose State University/NASA. Acoustic tolerance test and paste diet study for space shuttle rats.

EXPERT WITNESS WORK AND AMICUS BRIEFS

2022 Expert Witness Report – Laidlaw MK. C. P., by and through his parents, Patricia Pritchard and Nolle Pritchard; and PATRICIA PRITCHARD, Plaintiff, vs. BLUE CROSS BLUE SHIELD OF ILLINOIS, Defendants. Case No. 3:20-cv-06145-RJB

2022 Expert Witness Report – Laidlaw MK. DISTRICT COURT OF TRAVIS COUNTY, TEXAS 459th JUDICIAL DISTRICT. PFLAG, INC., ET AL., Plaintiffs, v. GREG ABBOTT, ET AL., Defendants. NO. D-1-GN-22-002569. 3 July 2022.

2022 Expert Witness Report #2 – Laidlaw MK. United States District Court for the District of Arizona. DH and John Doe, Plaintiffs, vs. Jami Snyder, Director of the Arizona Health Care Cost Containment System, in her official capacity, Defendant. Case No. 4:20-cv-00335-SHR. 24 Jun 2022. (Sealed under Protective Order).

2022 Expert Witness Report – Laidlaw MK. United States District Court for the Middle District of Alabama Northern Division. REV. PAUL A. EKNES-TUCKER, et al., Plaintiffs, v. KAY IVEY, in her official capacity as Governor of Alabama, et al., Defendants. Civil Action No. 2:22-cv-184-LCB. 2 May 2022.

2021 Brief of Amicus Curiae – Bursch, John J., McCaleb, Gary S., Van Meter, Quentin L., Laidlaw, Michael K., Van Mol, Andre, Hansen, Jeffrey E. Brief of Amicus Curiae. United States Court of Appeals for the Eight Circuit. DYLAN BRANDT, et al., Plaintiffs-Appellees v. LESLIE RUTLEDGE, in her official capacity as the Arkansas Attorney General, et. al. Defendants-Appellants. 23 Nov 2021.

2020 Expert Witness – JULIANA PAOLI v. JOSEPH HUDSON et al. heard in THE SUPERIOR COURT OF THE STATE OF CALIFORNIA, COUNTY OF TULARE. CASE NO. 279126. 2021.

2021 Brief of Amicus Curiae – Bursch, John J., McCaleb, Gary S., Grossman, Miriam, Van Meter, Quentin L., Laidlaw, Michael K., Van Mol, Andre, Hansen, Jeffrey E.

Brief of Amicus Curiae. United States Court of Appeals for the Eleventh Circuit. DREW ADAMS, Plaintiffs-Appellee v. SCHOOL BOARD OF ST. JOHNS COUNTY, FLORIDA, et. al. Defendants-Appellant. 26 Oct 2021.

2020 Expert Witness Affidavit 1 & 2 – Laidlaw MK. Supreme Court of British Columbia. File No. S2011599, Vancouver Registry. Between A.M. Plaintiff and Dr. F and Daniel McKee Defendants. 11/23/20 & 11/25/20.

2020 Brief of Amicus Curiae – Wenger, Randal L., McCaleb, Gary S., Grossman, Miriam, Laidlaw, Michael K., McCaleb, Gary S., Van Meter, Quentin L., Van Mol, Andre. Brief of Amicus Curiae. United States Court of Appeals for the Ninth Circuit. LINDSAY HECOX and JANE DOE, with her next friends Jean Doe and John Doe, Plaintiffs-Appellees v. BRADLEY LITTLE, in his official capacity as Governor of the State of Idaho, et. al. Defendant-Appellant. 19 Nov 2020

2020 Expert Witness Report – Laidlaw MK. United States District Court for the District of Arizona. DH and John Doe, Plaintiffs, vs. Jami Snyder, Director of the Arizona Health Care Cost Containment System, in her official capacity, Defendant. Case No. 4:20-cv-00335-SHR. 27 Sep 2020.

2019 Expert Witness Affidavit – Laidlaw MK. Court of Appeal File No. CA45940, Vancouver Registry. B.C. Supreme Court File No. E190334, between A.B. Respondent/Claimant, and C.D. Appellant/Respondent, and E.F. Respondent/Respondent. 24 Jun 2019.

2018 Brief of Amicus Curiae – Alliance Defending Freedom, Campbell, James A., Grossman, Miriam, Laidlaw, Michael K., McCaleb, Gary S., Van Meter, Quentin L., Van Mol, Andre. Brief of Amicus Curiae. United States Court of Appeals for the Eleventh Circuit. Drew Adams, Plaintiff-Appellee, v. School Board of St. Johns County, Florida, Defendant-Appellant. 12/27/2018.

PERSONAL

Languages: Conversational Spanish, French
Tutor: Biochemistry, computer science, High School mentor
Computers: Ruby, Rails, Javascript, C++, C, Java, and HTML programming

EXHIBIT 2

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

REBUTTAL EXPERT REPORT OF
MICHAEL K LAIDLAW, M.D.

DECLARATION OF MICHAEL K. LAIDLAW, M.D.

I, Michael K. Laidlaw, M.D., hereby declare as follows:

1. This supplemental rebuttal report is an addendum to, and incorporates and includes, my entire expert report in this matter of February 17, 2023. That initial report includes a discussion of my qualifications, publications, prior expert testimony, and compensation. I have read the Expert Reports of Daniel Shumer, MD and Johanna Olson-Kennedy, MD and provide the following rebuttal to the claims in those reports.

2. The bases for my opinions expressed in this report are my review of the Shumer and Olson-Kennedy reports, my professional experience as a physician, and my knowledge of the pertinent scientific literature, including those publications cited in this report. Specifically, I have first-hand personal experience in human research as a physician, having been involved in two studies one involving magnesium and bone density and the other involving ultrasound use for detecting recurrent thyroid cancer. For the latter study I helped to design an Institutional Review Board ("IRB") approved protocol. Furthermore, I received certification in the required course "Understanding the Fundamentals: Responsibilities and Requirements for the Protection of Human Subjects in Research" at the University of Southern California in 2003.

Sex vs Gender Identity

3. Dr. Shumer states, "Sex is comprised of several components, including, among others, internal reproductive organs, external genitalia, chromosomes, hormones, gender identity, and secondary sex characteristics (IOM, 2011)." (Shumer decl, ¶ 25).

4. Of note, Dr. Shumer states that the gender identity is a component of sex. This is false. What he states contradicts the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 TR) which states that "sex and sexual refer to the biological indicators of male and female (understood in the context of reproductive capacity), such as in sex chromosomes, gonads, sex hormones, and nonambiguous internal and external genitalia" (DSM-5 TR). Note that gender identity is not a component of biological sex as defined by the DSM 5.

5. Gender identity in the DSM 5 is defined separately: "Gender identity is a category of social identity and refers to an individual's identification as male, female, or, occasionally, some category other than male or female" (DSM 5-TR). So we can see that gender identity is a non-physical entity, here described as a social identity. In fact, the gender identity is a subjective identification known only once a patient makes it known. It cannot be identified by any physical means, cannot be confirmed by any outside observer, and can change over time. It has no correlate in the human body. In a letter to the editor from myself and colleagues critical of the

Endocrine Society's Guidelines we wrote: "There are no laboratory, imaging, or other objective tests to diagnose a 'true transgender' child" on the basis of gender identity (Laidlaw et al., 2019).

6. For example, one cannot do imaging of the human brain to find the gender identity. Likewise, there is no other imaging, laboratory tests, biopsy of tissue, autopsy of the brain, genetic testing, or other biological markers that can identify the gender identity. There is no known gene that maps to gender identity or to gender dysphoria. In other words, there is no objective physical measure to identify either gender identity or gender dysphoria. Dr. Olson-Kennedy states that gender identity "has a strong biological basis" (Olson-Kennedy decl, ¶ 18). Later she states that "multiple studies show that gender identity has a strong biological basis and cannot be changed"; yet she provides no evidence to support her claims (Olson-Kennedy decl, ¶ 25).

7. This is in contrast to all other endocrine disorders that have a measurable physical change in either hormone levels or gland structure which can be confirmed by physical testing. Therefore, gender dysphoria is a purely psychological phenomenon and not an endocrine disorder. But as my colleagues and I wrote in our letter, it becomes an endocrine condition through gender affirmative therapy: "Childhood gender dysphoria (GD) is not an endocrine condition, but it becomes one through iatrogenic puberty blockade (PB) and high-dose cross-sex

(HDCS) hormones. The consequences of this gender affirmative therapy (GAT) are not trivial and include potential sterility, sexual dysfunction, thromboembolic and cardiovascular disease, and malignancy" (Laidlaw et al. 2019).

8. Dr. Olson Kennedy states that the gender-affirmative model provides "support for them to evolve into their authentic gender selves, no matter at what age" (Olson-Kennedy decl, ¶ 18). However, she provides no definition, no evidence for existence, no objective test, nor any biological marker to identify the "authentic gender" self. She admits that it is a self-identification based on "child's self report" (Id.).

9. Dr. Shumer goes on to say in paragraph 29, "Scientific research and medical literature across disciplines demonstrates that gender identity, like other components of sex, has a strong biological foundation...In one such study, the volume of the bed nucleus of the stria terminalis (a collection of cells in the central brain) in transgender women was equivalent to the volume found in cisgender women (Chung, et al., 2002)." The study that Dr. Shumer references involved autopsies of 50 deceased persons brains to examine the tissue. This sort of examination obviously cannot be done on living persons and has not been validated in any way to confirm the gender identity. Likewise, there has been no imaging (such as an MRI or CT scan of the brain) to examine the nucleus of the stria terminalis that has been validated to confirm the gender identity of a patient.

10. Dr. Shumer states that "[t]win studies have shown that if an identical twin is transgender, the other twin is much more likely to be transgender compared to fraternal twins, a finding which points to genetic underpinnings to gender identity development (Heylens, et al., 2012)" (Shumer decl, ¶ 30). However, if gender identity is determined only by genes, then we would expect that identical twins would profess having the same gender identity nearly 100 percent of the time. This is not the case. In fact, the largest transexual twin study ever conducted included seventy-four pairs of identical twins (Diamond, 2013). They were studied to determine in how many cases both twins would grow up to identify as transgender. In only twenty-one of the seventy-four pairs (28 percent) did both identical twins identify as transgender. This is consistent with the fact that multiple factors play a role in determining gender identity, including psychological and social factors. This study in fact shows that those factors are more important than any potential genetic contribution. Furthermore, no genetic studies have ever identified a transgender gene or genes.

11. Sex is clearly identified in 99.98% of cases by chromosomal analysis (Sax, 2002). Sex is also clearly recognized at birth in 99.98% of cases (Id.). Therefore, sex is a clear, provable objective reality that can be identified through advanced testing such as karyotyping, or simple genital identification at birth by any layperson. The other 0.02% of cases have some disorder of sexual development

(DSD). DSDs do not represent an additional sex or sexes, but simply a disorder on the way to binary sex development (Chan et al., 2021).

12. Dr. Shumer states, "There is also ongoing research on how differences in fetal exposures to hormones may influence gender identity. This influence can be examined by studying a medical condition called congenital adrenal hyperplasia" (Shumer decl, ¶ 31). Congenital adrenal hyperplasia is a DSD. Dr. Shumer also provides no evidence that any of the plaintiffs suffered from fetal exposure to opposite sex hormones.

Gender Dysphoria and Psychology

13. Dr. Shumer states that "transgender and gender diverse identities are not conditions of mental ill health and classifying them as such can cause enormous stigma" (Shumer decl, ¶ 37). Ironically he refers to the Diagnostic and Statistical Manual of Mental Disorders to make his point: "gender dysphoria, a serious medical condition defined in both the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders" (Id. ¶ 36). In fact there is an entire chapter entitled "Gender Dysphoria" which addresses the condition (DSM 5-TR).

14. Dr. Shumer attempts to use ICD-11 (which is a coding system used for medical claims) to discuss "The Gender Icongruence diagnosis" which he states "is part of a new 'conditions related to sexual health' chapter in the ICD-11" (Shumer decl, ¶ 37). Similarly, Dr. Olson-Kennedy discusses ICD-11 coding changes (Olson-

Kennedy decl, ¶ 27). However, neither the State of Florida nor any other state in the union uses the ICD-11 medical coding system.

15. Dr. Shumer also states: "In children and adolescents, the diagnosis of gender dysphoria is made by a health provider including but not limited to a psychiatrist, psychologist, social worker, or therapist with expertise in gender identity concerns" (Shumer decl, ¶ 38).

16. However, the 2009 Endocrine Society guidelines (ESG) specifically state that a qualified mental health professional (MHP) should make the diagnosis of gender dysphoria (at that time referred to as gender identity disorder or GID): "Because GID may be accompanied with psychological or psychiatric problems…, it is necessary that the clinician making the GID diagnosis be able 1) to make a distinction between GID and conditions that have similar features; 2) to diagnose accurately psychiatric conditions; and 3) to undertake appropriate treatment thereof. Therefore, the SOC guidelines of the WPATH recommend that the diagnosis be made by a MHP (28). For children and adolescents, the MHP should also have training in child and adolescent developmental psychopathology" (Hembree et al., 2009, p. 3136).

17. The 2017 ESG offer similar recommendations "Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also

after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex" (Hembree, 2017).

18. Dr. Shumer states, "In children and adolescents, a comprehensive biopsychosocial assessment is typically the first step in evaluation, performed by a mental health provider with experience in gender identity" (Shumer decl, ¶ 43).

Desistance

19. Desistance is a term indicating that the child, adolescent, or adult who initially presented with gender incongruence has come to experience a realignment of their internal sense of gender and their physical body. “Children with [gender dysphoria] will outgrow this condition in 61% to 98% of cases by adulthood. There is currently no way to predict who will desist and who will remain dysphoric” (Laidlaw et al., 2019; Ristori & Steensma, 2016).

20. Dr. Shumer states that "data and personal experience shows that children whose gender dysphoria persists into adolescence are highly likely to be transgender" (Shumer decl, ¶ 59). Dr. Olson-Kennedy asserts that "research to date shows that if transgender identification persists into adolescence, then desistance is

incredibly rare" (Olson-Kennedy decl, ¶ 54). However, both of these assertions are contradicted by the evidence.

21. Puberty, which pertains to the physical development of the reproductive tract, breasts and associated secondary sex characteristics, can begin as early as age 8 in girls and age 9 in boys. The studies which have examined desistence involved adolescents and children aged twelve and under. For example, table 1 in Ristori and Steensma 2016 shows multiple studies involving minors. For the three most recent—Singh (2012), Wallien & Cohen-Kettenis (2008), and Drummond et al. (2008)—these involved age ranges from 3 to nearly 13 years old.[1] The desistence rate varied from 61 to 88%. Since the upper age was twelve (or slightly higher), 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[2]. Therefore we can infer that a high proportion of adolescents do in fact desist, contrary to what Drs. Shumer and Olson-Kennedy have stated.

---

1 "This study provided information on the natural histories of 25 girls with gender identity disorder (GID). Standardized assessment data in childhood (mean age, 8.88 years; range, 3-12 years)" (Drummond et al., 2008). "The mean age of the participating gender-referred children was 10.47 years (SD = 1.27; range, 8.11 – 12.77)" (Wallien et al., 2009). " Standardized assessment data in childhood (mean age, 7.49 years; range, 3 – 12 years) and at follow-up (mean age, 20.58 years; range, 13 – 39 years) were used to evaluate gender identity and sexual orientation outcome. At followup, 17 participants (12.2%) were judged to have persistent gender dysphoria." (Singh, 2012)

2 To my knowledge the desistance literature does not examine Tanner stages of puberty as part of their studies. However, one can infer based on the ages that many children had at least begun puberty (Tanner stage 2) or were at a more advanced stage of puberty.

Gender Affirmative Therapy

22. Gender affirmative therapy (GAT) of adults and minors consists of psychosocial, medical, and surgical interventions that attempt to psychologically and medically alter the patient so that they come to believe they may become similar to the physical sex which aligns with their gender identity (but not their biological sex) and thereby reduce gender dysphoria. GAT consists of four main parts that are discussed in the Endocrine Society Guidelines: 1) social transition, 2) blocking normal puberty or menstruation, 3) high dose opposite sex hormones, and 4) surgery of the genitalia and breasts (Hembree et al., 2017).

Poor Quality Evidence for Gender Affirmative Therapy (GAT)

23. Dr. Shumer states, "Options for treatment after the onset of puberty include the use of gonadotropin-releasing hormone agonists ('GnRHa') for purposes of preventing progression of pubertal development, and hormonal interventions such as testosterone and estrogen administration. These treatment options are based on robust research and clinical experience, which consistently demonstrate safety and efficacy" (Shumer decl, ¶ 46). However, he presents no evidence to back his claim of robust evidence.

24. In fact, with respect to the Endocrine Society's guidelines which he states he follows (Shumer decl, ¶ 56), the quality of evidence for the treatment of adolescents is rated "very low-quality evidence" and "low quality evidence"

(Hembree, 2018). "The quality of evidence for [puberty blocking agents] is noted to be low. In fact, all of the evidence in the guidelines with regard to treating children/adolescents by [gender affirmative therapy] is low to very low because of the absence of proper studies" (Laidlaw et al., 2019).

25. Further problems with the Endocrine Society's guidelines are highlighted in a recent BMJ Investigation article. It reads: "Guyatt, who co-developed GRADE[3] found 'serious problems' with the Endocrine Society guidelines, noting that the systematic reviews didn't look at the effect of the interventions on gender dysphoria itself, arguably 'the most important outcome.' He also noted that the Endocrine Society had at times paired strong recommendations—phrased as 'we recommend'—with weak evidence. In the adolescent section, the weaker phrasing 'we suggest' is used for pubertal hormone suppression when children 'first exhibit physical changes of puberty'; however, the stronger phrasing is used to 'recommend' GnRHa treatment. 'GRADE discourages strong recommendations with low or very low quality evidence except under very specific circumstances,' Guyatt told The BMJ. Those exceptions are 'very few and far between'" (Block, 2023).

---

3 "GRADE is a systematic approach to rating the certainty of evidence in systematic reviews and other evidence syntheses". GRADE is the method purportedly employed in the ESG. https://training.cochrane.org/grade-approach

26. Endocrinologists William Malone and Paul Hruz and colleagues have written that the ESG's "claim of effectiveness of these interventions is at odds with several systematic reviews, including a recent Cochrane review of evidence, and a now corrected population-based study that found no evidence that hormones or surgery improve long-term psychological well-being. Lastly, the claim of relative safety of these interventions ignores the growing body of evidence of adverse effects on bone growth, cardiovascular health, and fertility, as well as transition regret" (Malone et al., 2021; Haupt et al., 2020; "Correction", 2020).

27. In addition, the Endocrine Society's guidelines (ESG) specifically state that their "guidelines cannot guarantee any specific outcome, nor do they establish a standard of care" (Hembree at al, 2017, p. 3895).

WPATH

28. Dr. Olson-Kennedy states she has "been a member of the World Professional Association for Transgender Health (WPATH) since 2010" (Olson-Kennedy decl, ¶ 9). WPATH reports that its Standard of Care 7 is a "professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria" (WPATH, 2022). However, the "professional consensus" exists only within the confines of its advocacy organization.

29. Dr. Olson Kennedy states that the WPATH SOC 7 "are based on the best available science and expert professional consensus" (Olson-Kennedy decl, ¶ 29).

According to Dr. Shumer, "[t]he WPATH SOC 8 is based on rigorous review of the best available science and expert professional consensus in transgender health...Grading of evidence was performed by an Evidence Review Team which determined the strength of evidence presented in each individual study relied upon in the document (Coleman, et al., 2022)" (Shumer decl, ¶ 50).

30. With respect to the "rigorous review" of the evidence, the SOC 8 used a modification to the GRADE approach for systematic reviews that removed the grading of quality of evidence (which should be categorized as very low, low, moderate, and high quality). This modification meant that any recommendation of "recommend" was automatically assigned as high quality evidence. SOC 8 also failed to provide evidence profile tables which should include "an explicit judgment of each factor that determines the quality of evidence for each outcome" (Guyatt et al., 2021). Such modifications of GRADE are explicitly recommended against in the referenced GRADE document and in so doing, in my opinion, invalidates all of the SOC 8 recommendations as being evidence-based[4].

---

4 From the GRADE guidelines: "Some organizations have used modified versions of the GRADE approach. <u>We recommend against such modifications</u> because the elements of the GRADE process are interlinked because modifications may confuse some users of evidence summaries and guidelines, and because such changes compromise the goal of a single system with which clinicians, policy makers, and patients can become familiar" (Guyatt et al., 2011).

Puberty

31. "Puberty is a process of maturation heralded by production of sex hormones—testosterone and estrogen—leading to the development of secondary sex characteristics" (Shumer, ¶ 58). Dr. Shumer presents a very limited view of puberty. Puberty is an essential part of human development. Its purpose is to achieve full adult sexual function and reproductive capacity. Puberty is not optional. Adolescents should not be afraid to go through puberty, but need support and guidance throughout the process.

32. Puberty is a time of development of the sex organs, body, brain, and mind. There are well known changes in physical characteristics of the male such as growth of facial hair, deepening of the voice, and increasing size of the testicles and penis. Importantly the testicles will develop sperm under the influence of testosterone and become capable of ejaculation. Because of these changes, the male will become capable of fertilizing an egg. The inability to produce sperm sufficient to fertilize an egg is termed infertility.

33. For the female, pubertal development includes changes such as breast development, widening of the pelvis, and menstruation. The female will also begin the process of ovulation which is a part of the menstrual cycle and involves the release of an egg or eggs from the ovary. Once the eggs are released in a manner in which they can become fertilized by human sperm then the female is termed fertile.

The inability to release ovum that can be fertilized is infertility (Kuohong and Hornstein, 2021).

34. The Tanner staging system allows the stage of puberty to be known. Tanner stages are divided into five. Stage 1 is the pre-pubertal state before pubertal development of the child begins. Stage 5 is full adult sexual maturity. Stages 2 through 4 are various phases of pubertal development (Greenspan and Gardner, 2004). Awareness of the Tanner stage of the developing adolescent is also useful to assess for maturation of sex organ development leading to fertility. For girls, the first menstruation (menarche) occurs about two years after Tanner stage 2 and will typically be at Tanner stage 4 or possibly 3 (Emmanuel and Boker, 2022). The first appearance of sperm (spermarche) will typically be Tanner stages 4 (Id.). If puberty is blocked or disrupted before reaching these critical stages, the sex glands will be locked in a premature state and incapable of fertility.

GnRHa to Block Normal Pubertal Development and Maturation

35. Dr. Shumer states, "In transgender youth, it is most typical to use GnRHa [puberty blockers] from the onset of puberty (Tanner Stage 2) until mid-adolescence" (Shumer decl, ¶ 65). This is correct. However he also states "GnRHa have no long-term implications on fertility." That statement is incorrect. GnRHa have profound implications for fertility. This is why.

36. One can see that if the developing person is blocked at Tanner stage 2 as advocated by the guidelines, this is prior to becoming fertile. The gonads will remain in an immature, undeveloped state. If they remain blocked in an early pubertal stage then even the addition of opposite sex hormones will not allow for the development of fertility. In fact, high-dose opposite sex hormones may permanently damage the immature sex organs leading to sterilization. Certainly the removal of the gonads by surgery will ensure sterilization.

37. In a Dutch study by de Vries et al. that included seventy adolescents who took puberty blockers, all seventy decided to go on to hormones of the opposite sex (de Vries, et al. 2011). In a follow-up study by de Vries et al., the overwhelming majority went on to have sex reassignment surgery by either vaginoplasty for males or hysterectomy with ovariectomy for females (de Vries, et al. 2014). These surgeries resulted in sterilization. This is why puberty blockers, rather than being a "pause" to consider aspects of mental health, are instead a pathway towards future sterilizing surgeries.

38. Dr. Olson-Kennedy states that "[w]hile some argue that gender affirmation leads a child or adolescent down a path of inevitable transgender identity, no such evidence exists, either in the scientific or the clinical setting" (Olson-Kennedy decl, ¶ 36). I have not argued that gender affirmation leads to "an inevitable transgender identity". I do argue however, that it is clear from the de Vries studies

that gender affirmation therapy led to the overwhelming majority of adolescents ultimately being sterilized and suffering irreparable physical changes due to the therapy.

39. Dr. Olson-Kennedy states, "Fertility preservation is offered to all transgender patients prior to the initiation of gender affirming hormones" (Olson-Kennedy decl, ¶ 107).

40. However, even though procedures for fertility preservation (FP) are available, studies in North America show that less than 5% of adolescents receiving GAT even attempt it (Nahata, 2017). Ovarian and testicular tissue cryopreservation would be the only FP options in children blocked prior to spermarche and menarche and are high in cost and limited to specialized centers (Laidlaw et al., 2019). Even with FP there is no guarantee of having a child.

41. Dr. Shumer introduces the unproven idea that those adolescents who received puberty blockers in early puberty and then take opposite sex hormones (which will lock them in early puberty) may be able at some point as adults to stop all of these hormones and then advance through their normal physiologic puberty. He states, "If attempting fertility after previous treatment with GnRHa followed by hormone therapy is desired, an adult patient would withdraw from hormones and allow pubertal progression" (Shumer decl, ¶ 79). However, he provides no evidence that this is even possible.

42. With respect to blocking normal puberty in gender affirmative therapy, Dr. Olson Kennedy provides contradictory information as to when it begins. On the one hand she states, "Sometimes treatment begins with puberty delaying medications (also referred to as puberty blockers), later followed by gender-affirming hormones. Most youth, and certainly all adults, accessing treatment are already well into or have completed puberty" (Olson-Kennedy decl, ¶ 38 (emphasis added)). On the other hand, she states that "[b]oth the Endocrine Society and the WPATH's SOC, however, recommend initiation of puberty suppression at the earliest stages of puberty (usually, Tanner 2)..., regardless of chronological age" (Olson-Kennedy decl, ¶ 40 (emphasis added)).

43. In fact we know that Dr. Olson-Kennedy has recruited children as young as age 8 into the puberty blocker arm of her study "The Impact of Early Medical Treatment in Transgender Youth," and recruited children as young as age 11 into the cross-sex hormone arm.[5] She also reduced the age requirement for the cross-sex hormone arm from 13 to 8 years old.[6]

---

5 "Initial data from youth enrolled in the GnRHa cohort across all study sites (n=71) show that participants range in age from 8 to 14 years old, with a mean age of 11 +/- 1.4 years... Within the CSH cohort, 279 participants have been enrolled across all study sites.Participants range in age from 11 to 20 years old, with a mean age of 16 +/- 1.9 years" (Olson-Kennedy-progress-reports-so-far.pdf, p 61).

6 "In addition, the minimum age for the cross-sex hormone cohort inclusion criteria was decreased from 13 to 8 to ensure that a potential participant who could be eligible for cross-sex hormones based on Tanner Staging would not be excluded due to age alone " (Olson-Kennedy-progress-reports-so-far.pdf, p 44).

Dr. Shumer and Dr. Olson-Kennedy's Faulty Comparison of Using GnRHa for Precocious Puberty vs for Gender Dysphoria

44. Dr. Shumer states, "As an experienced pediatric endocrinologist, I treat patients with these same medications for both precocious puberty and gender dysphoria and in both cases the side effects are comparable and easily managed" (Shumer decl, ¶ 68).

45. Dr. Olson-Kennedy states, "Puberty suppression has been used safely for decades in children with other medical conditions, including precocious puberty, and is a reversible intervention" (Olson-Kennedy decl, ¶ 40).

46. In reality the physical effects, use case, and outcomes of using GnRHa for treating precocious puberty (which is an abnormal early puberty condition) versus stopping normal puberty in gender affirmative therapy are completely different. In the disease state of central precocious puberty, puberty begins at an abnormally young age, say age four. In order to halt this abnormally early puberty, a GnRH agonist (puberty blocker) may be administered. Here the action of the medication is to stop early sex hormone production and therefore stop abnormal pubertal development. Then, at a more normal time of pubertal development, say age 11, the medication is discontinued and normal puberty is allowed to proceed. The end result is to restore normal sex gland function and the normal timing of puberty. This is an FDA-approved, labeled use for a GnRH agonist medication.

47. What about the use of puberty blockers such as Lupron in gender affirmative therapy? In these cases, we have physiologically normal children who are just beginning puberty or are somewhere in the process of pubertal development. They have healthy pituitary glands and sex organs. However, a puberty-blocking medication is administered to stop normal pubertal development and maturation.

48. In this case, the condition of hypogonadotropic hypogonadism (a medical disease which results in the pituitary not communicating with the sex glands to make hormones) is deliberately induced by medication. This is an iatrogenic effect of treating the psychological condition of gender dysphoria. GnRH agonist medications have not been FDA approved for this use case and are experimental with respect to blocking normal physical development and maturation.

49. We can see that in precocious puberty an abnormal condition (early puberty) is halted by medication until the patient reaches the age of normal pubertal development and then puberty is allowed to proceed normally. In the case of gender affirmative therapy (GAT), normal pubertal development is stopped medically by inducing an abnormal condition of the pituitary. This abnormal pituitary condition will continue while the patient is given GnRHa and even when they start opposite sex hormones. Therefore the use of puberty blockers in GAT imposes a disease state on healthy adolescents which will continue indefinitely while they take hormonal treatment as a part of GAT.

GnRHa for Endometriosis is an FDA Approved Usage Contrary to Dr. Shumer's Claim

50. As Dr. Shumer also states, " I regularly prescribe GnRHa for patients who do not meet criteria for precocious puberty but who require pubertal suppression. Examples include...young women with endometriosis. As with gender dysphoria, the prescription of GnRHa to treat these conditions is 'off-label,' yet it is widely accepted within the field of endocrinology and not considered experimental." (Shumer decl, ¶ 69).

51. Dr. Shumer erroneously states that using GnRHa for the treatment of young women with endometriosis is an off-label usage. A reading of the labeling clearly reveals otherwise. Under "Indications and Usage", it reads "LUPRON DEPOT 11.25 mg for 3-month administration is a gonadotropin-releasing hormone (GnRH) agonist indicated for: Management of endometriosis, including pain relief and reduction of endometriotic lesions." (Lupron Depot Prescibing information, 2018). The same labeling provides no such information for using GnRHa in GAT, because it doesn't exist, and because using such medications for blocking normal pubertal development is an experimental use.

Puberty and Bone Health

52. Puberty is also a time of rapid bone development. This time of development is critical in attaining what we call peak bone density or the maximum bone density that one will acquire in their lifetime (Elhakeem, 2019). Any abnormal lowering of sex hormones occurring during this critical time will stop the rapid accumulation of bone and therefore lower ultimate adult bone density. If a person does not achieve peak bone density, they are at future risk for osteoporosis and the potential for debilitating spine and hip fractures as adults. Hip fractures for the older patient very significantly increase the risk of major morbidity and death (Bentler, 2009).

53. Puberty blockers used in adolescence will inhibit the normal accrual of bone density. This can be evaluated by DEXA bone density scans. In a study in the UK, 44 patients aged 12-15 with gender dysphoria were given puberty blockers and tests of bone density were done at baseline, 12 months, 24 months, and 36 months (Carmichael, 2021). The average baseline z score was about 32% compared to peers of similar age and sex. At 12 months this had decreased to about 15%, and by 24 months it had declined further to about 5% compared to their peers and remained at this low level. What this shows is that puberty blockers in adolescents is not safe for bones and in fact caused a considerable drop in bone density compared to their same age peers.

54. Dr. Shumer states, "The treatment [puberty blockade] works by pausing endogenous puberty at whatever stage it is at when the treatment begins, limiting the influence of a person's endogenous hormones on their body" (Shumer decl, ¶ 63). Dr. Olson-Kennedy states, "Puberty suppression, which involves the administration of gonadotrophin-releasing hormone analogues (GnRHa), essentially pauses puberty," (Olson-Kennedy decl, ¶ 39). In actuality, allowing a "pause" in puberty for any period of time leads to an inability to attain peak bone density and puts the patient at future risk for osteoporosis and serious fractures. GnRHa do not pause endogenous puberty, they irreversibly harm normal human development and maturation.

Opposite Sex Hormones

55. Unlike some other recommendations for adolescent GAT, the Endocrine Society's guidelines do not include any grading of the quality of evidence specifically for their justification of laboratory ranges of testosterone or estrogen. In spite of this, Dr. Shumer states, "When treated with testosterone or estrogen, the goal is to maintain the patient's hormone levels within the normal range for their gender" (Shumer decl, ¶ 74). When Dr. Shumer refers to gender, he means gender identity.

56. This is because recommendations from the Endocrine Society's clinical guidelines related to GAT are to ultimately raise female levels of testosterone to 320 to 1000 ng/dL which is in the normal reference range for adult men (Hembree, 2017).

However, they are of the same order of magnitude as dangerous endocrine tumors for women. A simple calculation shows this level for the adult female may be anywhere from 6 to 100 times higher than native female testosterone levels.[7] In doing so they are inducing severe hyperandrogenism. These extraordinarily high levels of testosterone are associated with multiple risks to the physical and mental health of the patient.

57. For example, with respect to testosterone and cardiovascular risk, "[s]tudies of transgender males taking testosterone have shown up to a nearly 5-fold increased risk of myocardial infarction relative to females not receiving testosterone" (Laidlaw et al.,2021; Alzahrani et al., 2019). Severe hyperandrogensim causes permanent physical changes that include deepening of the voice and hirsutism. Changes to the genitourinary system due to hyperandrogenism include polycystic ovaries, clitoromegaly and atrophy of the lining of the uterus and vagina. Potential cancer risks from high dose testosterone include ovarian and breast cancer (Hembree, 2017).

58. Severe hyperandrogenism also causes erythrocytosis or high red blood cell levels. Any level of erythrocytosis in young women has been shown to be an

---

7 The normal adult female reference range for testosterone is approximately 10-50 ng/dL.

independent risk factor for cardiovascular disease, coronary heart disease and death due to both (Gagnon, 1994).

59. According to research, anabolic steroid abuse with androgens like testosterone has been shown to predispose individuals towards mood disorders, psychosis, and psychiatric disorders. The "most prominent psychiatric features associated with AAS [anabolic androgenic steroids, i.e. testosterone] abuse are manic-like presentations defined by irritability, aggressiveness, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior. Other psychiatric presentations include the development of acute psychoses, exacerbation of tics and depression, and the development of acute confusional/delirious states" (Hall, 2005). Moreover, "[s]tudies... of medium steroid use (between 300 and 1000 mg/week of any AAS) and high use (more than 1000 mg/week of any AAS) have demonstrated that 23% of subjects using these doses of steroids met the DSM-III-R criteria for a major mood syndrome (mania, hypomania, and major depression) and that 3.4% — 12% developed psychotic symptoms" (Hall, 2005).

Surgeries

60. Dr. Shumer states that "The transition process in adolescence typically includes (i) social transition and/or (ii) medications, including puberty-delaying medication and hormone therapy" (Shumer decl, ¶ 57). However, Dr. Shumer neglects to describe surgeries as a part of the transition process. This is important to

note because although endocrinologists like he and I do not typically perform surgery, we do refer patients for surgeries, and need to be aware of the risks, benefits, complications, and long-term outcomes. This is also important to note because transition surgeries, in particular mastectomies, are being performed on minors throughout the country.

61. Mastectomies are the surgical removal of the breasts. The procedure is used in GAT in an attempt to make the chest appear more masculine. The surgery results in a permanent loss of the ability to breastfeed and significant scarring of 7 to 10 inches. The scars are prone to widening and thickening due to the stresses of breathing and arm movement. Other potential complications include the loss of normal nipple sensation and difficulties with wound healing (American Cancer Society, 2022). It is important to note that this operation cannot be reversed. The female will never regain healthy breasts capable of producing milk to feed a child (Mayo Clinic, Top Surgery, 2022). The Endocrine Society provides no grading of the quality of evidence for this surgery in adolescents.

62. Good quality studies specifically showing that mastectomy surgery is safe, effective, and optimal for treating minors with gender dysphoria do not exist. For example, there is a study by Dr. Olson-Kennedy titled "Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults Comparisons of Nonsurgical and Postsurgical Cohorts" (Olson-Kennedy, 2018). This study

contained 68 natal female patients who had mastectomy surgery as a part of GAT. The age range was 13-24 years old. Of these subjects, 33 were under the age of 18 including two thirteen-year-olds and five fourteen-year-olds.

63. The study authors conclude that "[c]hest dysphoria was high among presurgical transmasculine youth, and surgical intervention positively affected both minors and young adults." However, there are a number of problems with this study. First, the term "chest dysphoria" is a creation of the study authors and is not found as a diagnosis or even referenced in the DSM-5. Second the "chest dysphoria scale" is a measuring tool created by the authors, but which the authors state "is not yet validated." (Id., p. 435) Third, the mastectomies were performed on girls as young as 13 and 14 years old and who thereby lacked the maturity and capacity of good judgment for truly informed consent for this life-altering procedure. For this reason, in my professional opinion, the research and surgeries performed were flawed and unethical.

64. There exists another poorly designed study which suffers from similar methodological and ethical problems as the Olson-Kennedy study. A 2021 study published in Pediatrics examined females aged 13-21 recruited from a gender clinic. Thirty young females had mastectomy procedures and sixteen had not. The average age at surgery was 16.4 years (Mehringer, 2021). The follow up time after surgery was only 19 months and no data is provided or analyzed about key psychiatric

information such as comorbid psychological illnesses, self-harming behaviors, psychiatric hospitalizations, psychiatric medication use, or suicide attempts.

65. Information returned from the study surveys were all qualitative and included responses such as "[My chest dysphoria] made me feel like shit, honestly. It made me suicidal. I would have breakdowns". Another respondent stated, "I've been suicidal quite a few times over just looking at myself in the mirror and seeing [my chest]. That's not something that I should have been born with" (Mehringer, 2021). The omission of psychiatric data is a major flaw in the study and also irresponsible given the obviously dangerous psychological states that some of these young people were in.

66. Since such a high proportion of subjects were using testosterone (83%), some of the responses could be attributed to adverse effects of testosterone. For example, high-dose testosterone can manifest in irritability and aggressiveness. One study subject responded, "I get tingly and stuff and it kind of makes me want to punch something" (Mehringer, 2022).

67. The testosterone labeling also indicates nausea and depression as adverse reactions which are described by another study subject: "There's a feeling of hopelessness, of desperation, of—almost makes me feel physically sick" (Actavis Pharma, Inc., 2018; Mehringer, 2022).

68. The study appears to have been designed, at least in part, to justify insurance companies paying for mastectomy procedure for adolescents with gender dysphoria, even though they have provided no long-term statistical evidence of benefit: "These findings...underscore the importance of insurance coverage not being restricted by age" (Mehrniger, 2021). This also appears to be part of the aim of the flawed Olson-Kennedy study which stated that "changes in clinical practice and in insurance plans' requirements for youth with gender dysphoria who are seeking surgery seem essential" (Olson-Kennedy, 2018). So these two studies, rather than being a thorough examination of the psychological and physical risks and benefits of mastectomy surgery over the long-term, appear instead to exist, at least in part, to validate the need for insurance companies to insure the costs of these dubious procedures for minors.

Nations Reverse Course due to Lack of Evidence for GAT

69. Dr. Shumer states "There are several studies demonstrating positive results of gender affirming care in adolescents and adults (de Vries, et al., 2014; de Vries, et al., 2011; Green, et al., 2022; Smith, et al., 2005; Turban, et al., 2022)" (Shumer decl, ¶ 35). I've already discussed the negative long-term risks in the de Vries studies as a pathway to sterilization and other damages from hormones.

70. The Smith et al. study of 2005, which Dr. Shumer references, contained initially "325 consecutive adolescent and adult applicants for sex reassignment".

However only 222 started hormone therapy and 34 dropped out of treatment altogether. The study states that "[o]nly data of the 162 adults were used to evaluate treatment" and not adolescents. So the study had a high dropout rate, and the limited remaining results were only applicable to adults.

71. With respect to the Turban et al. 2022 study, it was not a randomized controlled study nor a prospective observational study. Rather the study relied upon the 2015 U.S. Transgender Survey (USTS), which has been severely criticized for its serious limitations and weaknesses. D'Angelo et al. have written about the 2015 USTS survey as part of the criticism of another flawed study in the journal Pediatrics by Jack Turban titled "Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation" (Turban, 2020). They write in their critique of the USTS that it is "a convenience sampling, a methodology which generates low-quality, unreliable data." (Bornstein, Jager, & Putnick, 2013). Specifically, the participants were recruited through transgender advocacy organizations and subjects were asked to 'pledge' to promote the survey among friends and family. This recruiting method yielded a large but highly skewed sample...Their analysis is compromised by serious methodological flaws, including the use of a biased data sample, reliance on survey questions with poor validity, and the omission of a key control variable, namely subjects' baseline mental health status." They also state that "[s]tigmatizing non-'affirmative' psychotherapy for GD [gender dysphoria] as 'conversion' will reduce

access to treatment alternatives for patients seeking non-biomedical solutions to their distress" (D'Angelo et al., 2021).

72. In contrast with the few low-quality studies that Dr. Shumer presents, entire nations are questioning and reversing course regarding gender affirmative therapy based on reviews of the evidence. For example, in the Bell v. Tavistock Judgment in the UK regarding puberty blockers in GAT, the court concluded that "there is real uncertainty over the short and long-term consequences of the treatment

74. In the bulletin of the Royal College of Psychiatrists in 2021, in a reevaluation of the evidence, Griffin and co-authors write, "As there is evidence that many psychiatric disorders persist despite positive affirmation and medical transition, it is puzzling why transition would come to be seen as a key goal rather than other outcomes, such as improved quality of life and reduced morbidity. When the phenomena related to identity disorders and the evidence base are uncertain, it might be wiser for the profession to admit the uncertainties. Taking a supportive, exploratory approach with gender-questioning patients should not be considered conversion therapy" (Griffin et al., 2021).

75. In 2020, Finland recognized that "[r]esearch data on the treatment of dysphoria due to gender identity conflicts in minors is limited," and recommended prioritizing psychotherapy for gender dysphoria and mental health comorbidities over medical gender affirmation (Council for Choices in Healthcare in Finland, 2020). Additionally, "[s]urgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors".

76. In 2021, Sweden's largest adolescent gender clinic announced that it would no longer prescribe puberty blockers or cross-sex hormones to youth under 18 years outside clinical trials (SEGM, 2021). "In December 2019, the SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) published an overview of the knowledge base which showed a lack of

evidence for both the long-term consequences of the treatments, and the reasons for the large influx of patients in recent years. These treatments are potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis. This makes it challenging to assess the risk / benefit for the individual patient, and even more challenging for the minors or their guardians to be in a position of an informed stance regarding these treatments" (Gauffen and Norgren, 2021).

77. Dr. Hilary Cass "was appointed by NHS England and NHS Improvement to chair the Independent Review of Gender Identity Services for children and young people in late 2020" (The Cass Review website, 2022). In her interim report dated February 2022, it states that "[e]vidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally" (Cass, 2022). This led to the shutting down of their Tavistock child gender identity clinic.

Gender Affirmative Therapy and Death by Suicide

78. Dr. Olson-Kennedy states that "The claim that treating gender dysphoria with medically supervised and recommended hormone treatment is particularly risky or causes serious mental health effects is not supported by data," (Olson-Kennedy decl, ¶ 103 (emphasis added)). The data from her own study show otherwise.

79. Death by suicide would be considered by most to be the most serious detrimental mental health outcome. Psychiatric hospitalizations and suicidal ideation would be other serious mental health effects.

80. The most comprehensive study of gender affirmative therapy is from Sweden in 2011. They examined data of 324 patients in Sweden over 30 years who had taken opposite sex hormones and had undergone sex reassignment surgery and compared them to matched population controls (Dhejne, 2011). The gender affirmative therapy group had nineteen times the rate of completed suicides and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to the general population of Sweden.

81. The recent study published by Chen and Olson-Kennedy et al. confirms the inherent danger of gender affirmative therapy found in the Dhejne study. The New England Journal of Medicine recently published "Psychosocial Functioning in Transgender Youth after 2 Years of Hormones" in which Dr. Olson-Kennedy is the principal investigator (Chen, Olson-Kennedy, et al., 2023). This arm of her study included 315 adolescents aged 12 to 20 years old who were taking high dose hormones of the opposite sex[8]. The study was not randomized and had no control

---

8 "[T]he US Department of Health and the Food and Drug Administration reference approximate age ranges for these phases of life, which consist of the following: (1) infancy, between birth and 2 years of age; (2) childhood, from 2 to 12 years of age; and (3) adolescence, from 12 to 21 years of age. Additionally, Bright Futures guidelines from the American Academy of Pediatrics identify adolescence as 11 to 21 years of age, dividing the group into early (ages

group. The authors report that 2 out 315 subjects died by suicide. The authors also report "The most common adverse event was suicidal ideation" in 11 subjects. Unfortunately, unlike the Dhejne study, the Olson-Kennedy study provides little other useful data about outcomes such as psychiatric hospitalizations, suicide attempts, or rates of comorbid psychiatric illness.

82. The death by suicide of 2 out of 315 subjects equates to approximately 317 suicide deaths per 100,000 patient-years. If we compare this figure to that of the UK's largest gender identity service, Tavistock, the "annual suicide rate is calculated as 13 per 100,000" patient-years (Biggs, 2021). The death-by-suicide rate was approximately 24 times higher in Dr. Olson-Kennedy's study compared to the much larger Tavistock Clinic. In fact, Professor Biggs reports that two of the four suicide deaths from the Tavistock data were of patients who were on the waiting list and "would not have obtained treatment" (Id.). This strongly suggests that the use of high dose opposite sex hormones in Dr. Olson-Kennedy's study was associated with

---

11 – 14 years), middle (ages 15 – 17 years), and late (ages 18 – 21 years) adolescence. The American Academy of Pediatrics has previously published a statement on the age limit of pediatrics in 1988, which was reaffirmed in 2012 and identified the upper age limit as 21 years with a note that exceptions could be made when the pediatrician and family agree to an older age, particularly in the case of a child with special health care needs. Recent research has begun to shed more light on the progression of mental and emotional development as children progress through the adolescent years into young adulthood. It is increasingly clear that the age of 21 years is an arbitrary demarcation line for adolescence because there is increasing evidence that brain development has not reliably reached adult levels of functioning until well into the third decade of life" (Hardin, 2017).

a much higher death rate in her experimental study. Unfortunately, of the many side effects of hormone therapy listed on the study's consent forms, death by suicide or by any cause is not listed (NIH FOIA 51365 April 17 2020 Production of consent forms.pdf).

83. Dr. Olson-Kennedy did not discuss these facts in her declaration. She also did not discuss the types of mental health conditions the subjects had nor the mental health care (if any) that these research subjects received. She did not discuss the dosages of opposite-sex hormones these subjects were taking, the serum levels of these hormones, nor post-mortem hormone levels. She did not discuss if these deceased subjects had autopsy reports or exactly how the cause of death was determined. She did not discuss if any other human subjects have died, been hospitalized, or have been seriously injured in the other arm of her study or any of her other studies.

84. These facts would be useful to know to determine how high-dose opposite hormones and gender affirmative therapy affect overall health and their association with death by suicide. All of the data collected to date in Dr. Olson-Kennedy's publicly funded study the "The Impact of Early Medical Treatment in Transgender Youth" should be released to the public so that other researchers and clinicians can determine how puberty blockers, opposite sex hormones, and mastectomy surgeries affect adolescent physical and mental health.

85. Some portion of the Olson-Kennedy study subjects did not have the legal capacity to give consent either due to age or vulnerability due to mental illness. There was an element of coercion insofar as parents and children may have been convinced that to not undergo gender affirmative therapy would lead to suicide and self-injury. Dr. Olson-Kennedy discusses this in her declaration: "The denial of gender-affirming care, on the other hand, is harmful to transgender people. It exacerbates their dysphoria and may cause anxiety, depression, and suicidality, among other harms" (Olson-Kennedy decl, ¶ 113).

86. The majority of young adolescents certainly would not have significant comprehension of the elements of the subject matter involved (particularly infertility, sexual dysfunction, and potential for sterility) to make an understanding and enlightened decision regarding these life altering effects of opposite sex hormones.

87. Further, with regard to informed consent, Dr. Olson-Kennedy's article states, "[p]articipants provided written informed consent or assent; parents provided permission for minors to participate" (Chen, Olson-Kennedy, et al., 2023). However, it is not possible for adolescents as young as age 12 to assent or consent to the permanent physical harms of gender affirmative therapy, including sterility or death. Parents cannot ethically provide "permission" for procedures that may result in either harmful outcome based on the non-objective, non-verifiable, non-biologically provable gender identity. This is very different than, for example, a parent providing

informed consent on behalf of a minor child for a potentially sterilizing or life threatening cancer treatment. Such treatment is based on an objective and verifiable physical examination, typically the biopsy of a cancerous tumor. Again, no such objective validation of an immutable gender identity exists.

88. In an article entitled "Considerations for Stopping a Clinical Trial", the first reason given is safety (Deichmann et al., 2016). The authors write, "Ethically, clinical trials must sometimes be stopped early when the results show no justification for exposing human subjects to additional potential risk by continuing the trial." (Id.). The authors discuss stopping a research trial when "[t]he risks to human subjects unexpectedly outweigh the benefits because of unexpected severe adverse events" such as "serious illness or death in human subjects" (Id.).

89. The physical harms caused by high-dose testosterone and estrogen as well as the numerous adverse reactions reportedare significant Death is one of those adverse reactionsSubjects were not offered other less risky options such as watchful waiting with psychological support to alleviate their gender dysphoria or psychological therapy to help manage comorbid mental illness. Dr. Olson-Kennedy states, however, that an “untreated control group is unethical in this context” (Olson-Kennedy decl, ¶ 73). What she means to say by “untreated” is to not be treated with hormones and surgeries. Psychotherapy, treatment of neurodevelopmental conditions like autism, cognitive behavioral therapy, trauma-based therapy, family

therapy and other alternate treatments of less risk are all possible to help these suffering adolescents[9].

9 "Turban et al.' s (2020) singular endorsement of 'affirmative' therapies, which their data failed to substantiate, contributes to the alarming trend to frame any non-'affirming' approaches as harmful... We believe that exploratory psychotherapy that is neither 'affirmation' nor 'conversion' should be the first-line treatment for all young people with GD, potentially reducing the need for invasive and irreversible medical procedures" (D'Angelo et al., 2021).

"A psychoanalytic understanding of trauma can help clinicians develop a picture of the psychological structure of an individual' s mind, including patterns of relating, defensive structures and the capacity to reflect upon the self. When clinicians can tune into their patients' states of mind and preoccupations, they can help introduce different ways of thinking about them. This can foster a dialogue about planned actions and treatments. It is essential for healthcare professionals to explore patients' thinking, hopes and beliefs before commencing any irreversible medical intervention" (Evans, 2023).

Conclusion

90. For the reasons set forth above and in my prior declaration, in my professional opinion as an endocrinologist, no child or adolescent should receive puberty blockers to block normal puberty, nor should they receive supraphysiologic doses of opposite sex hormones to attempt to alter secondary sex characteristics, nor should they have surgeries to remove or alter the breasts, genitalia or reproductive tracts as part of GAT. These treatments have not been shown to be safe, effective, or medically necessary. The child cannot consent or assent to these procedures. The parent or guardian also cannot consent to the life-altering changes resulting from GAT. There exists insufficient evidence of benefit for adults, but serious concerns for risk of harm.

91. Finally, the June 2022 AHCA GAPMS report states: "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" (FL Medicaid GAPMS, 2022). I strongly agree with that statement.

I declare under penalty of perjury, pursuant to 28 U.S.C. § 1746, that the foregoing is true and correct.

Executed this 10th day of March 2023.

/s/ Michael K. Laidlaw

Michael K. Laidlaw, M.D.

References

Actavis Pharma, Inc. Testosterone Cypionate injection. Actavis Pharma, Inc., 2018. Accessed May 8, 2022 via https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7b57b68-dca6-4df2-b3f2-7017d7b69f17&msclkid=4ed2db18cd5411ecba911bd6e4bded62

Alberts B, Johnson A, Lewis J, et al. "Sperm" in Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002.

Almazan AN, Keuroghlian AS. "Association Between Gender-Affirming Surgeries and Mental Health Outcomes". JAMA Surgery 2021; 156(7): 611–618.

Alzahrani T, Nguyen T, Ryan A, et al. "Cardiovascular disease risk factors and myocardial infarction in the transgender population". Circ Cardiovasc Qual Outcomes. 2019;12(4):e005597

The American Cancer Society medical and editorial team. "Mastectomy". American Cancer Society. https://www.cancer.org/cancer/breast-cancer/treatment/surgery-for-breast-cancer/mastectomy.html accessed 06/24/22

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders* (5th ed., text rev.) 2022. https://doi.org/10.1176/appi.books.9780890425787

Anckarsäter, H., (MD, Ph.D.) and Gillberg, C., (M.D., Ph.D.) "Methodological Shortcomings Undercut Statement in Support of Gender-Affirming Surgery". Am J Psychiatry 2020; 177:764– 765; doi: 10.1176/appi.ajp.2020.19111117.

Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. "Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome". J Clin Endocrinol Metab. 2005;90(4):1929. Epub 2004 Dec 28.

Arain, et al. Neuropsychiatric Disease and Treatment. “Maturation of the adolescent brain”. Neuropsychiatric Disease and Treatment. 2013:9 449–461

Banikarim, C. “Primary Dysmneorrhea in Adolescents”. UpToDate. Feb 10, 2021.

Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Wallace RB, Ohsfeldt RL, Jones MP, Rosenthal GE, Wolinsky FD "The aftermath of hip fracture: discharge placement, functional status change, and mortality." Am J Epidemiol. 2009;170(10):1290. Epub 2009 Oct 4.

Bell & Mrs A v The Tavistock And Portman NHS Foundation Trust. Approved Judgment.[2020] EWHC 3274 (Admin) (01 December 2020). https://www.judiciary.uk/wp-content/uploads/2020/12/Bell-v-Tavistock-Judgment.pdf

Bell & Mrs A v The Tavistock And Portman NHS Foundation Trust. Appeal No. C1/2020/2142 (17 September 2021).

Bentler SE, Liu L, Obrizan M, Cook EA, Wright KB, Geweke JF, Chrischilles EA, Pavlik CE, Wallace RB, Ohsfeldt RL, Jones MP, Rosenthal GE, Wolinsky FD "The aftermath of hip fracture: discharge placement, functional status change, and mortality." Am J Epidemiol. 2009;170(10):1290. Epub 2009 Oct 4.

Block J. Gender dysphoria in young people is rising-and so is professional disagreement. BMJ. 2023 Feb 23;380:p382. doi: 10.1136/bmj.p382. PMID: 36822640.

BMJ. The Nuremberg Code (1947) BMJ 1996; 313 doi: https://doi.org/10.1136/bmj.313.7070.1448

Bouraïma H, Lireux B, Mittre H, Benhaim A, Herrou M, Mahoudeau J, Guillon-Metz F, Kottler ML, Reznik Y. Major hyperestrogenism in a feminizing

adrenocortical adenoma despite a moderate overexpression of the aromatase enzyme. Eur J Endocrinol. 2003 Apr;148(4):457-61. doi: 10.1530/eje.0.1480457. PMID: 12656667.

Bränström R, Pachankis JE. "Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study". Am J Psychiatry 2020; 177:727–734

Bränström R, Pachankis JE. "Toward Rigorous Methodologies for Strengthening Causal Inference in the Association Between Gender-Affirming Care and Transgender Individuals' Mental Health: Response to Letters". Am J Psychiatry 2020; 177:769–772; doi: 10.1176/appi.ajp.2020.20050599.

Brown BB & Larson J. Handbook of Adolescent Psychology. 3 Peer Relationships in Adolescence. John Wiley & Sons, Inc. 2009.

Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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. PLoS One. 2021 Feb 2;16(2):e0243894. doi: 10.1371/journal.pone.0243894. PMID: 33529227; PMCID: PMC7853497.

Cass, Hillary. The Cass Review Interim Report. Feb, 2022. https://cass.independent-review.uk/publications/interim-report/

The Cass Review. Website. The Chair. Accessed on-line April 29, 2022. https://cass.independent-review.uk/about-the-review/the-chair/

Cavlan D, Bharwani N, Grossman A. Androgen- and estrogen-secreting adrenal cancers. Semin Oncol. 2010 Dec;37(6):638-48. doi: 10.1053/j.seminoncol.2010.10.016. PMID: 21167382.

CDC. "What is Venous Thromboembolism?" Accessed online 04/27/2022.

https://www.cdc.gov/ncbddd/dvt/facts.html?msclkid=7406875bc6a411ecb67829f71b182f45

Chan Y, et al. "Evaluation of the infant with atypical genital appearance (difference of sex development)" UpToDate. Feb 18, 2021.

Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, Rosenthal SM, Tishelman AC, Olson-Kennedy J. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023 Jan 19;388(3):240-250. doi: 10.1056/NEJMoa2206297. PMID: 36652355.

Christel J M de Blok, et al. "Breast cancer risk in transgender people receiving hormone treatment: nationwide cohort study in the Netherlands" BMJ 2019; 365 doi: https://doi.org/10.1136/bmj.l1652 (Published 14 May 2019)

Coleman E, et al. "Standards of Care for the Health of Transgender and Gender Diverse People, Version 8". International Journal of Transgender Health. 06 Sep 2022. International Journal of Transgender Health. https://doi.org/10.1080/26895269.2022.2100644.
https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2100644

Collet S, Gieles NC, Wiepjes CM, Heijboer AC, Reyns T, Fiers T, Lapauw B, den Heijer M, T'Sjoen G. Changes in Serum Testosterone and Adrenal Androgen Levels in Transgender Women With and Without Gonadectomy. J Clin Endocrinol Metab. 2023 Jan 17;108(2):331-338. doi: 10.1210/clinem/dgac576. PMID: 36201493; PMCID: PMC9844963.

"Correction to Bränström and Pachankis," Am J Psychiatry, 177:8 (Aug. 2020).

Correction, International Journal of Transgender Health, 23:sup1, S259-S261, DOI: 10.1080/26895269.2022.2125695

Council for Choices in Healthcare in Finland, Medical treatment methods for dysphoria associated with variations in gender identity in minors—recommendation, June 11, 2020, https://bit.ly/Cohere_Finland_GDAinMinorsRx.

Curtis, D. “Study of Transgender Patients: Conclusions Are Not Supported by Findings”. Am J Psychiatry 2020; 177:766; doi: 10.1176/appi.ajp.2020.19111131 ;

de Vries AL, Steensma T, Doreleijers TA, Cohen-Kettenis PT. “Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study”. J Sex Med. 2011 Aug;8(8):2276-83.

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 (2014) 134 (4): 696–704.

D’Angelo R, et al. "One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria". Archives of sexual behavior 2021; 50(1): 7–16.

DEA. Diversion Control Division. Controlled Substance Schedules. Accessed May 1, 2022. https://www.deadiversion.usdoj.gov/schedules/

Deichmann RE, Krousel-Wood M, Breault J. Bioethics in Practice: Considerations for Stopping a Clinical Trial Early. Ochsner J. 2016 Fall;16(3):197-8. PMID: 27660563; PMCID: PMC5024796.

Dhejne, et al., “Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden,” PLoS One, vol. 6, issue 2 (Feb. 22, 2011)

Diamond M,Transsexuality Among Twins: Identity Concordance, Transition, Rearing, and Orientation, International Journal of Transgenderism. 2013.14:1, 24-38, DOI: 10.1080/15532739.2013.750222

Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. Dev Psychol. 2008 Jan;44(1):34-45. doi: 10.1037/0012-1649.44.1.34. PMID: 18194003.

Dunaif A, Segal KR, Futterweit W, Dobrjansky A. “Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome”. Diabetes. 1989;38(9):1165.

Elhakeem A, et al. “Association Between Age at Puberty and Bone Accrual From 10 to 25 Years of Age”. JAMA Network Open. 2019;2(8):e198918. doi:10.1001/jamanetworkopen.2019.8918

Emmanuel M & Bokor B. Tanner Stages. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK470280/

Evans M. Assessment and treatment of a gender-dysphoric person with a traumatic history. J of Child Psychotherapy. Received 07 Nov 2022, Accepted 22 Jan 2023, Published online: 21 Feb 2023.

FDA.gov, regarding celecoxib https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020998s026lbl.pdf accessed 10/01/22

FDA.gov sumatriptan. "HIGHLIGHTS OF PRESCRIBING INFORMATION..IMITREX (sumatriptan)". https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/020080s054lbl.pdf accessed 10/01/2022.

Florida Department of Health website. https://mqa-internet.doh.state.fl.us/MQASearchServices/HealthCareProviders accessed 09/29/22-10/01/22.

Gagnon DR, Zhang T, Brand FN, Kannel WB. “Hematocrit and the risk of cardiovascular disease—The Framingham Study: a 34-year follow-up”. Am Heart J. 1994;127(3):674-682.

Gaufen D and Norgren S. "Policy Change Regarding Hormonal Treatment of Minors with Gender Dysphoria at Tema Barn - Astrid Lindgren Children’s

Hospital". 2021.
https://segm.org/sites/default/files/Karolinska%20Guideline%20K2021-4144%20April%202021%20%28English%2C%20unofficial%20translation%29.pdf

Greenpsan FS & Gardner DG. Basic & Clinical Endocrinology, 7th edition. Puberty. Lange Medical Books/McGraw-Hill. 2004.

Griffin, L., Clyde, K., Byng, R., & Bewley, S. (2021). "Sex, gender and gender identity: A re-evaluation of the evidence". BJPsych Bulletin, 45(5), 291-299. doi:10.1192/bjb.2020.73

Grynberg M, Fanchin R, Dubost G, Colau J, Brémont-Weil C, Frydman R, Ayoubi J. "Histology of genital tract and breast tissue after long-term testosterone administration in a female-to-male transsexual population". Reprod Biomed Online. 2010 Apr;20(4):553-8.

Guyatt GH, Oxman AD, Schünemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol. 2011 Apr;64(4):380-2. doi: 10.1016/j.jclinepi.2010.09.011. Epub 2010 Dec 24. PMID: 21185693. https://www.jclinepi.com/article/S0895-4356(10)00330-6/fulltext

Hall Ryan CW, Hall Richard CW, Chapman MJ. "Psychiatric Complications of Anabolic Steroid Abuse". Psychosomatics 46:4, July-August 2005.

Hardin AP, Hackell JM; COMMITTEE ON PRACTICE AND AMBULATORY MEDICINE. Age Limit of Pediatrics. Pediatrics. 2017 Sep;140(3):e20172151. doi: 10.1542/peds.2017-2151. Epub 2017 Aug 21. PMID: 28827380.

Haupt C, Henke M, Kutschmar A, et al. Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database Syst Rev. 2020;11:CD013138.

Hembree WC, et al., “Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline,” The Journal of Clinical Endocrinology & Metabolism, Volume 102, Issue 11 (Nov. 1, 2017).

Irwig MS. "Cardiovascular health in transgender people." Rev Endocr Metab Disord. 2018;19(3):243–251.

Joham AE, Ranasinha S, Zoungas S, Moran L, Teede HJ. “Gestational diabetes and type 2 diabetes in reproductive-aged women with polycystic ovary syndrome”. J Clin Endocrinol Metab. 2014 Mar;99(3):E447-52.

Kalin, N.H. “Reassessing Mental Health Treatment Utilization Reduction in Transgender Individuals After Gender-Affirming Surgeries: A Comment by the Editor on the Process by the Editor-in-Chief The American Journal of Psychiatry”. Am J Psychiatry 2020; 177:7 64; doi: 10.1176/appi.ajp.2020.20060803

Kaltiala-Heino R, Sumia M, Työläjärvi M, Lindberg N. “Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development”. Child and Adolescent Psychiatry and Mental Health (2015) 9:9.

Kuohong W and Hornstein MD. "Causes of female infertility". UpToDate. Jul 22, 2021.

Labcorp. Estradiol. https://www.labcorp.com/tests/004515/estradiol

Accessed 02/04/23.

Laidlaw MK. “Gender Dysphoria and Children: An Endocrinologist’s Evaluation of ‘I am Jazz’”. Public Discourse, 5 Apr 2018. https://www.thepublicdiscourse.com/2018/04/21220/

Laidlaw MK. "The Gender Identity Phantom", gdworkinggroup.org, Oct. 24, 2018.
http://gdworkinggroup.org/2018/10/24/the-gender-identity-phantom/

Laidlaw MK, Cretella M, Donovan K. "The Right to Best Care for Children Does Not Include the Right to Medical Transition". The American Journal of Bioethics. 19(2), Feb 2019.

Laidlaw MK, Van Meter Q, Hruz P, Van Mol W, & Malone W, "Letter to the Editor: Endocrine Treatment of Gender-Dsyphoria/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," J Clin Endocrinol Metab, 104(3) (March 2019).

Laidlaw MK, Van Mol A, Van Meter Q, Hansen JE. Letter to the Editor from M Laidlaw et al.: "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years." The Journal of Clinical Endocrinology & Metabolism, Volume 106, Issue 12, December 2021, Pages e5275–e5276, https://doi.org/10.1210/clinem/dgab514

Landén, M. "The Effect of Gender-Affirming Treatment on Psychiatric Morbidity Is Still Undecided". Am J Psychiatry 2020; 177:767–768; doi: 10.1176/appi.ajp.2020.19111165.

Larsen PR, et al. Williams Textbook of Endocrinology, 10th edition. Philadelphia, W.B. Saunders Company, 2003.

Littman L. "Rapid-onset gender dysphoria in adolescents and young adults: a study of parental reports". PLoS One. 2018;13(8): e0202330

Lupron Depot Prescribing Information. AbbVie Inc, 2018.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020708s035lbl.pdf
Accessed on-line 02/26/2023.

Madsen MC, van Dijk D, Wiepjes CM, Conemans EB, Thijs A, den Heijer M. “Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants, and Exposure Years”. J Clin Endocrinol Metab. 2021 May 13;106(6):1710-1717. doi: 10.1210/clinem/dgab089.

Malone, W. and Roman, S. "Calling Into Question Whether Gender-Affirming Surgery Relieves Psychological Distress". Am J Psychiatry 2020; 177:766–767; doi: 10.1176/appi.ajp.2020.19111149

Mayo Clinic. “Feminizing Surgery”.
https://www.mayoclinic.org/tests-procedures/feminizing-surgery/about/pac-20385102
Accessed 07/01/2022

Mayo Clinic. "Masculinizing Surgery". https://www.mayoclinic.org/tests-procedures/masculinizing-surgery/about/pac-20385105 accessed 06/24/2022

Mayo Clinic. "Top surgery for transgender men and nonbinary people". https://www.mayoclinic.org/tests-procedures/top-surgery-for-transgender-men/about/pac-20469462 accessed 06/24/2022.

McCartney CR, Corrigan MD, Drake MT, El-Hajj Fuleihan G, Korytkowski MT, Lash RW, Lieb DC, McCall AL, Muniyappa R, Piggott T, Santesso N, Schünemann HJ, Wiercioch W, McDonnell ME, Murad MH. Enhancing the Trustworthiness of the Endocrine Society's Clinical Practice Guidelines. J Clin Endocrinol Metab. 2022 Jul 14;107(8):2129-2138. doi: 10.1210/clinem/dgac290. PMID: 35690966.

Mehringer JE, et al. "Experience of Chest Dysphoria and Masculinizing Chest Surgery in Transmasculine Youth". Pediatrics (2021) 147 (3): e2020013300.

Nahata L, Tishelman AC, Caltabellotta NM, Quinn GP. “Low fertility preservation utilization among transgender youth”. J Adolesc Health. 2017;61(1):40–44.

National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002 Dec 17;106(25):3143-421. PMID: 12485966.

Olson-Kennedy J, Okonta V, Belzer M, Clark LF. Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts. JAMA Pediatr. 2018 May 1;172(5):431-436.

Pagadala M. "Comparison of the Concentration of Estrogen and Testosterone Ratio in Male Patients With Cirrhosis and Hypotension". ClinicalTrials.gov.

https://clinicaltrials.gov/ct2/show/NCT05051293

Accessed 02/05/23

Palko. Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland). 2020. https://genderreport.ca/wp-content/uploads/2021/04/Finland_Guidelines_Gender_Variance_In_Minors.pdf

Pretorius M, et al. "Mortality and Morbidity in Mild Primary Hyperparathyroidism: Results From a 10-Year Prospective Randomized Controlled Trial of Parathyroidectomy Versus Observation". Ann Intern Med. 2022 Apr 19. doi: 10.7326/M21-4416. Online ahead of print.

Quest Diagnositics. Estrogen, Total, Serum.

https://testdirectory.questdiagnostics.com/test/test-detail/439/estrogen-total-serum?cc=MASTER

accessed on-line 02/05/23

Quest Diagnostics. Hematocrit.

https://testdirectory.questdiagnostics.com/test/test-detail/509/hematocrit?cc=MASTER

accessed on-line 02/05/23

Quest Diagnostics. Testosterone, Total, MS.

https://testdirectory.questdiagnostics.com/test/test-detail/15983/testosterone-total-ms?cc=MASTER

accessed on-line 01/12/23

Reuters. "Sex-reassignment surgery yields long-term mental health benefits, study finds". NBC News. Nov 8, 2019. https://www.nbcnews.com/feature/nbc-out/sex-reassignment-surgery-yields-long-term-mental-health-benefits-study-n1079911

Ristori J, Steensma TD. Gender dysphoria in childhood. Int Rev Psychiatry. 2016;28(1):13-20. doi: 10.3109/09540261.2015.1115754. Epub 2016 Jan 12. PMID: 26754056.

Santoro N. Update in hyper- and hypogonadotropic amenorrhea. J Clin Endocrinol Metab. 2011 Nov;96(11):3281-8. doi: 10.1210/jc.2011-1419. PMID: 22058375.

Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. "Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention." Circulation. 2003;108(17):2154.

Sax L. "How Common is Intersex? A Response to Anne Fausto-Sterling," Journal of Sex Research 39:3 (August 2002), pp. 174-178.

Singh, D. (2012). A follow-up study of boys with gender identity disorder. Unpublished doctoral dissertation, University of Toronto.

Society for Evidence Based Gender Medicine (SEGM). Sweden's Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies (May 5, 2021), https://bit.ly/SEGM_SwedenStops Hormones.

Society for Evidence Based Gender Medicine (SEGM). National Academy of Medicine in France Advises Caution in Pediatric Gender Transition. (Mar 3, 2022), https://segm.org/France-cautions-regarding-puberty-blockers-and-cross-sex-hormones-for-youth

Statement of Removal, International Journal of Transgender Health, 23:sup1, S259-S259. 2022. DOI: 10.1080/26895269.2022.2125695 https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2125695

Steinberg L. "A social neuroscience perspective on adolescent risk-taking". Dev Rev. 2008;28(1):78-106.

TLC UK. Bottom Surgery | I am Jazz. Youtube. Accessed May 1, 2022. https://www.youtube.com/watch?v=lG-U8oFpa8o

Turban JL, King D, Carswell JM, et al. "Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation". Pediatrics 2020, 145 (2) e20191725.

Van Mol, A., Laidlaw, M. K., Grossman, M., McHugh, P. "Gender-Affirmation Surgery Conclusion Lacks Evidence" Am J Psychiatry 177:8, August 2020 ajp.psychiatryonline.org 765.

Wang AMQ, Tsang V, Mankowski P, Demsey D, Kavanagh A, Genoway K. Outcomes Following Gender Affirming Phalloplasty: A Systematic Review and Meta-Analysis. Sex Med Rev. 2022 Aug 25:S2050-0521(22)00012-9. doi: 10.1016/j.sxmr.2022.03.002. Epub ahead of print. PMID: 36031521.

Wallien, M.S.C., Veenstra, R., Kreukels, B.P.C. et al. Peer Group Status of Gender Dysphoric Children: A Sociometric Study. Arch Sex Behav 39, 553–560 (2010). https://doi.org/10.1007/s10508-009-9517-3

Weitzer, D. "Transgender surgery linked with better long-term mental health, study shows". ABC News. Oct 8, 2019. https://abcnews.go.com/Health/transgender-surgery-linked-long-term-mental-health-study/story?id=66125676

Wilson D and Bruno B. Embryology, Mullerian Ducts (Paramesonephric Ducts). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022. https://www.ncbi.nlm.nih.gov/books/NBK557727/

Wold, A. (M.D., Ph.D.) Gender-Corrective Surgery Promoting Mental Health in Persons With Gender Dysphoria Not Supported by Data Presented in Article, Am J Psychiatry 2020; 177:768; doi: 10.1176/appi.ajp.2020.19111170

WPATH member search. https://www.wpath.org/member/search accessed 09/29/2022 and 10/01/2022.

Yelehe M. et al. "Adverse effects of gender-affirming hormonal therapy in transgender persons: Assessing reports in the French pharmacovigilance database." Fundamental and Clinical Pharmacology. June 2, 2022.

Zucker KJ. “Debate: Different strokes for different folks”. Child and Adolescent Mental Health, Volume 25, Issue 1 (Feb 2020).

EXHIBIT 3

Appendix Attachment

11

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

AUGUST DEKKER, et al.,

Plaintiffs,

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

SIMONE MARSTILLER, et al.,

Defendants.
_____/

Expert Declaration of Michael K. Laidlaw, MD

I, Michael K. Laidlaw, M.D., hereby declare as follows:

1. I am over the age of eighteen and submit this expert declaration based on my personal knowledge and experience.

2. I am a board-certified endocrinologist. I received my medical degree from the University of Southern California in 2001. I completed my residency in internal medicine at Los Angeles County/University of Southern California Medical Center in 2004. I also completed a fellowship in endocrinology, diabetes and metabolism at Los Angeles County/University of Southern California Medical Center in 2006.

3. The information provided regarding my professional background and publications are detailed in my curriculum vitae. A true and correct copy of my curriculum vitae is attached as Exhibit A.

4. In my clinical practice as an endocrinologist, I evaluate and treat patients with hormonal and/or gland disorders. Hormone and gland disorders can cause or be associated with psychiatric symptoms, such as depression, anxiety, and other psychiatric symptoms. Therefore, I frequently assess and treat patients demonstrating psychiatric symptoms and determine whether their psychiatric symptoms are being caused by a hormonal issue, gland issue, or something else.

5. I have been retained by Defendants in the above-captioned lawsuit to provide an expert opinion on the efficacy and safety of sex reassignment treatment.

6. If called to testify in this matter, I would testify truthfully and based on my expert opinion. The opinions and conclusions I express herein are based on a reasonable degree of scientific certainty.

7. I am being compensated at an hourly rate of $450 per hour plus expenses for my time spent preparing this declaration, and to prepare for and provide testimony in this matter. I am being compensated at an hourly rate of $650 for testimony at depositions or trial. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I may provide.

8. My opinions contained in this report are based on: (1) my clinical experience as an endocrinologist; (2) my clinical experience evaluating individuals who have or have had gender incongruence including a detransitioner; (3) my knowledge of research and studies regarding the treatment of gender dysphoria, including for minors and adults; and (4) my review of the various declarations submitted by Plaintiffs

9. I was provided with and reviewed the following case-specific materials: The Florida Medicaid's "Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria"; the expert declaration of Johanna Olson-Kennedy; the expert declaration of Loren Schechter; the expert declaration of Dan H. Karasic; the expert declaration of Armand H. Matheny Antommaria; the declaration of Brit Rothstein; the declaration of August Dekker; the declaration of Jane Doe; the declaration of Jade Ladue; files from Florida Medicaid.

10. In my professional opinion, treatment interventions on behalf of children and adults diagnosed with gender dysphoria must be held to the same scientific standards as other medical treatments. These interventions must be optimal, efficacious, and safe. Any treatment which alters biological development in children should be used with extreme caution. Except in the case of a fatal injury or disease, the minor will become an adult and present to the adult physician. The adult physician must be able to have a thorough understanding of any condition which alters the biological development of children and, in the case of the endocrinologist, be knowledgeable about the long term effects of hormones

on the human body, particularly when the hormones are being used in ways that alter development.

11. The following expresses my expert opinion regarding minors and adults who present with a disparity between their biological sex and internal feeling about their gender, specifically with regard to the use of social transition, medications which block normal pubertal development, the applications of hormones of the opposite sex, and surgical procedures that alter the genitalia and/or breasts for those individuals.

I. Background

A. Endocrine Disorders

Before discussing gender dysphoria and gender affirmative therapy from the perspective of an endocrinologist, it is helpful to discuss the background of endocrine diseases. This background demonstrates the difference in gender dysphoria, which is a psychological diagnosis, and other conditions treated by endocrinologists, which are physical diagnoses.

Endocrinology is the study of glands and hormones. Endocrine disorders can be divided into three main types: those that involve hormone excess, those that involve hormone deficiency, and those that involve structural abnormalities of the glands such as cancers.

It is important for the endocrinologist to determine the cause of hormone gland excess or deficiency in order to devise an appropriate treatment plan. The plan will generally be to help bring the hormones back into balance and thus bring the patient back to health.

To give an example of hormone excess, hyperthyroidism is a term which means overactivity of the thyroid gland. In this condition excess thyroid hormone is produced by the thyroid gland. This results in various physical and psychological changes for the afflicted patient. Examples of physical changes can include tachycardia or fast heart rate, hand tremors, and weight loss. Examples of psychological symptoms include anxiety, panic attacks, and sometimes even psychosis.

An endocrinologist can recognize thyroid hormone excess in part by signs and symptoms, but can also confirm the diagnosis with laboratory testing that shows the thyroid hormones to be out of balance. Once this is determined and the degree of excess is known, then

treatments can be given to bring these levels back into balance to benefit the patient's health and to prevent other disease effects caused by excess hormone.

To give another example, consider a deficiency of insulin. Insulin is a hormone which regulates blood glucose levels. If there is damage to the pancreas such that insulin levels are very low, then blood glucose levels will rise. If the glucose levels rise to a certain abnormally high level, then this is considered diabetes. In the case of type 1 diabetes, insulin levels are abnormally low and therefore blood glucose levels are abnormally high leading to a variety of signs and symptoms. For example, the patient may have extreme thirst, frequent urination, muscle wasting, and weight loss. They may often experience lethargy and weakness.

In this case laboratory tests of glucose and insulin levels can confirm the diagnosis. Once diabetes is confirmed, the patient is then treated with insulin to help restore glucose balance in the body and prevent long-term complications of diabetes.

To give an example of a structural abnormality, a patient may have a lump on the thyroid gland in the neck. This may be further examined by an imaging test such as an ultrasound. A needle biopsy can be performed so that the cells can be examined under a microscope. A trained medical professional such as a pathologist can then examine the cells to determine if they are benign or cancerous. In the case of a thyroid cancer, a surgical procedure known as a thyroidectomy may be performed to remove the diseased thyroid gland in order to treat the cancer.

Noteworthy in the preceding three examples is that all three disease conditions are diagnosed by physical observations. In other words, a laboratory test of a hormone, an imaging test of an organ, an examination of cells under a microscope, or all three may be employed in the diagnosis of endocrine disease.

B. Gender Dysphoria is a Psychological Diagnosis

Gender dysphoria, on the other hand, is not an endocrine diagnosis, it is in fact a psychological diagnosis. It is diagnosed purely by psychological methods of behavioral observation and questioning.

Likewise what is termed gender identity is a psychological concept. It has no correlate in the human body. In the letter to the editor I wrote with my colleagues, discussed above, we

wrote in our critique of the Endocrine Society Guidelines that "There are no laboratory, imaging, or other objective tests to diagnose a 'true transgender' child" (Laidlaw et al., 2019).

For example, one cannot do imaging of the human brain to find the gender identity. Likewise, there is no other imaging, laboratory tests, biopsy of tissue, autopsy of the brain, genetic testing, or other biological markers that can identify the gender identity. There is no known gene that maps to gender identity or to gender dysphoria. In other words, there is no objective physical measure to identify either gender identity or gender dysphoria.

This is in contrast to all other endocrine disorders which have a measurable physical change in either hormone levels or gland structure which can be confirmed by physical testing. Therefore, gender dysphoria is a purely psychological phenomenon and not an endocrine disorder. But as my colleagues and I wrote in our letter to the editor, it becomes an endocrine condition through gender affirmative therapy: "Childhood gender dysphoria (GD) is not an endocrine condition, but it becomes one through iatrogenic puberty blockade (PB) and high-dose cross-sex (HDCS) hormones. The consequences of this gender-affirmative therapy (GAT) are not trivial and include potential sterility, sexual dysfunction, thromboembolic and cardiovascular disease, and malignancy" (Laidlaw et al. 2019).

As a practicing endocrinologist and scientist, I have made a study of GD and its treatment for two reasons: 1) I want to be sure that my colleagues and I understand the science before we treat any patients with GD; and 2) I am concerned that the medical society that claims to speak for me and other endocrinologists has abandoned scientific principles in endorsing treatments for GD that have questionable scientific support. The opinions expressed in this report are the result of my own experience, studies, education, and review of the scientific literature related to GD.

C. Gender Dysphoria and Desistance

GD is a persistent state of distress that stems from the feeling that one's gender identity does not align with their physical sex (American Psychiatric Association, 2013). It has been a relatively rare condition in children and adolescents. However there have been very significant increases in referrals for this condition noted around the globe.

For example, in the UK, "The number of referrals to GIDS [Gender Identity Development Service] has increased very significantly in recent years. In 2009, 97 children and young

people were referred. In 2018 that number was 2519" (Bell v Tavistock Judgment, 2020). There is evidence that this increase may be in part due to social contagion and fueled by social media/internet use (Littman, 2018).

The French National Academy of Medicine wrote recently: "Parents addressing their children's questions about transgender identity or associated distress should remain vigilant regarding the addictive role of excessive engagement with social media, which is both harmful to the psychological development of young people and is responsible for a very significant part of the growing sense of gender incongruence" (SEGM, 2022).

In "a study of the Finnish gender identity service, '75% of adolescents [assessed] had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria' (Kaltiala-Heino, 2015). In fact, '68% had their first contact with psychiatric services due to other reasons than gender identity issues.' The same study also showed that 26% percent had an autistic spectrum disorder and that a disproportionate number of females (87%) were presenting to the gender clinics compared to the past" (Laidlaw in gdworkinggroup.org, 2018).

Desistance is a term indicating that the child, adolescent, or adult who initially presented with gender incongruence has come to experience a realignment of their internal sense of gender and their physical body. "Children with [gender dysphoria] will outgrow this condition in 61% to 98% of cases by adulthood. There is currently no way to predict who will desist and who will remain dysphoric" (Laidlaw et al., 2019; Ristori & Steensma, 2016).

Because there is no physical marker to diagnose gender identity, and because it is not possible to predict which child or adolescent will desist, it is not possible to know which young person will remain transgender identified as adults. Also, because the 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.

Dr. Olson-Kennedy states that "[t]he studies pertaining to desistance upon which the GAPMS Memo relies pertain to prepubertal youth, not adolescents. In fact, contrary to the GAPMS Memo's assertion, studies show that if gender dysphoria is present in adolescence, it usually persists (DeVries, et al., 2011)." (Oslon-Kennedy decl, p. 22).

Dr. Olson-Kennedy confuses prepubertal (a medical term) with preadolescence (a psychological designation). Puberty which pertains to the phsyical development of the reproductive tract, breasts and associated secondary sex characterestics can begin as early as age 8 in girls and age 9 in boys. The studies which have examined desistance involved children aged twelve and under. For example table 1 in Ristori and Steensma 2016 shows multiple studies involving children. For the three most recent - Singh (2012), Wallien & Cohen-Kettenis (2008), and Drummond et al. (2008) - these involved age ranges from 3 to nearly 13 years old.[1] The desistance rate varied from 61 to 88%. Since the upper age was twelve (or slightly higher), this would include children in the age range of 8-12 years old many of whom were going through puberty based on their age and were therefore not Tanner stage 1 (pre-pubertal).[2] Therefore Dr. Olson-Kennedy's statement that "[t]he studies pertaining to desistance upon which the GAPMS Memo relies pertain to prepubertal youth" is incorrect.

D. Biological Sex in Contrast to Gender Identity

A recognition and understanding of biological sex is critical to my practice as an endocrinologist because the endocrine physiology of men and women, boys and girls, differ.

Biological sex is the objective physical condition of having organs and body parts which correspond to a binary sex. There are only two physical sexes, male and female. The male is identified as having organs and tissues such as the penis, testicles and scrotum. The female sex is identified by having organs and tissues such as the labia, vagina, uterus, and ovaries. Biological sex is easily identified by physical observation such that adults and even young children can identify the biological sex of a newborn baby.

---

[1] "This study provided information on the natural histories of 25 girls with gender identity disorder (GID). Standardized assessment data in childhood (mean age, 8.88 years; range, 3-12 years)" (Drummond et al., 2008).
"The mean age of the participating gender-referred children was 10.47 years (SD = 1.27; range, 8.11–12.77)" (Wallien et al., 2009).
" Standardized assessment data in childhood (mean age, 7.49 years; range, 3–12 years) and at follow-up (mean age, 20.58 years; range, 13–39 years) were used to evaluate gender identity and sexual orientation outcome. At follow-up, 17 participants (12.2%) were judged to have persistent gender dysphoria." (Singh, 2012).

[2] To my knowledge the desistance literature does not examine Tanner stages of puberty as part of their studies. However one can infer based on the ages that many children had at least begun puberty (Tanner stage 2) or were at a more advanced stage of puberty.

This is in contrast to gender identity, which does not exist in any physical sense. It is a subjective identification known only once a patient makes it known. It cannot be identified by any physical means, cannot be confirmed by any outside observer, and can change over time.

It is also noteworthy that the physical organs described above as representing biological sex have a physical genetic correlate. In other words, it is a well-established scientific fact that two X chromosomes identify the cells correlating to a female person, and an X and a Y chromosome correlate to a male person.

Sex is clearly identified in 99.98% of cases by chromosomal analysis (Sax, 2002). Sex is also clearly recognized at birth in 99.98% of cases (Id.). Therefore, sex is a clear provable objective reality that can be identified through advanced testing such as karyotyping, or simple genital identification at birth by any layperson. The other 0.02% of cases have some disorder of sexual development (DSD). DSDs do not represent an additional sex or sexes, but simply a disorder on the way to binary sex development (Chan et al., 2021).

E. Human Sexual Development

1. Embryologic development

Another confirmation that there are only two biological sexes comes from what is known about embryologic development and fertilization. The biologic development of the human person begins with a gamete from a female termed an ovum or egg and a gamete from a biological male which is termed sperm. The fertilization of the egg by the sperm begins the process of human biological development. The cells of the fertilized ovum then multiply and the person undergoes the incredible changes of embryologic development.

It is noteworthy that the male sperm comes from the biological male and the female egg comes from the biological female. There is no other third or fourth or fifth type of gamete that exists to begin the development of the human person. This is consistent with the binary nature of human sex (Alberts et al., 2002).

The sex binary of the human embryo is further developed between roughly weeks 8 to 12 of human development. There are two primitive structures present within the developing embryo called the Wolffian duct and Mullerian ducts (Larsen et al., 2003). The Wolffian ducts develop into substructures of the genitalia including the vas deferens and epididymis

which belong exclusively to the male sex. For the female, the Mullerian ducts go on to form the uterus, fallopian tubes, cervix and upper one third of the vagina which belong exclusively to the female sex (Id.)

Significantly once the male structures are developed from Wolffian ducts, the Mullerian ducts are obliterated. This means that throughout the rest of embryological development the Mullerian ducts will not form into biological female structures. Likewise, in the female, the Wolffian ducts are destroyed by week 12 and will not form male structures at any point in the future (Id.).

Thus we can see in very early development that the sex binary is imprinted physically not only in the chromosomes, but also on the very organs that the body produces. Additionally, the potential to develop organs of the opposite sex is eliminated. Thus, in the human being there are only two physical tracts that one may progress along, the one being male and the other being female (Wilson and Bruno, 2022).

2. Pubertal Development

As mentioned previously, at the time of birth an infant's sex is easily identified through observation of the genitalia. Corresponding internal structures could also be confirmed through imaging if needed.

In early childhood, some low level of sex hormones are produced by the sex glands. The male testes produce testosterone. The female ovaries produce primarily the hormone estrogen. These sex glands remain quiescent for the most part, producing low levels of sex hormones until the time of pubertal development.

Puberty is a time of development of the sex organs, body, brain and mind. There are well known changes in physical characteristics of the male such as growth of facial hair, deepening of the voice, and increasing size of the testicles and penis. Importantly the testicles will develop sperm under the influence of testosterone and become capable of ejaculation. Because of these changes, the male will become capable of fertilizing an egg. The inability to produce sperm sufficient to fertilize an egg is termed infertility.

For the female, pubertal development includes changes such as breast development, widening of the pelvis, and menstruation. The female will also begin the process of ovulation which is a part of the menstrual cycle and involves the release of an egg or eggs

from the ovary. Once the eggs are released in a manner in which they can become fertilized by human sperm then the female is termed fertile. The inability to release ovum that can be fertilized is infertility (Kuohong and Hornstein, 2021).

3. Tanner stages of development

From a medical perspective it is important to know the stage of pubertal development of the developing adolescent. This can be determined through a physical examination of the body. The female will have changes in breast characteristics and pubic hair development. Similarly, the male will have changes in testicular size and pubic hair development. These findings can be compared to the Tanner staging system which will allow the stage of puberty to be known.

Tanner stages are divided into five. Stage 1 is the pre-pubertal state before pubertal development of the child begins. Stage 5 is full adult sexual maturity. Stages 2 through 4 are various phases of pubertal development (Greenspan and Gardner, 2004).

Awareness of the Tanner stage of the developing adolescent is also useful to assess for maturation of sex organ development leading to fertility. For girls, the first menstruation (menarche) occurs about two years after Tanner stage 2 and will typically be at Tanner stage 4 or possibly 3 (Emmanuel and Boker, 2022). The first appearance of sperm (spermarche) will typically be Tanner stages 4 (Id.). If puberty is blocked or disrupted before reaching these critical stages, the sex glands will be locked in a premature state and incapable of fertility.

4. Biological Sex Cannot Be Changed

It is not possible for a person to change from one biological sex to the other, and there is no technology that allows a biological male to become a biological female or vice-versa. It is not technologically possible at this time to change sex chromosomes; these will remain in every cell throughout life. It is not technologically possible to transform sex glands from one to the other. In other words, there are no hormones or other means currently known to change an ovary into a testicle or a testicle into an ovary.

Furthermore, as noted earlier, several of the sex specific structures (such as the epidymis of the male or uterus of the female) are produced early in embryological development from around weeks 8 to 12. The primitive ducts which lead to these organs of the opposite sex

are obliterated. There is no known way to resuscitate these ducts and continue development of opposite sex structures.

It is also not possible to produce gametes of the opposite sex. In other words, there is not any known way to induce the testicles to produce eggs. Nor is there any known way to induce the ovaries to produce sperm. Therefore, creating conditions for a biological female to create sperm capable of fertilizing another ovum is impossible. The induction of opposite sex fertility is impossible.

In fact, as I will discuss, gender affirming therapy actually leads to infertility and potential sterilization.

F. Iatrogenic Harms

The term iatrogenic is used in medicine to describe harms or newly created medical conditions that are the result of medications, surgeries, or even psychological treatments. In this section I will discuss the iatrogenic harms of "gender affirmative treatment," for females. Each of the four interventions which I will describe (social transition, blocking normal puberty, opposite sex hormones, and surgery) lead to iatrogenic harms to the patient. These harms will be described in detail below. I speak of these harms because it is important to understand that once a patient begins GAT it is more likely the patient will continue on to surgery (de Vries et al., 2014). Thus, GAT interrupts the natural desistence process and instead places the patient on a lifetime regimen of hormonal and surgical care. A good understanding of these harms is also critical to my practice as an endocrinologist, because if I did not understand these harms, I could not advise patients of the risks associated with GAT.

G. Gender Affirmative Therapy

The approaches to gender dysphoria in minors may be divided into three main types. (Zucker, 2020). One is psychosocial treatment that helps the young person align their internal sense of gender with their physical sex. Another would be to "watch and wait" and allow time and maturity to help the young person align sex and gender through natural desistance. The third option, which is the focus of that which follows, is referred to as gender affirmative therapy.

Gender affirmative therapy (GAT) of adults and minors consists of psychosocial, medical, and surgical interventions that attempt to psychologically and medically alter the patient so that they come to believe they may become similar to the physical sex which aligns with their gender identity (but not their biological sex) and thereby reduce gender dysphoria. GAT consists of four main parts: 1) social transition, 2) blocking normal puberty or menstruation, 3) high dose opposite sex hormones, and 4) surgery of the genitalia and breasts.

The application of this medical therapy to minors is a fairly new intervention and is associated with a number of harms both known and unknown. GAT suffers from a lack of a quality evidence-base, poorly performed studies, and ongoing unethical human experimentation.

1. Social transition

The first stage of gender affirmative therapy is termed social transition. Social transition is a psychological intervention. The child may be encouraged to adopt the type of clothing and mannerisms or behaviors which are stereotypical of the opposite sex within a culture. For example, in the United States a boy might wear his hair long and wear dresses in order to socially transition. A girl may cut her hair short and wear clothes from the boys' section of a department store.

Social transition of the child has been noted by expert researcher in the field of child gender dysphoria, Ken Zucker, to itself be a form of iatrogenic harm (Zucker, 2020). This is because the social transition process may solidify the young person's belief that they are in fact the sex opposite of their biological sex.

From an endocrine point of view, it is understandable that a child having the outward appearance of the opposite sex, would believe that he or she is destined to go through puberty of the opposite sex as they have only a poor understanding of the internal structures of the body, the function of the sex glands, the role of the sex glands in fertility and so forth.

Therefore, it would be quite frightening for a boy who believes he is a girl to be turning into a man with all of the adult features that accompany manhood. Vice versa, the girl who has become convinced that she is a boy will be frightened by the physical changes brought on by womanhood.

In fact, it would appear that in the minds of the children and adolescents that they are anticipating a sort of disease state in the future by the hormone changes that will occur as a normal and natural part of human development. Until relatively recently in human history, it has not been possible to interfere with puberty through pharmaceutical means.

2. Medications which Block Pubertal Development

a. Background

A second stage of gender affirmative therapy may involve blocking normal pubertal development. This may be done with puberty blocking medications that act directly on the pituitary.

In order to understand what is occurring in this process, it is helpful to be aware of normal hormone function during pubertal development.

There is a small pea-sized gland in the brain called the pituitary. It is sometimes referred to as the "master gland" as it controls the function of several other glands. One key function for our purposes is the control of the sex glands. There are two specific hormones produced by the pituitary referred to as luteinizing hormone (LH) and follicle stimulating hormone (FSH). These are responsible for sex hormone production and fertility. The LH and FSH act as signals to tell the sex glands begin or continue their function.

In the adult male, the production of LH will cause adult levels of testosterone to be produced by the testicles. In the adult female, the production of LH will cause adult levels of estrogen to be produced by the ovaries.

In early childhood, prior to the beginning of puberty, the pituitary function with respect to the sex glands is quiescent. However, during pubertal development LH will signal the testicle to increase testosterone production and this carries the boy through the stages of pubertal development into manhood. Likewise for the female, the interaction of LH with the ovaries increases estrogen production and carries the girl through the stages of development into womanhood.

There are conditions diagnosed by endocrinologists which involve a disruption of this normal communication between the pituitary and the sex glands. There is a medical condition called hypogonadotropic hypogonadism. The meaning of this term is that the pituitary is not sending the hormonal signals (LH and FSH) to the sex glands and therefore the sex glands are unable to make their sex hormones. The result is hormonal deficiencies of LH, FSH, and either testosterone or estrogen.

If this condition occurs during puberty, the effect will be to stop pubertal development. This is a disease state which is diagnosed and treated by the endocrinologist.

Medications such as GnRH agonists act on the pituitary gland to lower the pituitary release of LH and FSH levels dramatically. The result is a blockage of the signaling of the pituitary to the testicles or ovaries and therefore underproduction of the sex hormones. This will stop normal menstrual function for the female and halt further pubertal development. For the male this will halt further pubertal development. If the male had already reached spermarche, then production of new sperm will stop.

b. GnRH Agonist Medication Effects Vary by Use Case

There are a variety of uses for GnRH agonists. The use and outcome can be very different for different applications.

For example, the initial development of the medication called Lupron was for the treatment of prostate cancer. The idea being that blocking pituitary hormones will block the adult male's release of testosterone from the testicles. Since testosterone will promote the growth of prostate cancer, the idea is to lower testosterone levels to a very low amount and therefore prevent the growth and spread of prostate cancer. This is a labeled use of the medication. In other words, there is FDA approval for this use.

Another labeled use of GnRH agonist medication is for the treatment of central precocious puberty. In the disease state of central precocious puberty, pituitary signaling is activated at an abnormally young age, say age four, to begin pubertal development. In order to halt puberty which has begun at an abnormally early time, a GnRH agonist may be used. Here the action of the medication on the pituitary will disrupt the signaling to the sex glands, stop early sex hormone production, and therefore stop abnormal pubertal development.

Then, at a more normal time of pubertal development, say age 11, the medication is stopped and puberty is allowed to proceed. The end result is to restore normal sex gland function and timing of puberty. This is a labeled use for a GnRH agonist medication.

What about the use of puberty blockers such as Lupron in gender affirmative therapy? In these cases, we have physiologically normal children who are just beginning puberty or are somewhere in the process of pubertal development. They have healthy pituitary glands and sex organs. However, a puberty blocking medication is administered to stop normal pubertal development.

In this case the condition of hypogonadotropic hypogonadism described above (a medical disease) is induced by medication and is an iatrogenic effect of treating the psychological condition of gender dysphoria. GnRH agonist medications have not been FDA approved for this use.

c. Adverse Health Consequences of Blocking Normal Puberty

There are a number of serious health consequences that occur as the result of blocking normal puberty. The first problem is infertility. The Endocrine Society Guidelines recommend beginning puberty blockers as early as Tanner stage 2. As discussed earlier, this is the very beginning of puberty. Fertility development happens later generally in Tanner stage 4. One can see that if the developing person is blocked at Tanner stage 2 or 3 as advocated by the guidelines, this is prior to becoming fertile. The gonads will remain in an immature, undeveloped state.

Dr. Antommaria writes that "The [Endocrine Society] guideline recommends that informed consent for pubertal blockers and gender-affirming hormones include a discussion of the implications for fertility and options for fertility preservation (Antommaria decl, p.23). However, even though procedures to preserve fertility are available, studies show that less than 5% of adolescents receiving GAT even attempt fertility preservation (FP) (Nahata, 2017). Moreover, "ovarian tissue cryopreservation is still considered experimental in most centers and testicular tissue cryopreservation remains entirely experimental. These experimental forms of FP would be the only options in children [with puberty] blocked prior to spermarche and menarche and are high in cost and limited to specialized centers. Even with FP there is no guarantee of having a child" (Laidlaw, Cretella, et al., 2019).

Naturally, these children are at a developmental age where they are not thinking about adult related concepts such as having children as they are children themselves. This is only natural and to be expected. The medical problem imposed on them is that if they remain blocked in an early pubertal stage then even the addition of opposite sex hormones will not allow for the development of fertility. In fact, high dose opposite sex hormones may permanently damage the immature sex organs leading to sterilization. Certainly the removal of the gonads, which will be discussed later, will ensure sterilization.

Another problem with blocking puberty at an early stage is sexual dysfunction. The child will continue their chronological age progression toward adulthood and yet remain with undeveloped genitalia. This will lead to sexual dysfunction including potential erectile dysfunction and inability to ejaculate and orgasm for of the male. For the female with undeveloped genitalia potential sexual dysfunction may include painful intercourse and impairment of orgasm.

The impairment of sexual function was evident in the TLC reality show "I am Jazz". In the show Jazz who was identified male at birth has been given puberty blockers at an early pubertal stage. In an episode where Jazz visits a surgeon and has a discussion about sexual function, Jazz states: “I haven’t experienced any sexual sensation.” Regarding orgasm, Jazz says: “I don’t know, I haven’t experienced it”[3] (TLC, accessed 2022).

In addition to direct effects on the developing genitalia and fertility there are other important aspects of puberty that are negatively affected. For example, puberty is a time of rapid bone development. This time of development is critical in attaining what we call peak bone density or the maximum bone density that one will acquire in their lifetime (Elhakeem, 2019).

Any abnormal lowering of sex hormones occurring during this critical time will stop the rapid accumulation of bone and therefore lower ultimate adult bone density. If a person does not achieve peak bone density, they would be expected to be at future risk for osteoporosis and the potential for debilitating spine and hip fractures as adults. Hip fractures for the older patient very significantly increase the risk of major morbidity and death (Bentler, 2009). Allowing a "pause" in puberty for any period of time leads to an inability to attain peak bone density.

[3] Jazz's age is somewhere in the mid-teens during this episode.

Another consideration is maturation of the human brain. Much of what happens is actually unknown. However, “sex hormones including estrogen, progesterone, and testosterone can influence the development and maturation of the adolescent brain” (Arain, 2013). Therefore there are unknown, but likely negative consequences to blocking normal puberty with respect to brain development.

A third major problem with blocking normal puberty involves psychosocial development. Adolescence is a critical time of physical, mental, and emotional changes for the adolescent. It is important that they develop socially in conjunction with their peers. This is well recognized in the psychological literature: “For decades, scholars have pointed to peer relationships as one of the most important features of adolescence.” (Brown, 2009). If one is left behind for several years under the impression that they are awaiting opposite sex puberty, they will miss important opportunities for socialization and psychological development. Psychosocial development will be necessarily stunted as they are not developing with their peers. This is a permanent harm as the time cannot be regained.

Aside from the multiple serious problems that are iatrogenically acquired by blocking normal puberty, there appear to be independent risks of the puberty blocking medication themselves. For example, one can read the labeling of a common puberty blocking medication called Lupron Depot-Ped and find under psychiatric disorders: "emotional lability, such as crying, irritability, impatience, anger, and aggression. Depression, including rare reports of suicidal ideation and attempt. Many, but not all, of these patients had a history of psychiatric illness or other comorbidities with an increased risk of depression” (Lupron, 2022). This is particularly concerning given the high rate of psychiatric comorbidity with gender dysphoria discussed previously.

d. The Effect of Puberty Blockers on Desistance

As stated earlier a very high proportion of minors diagnosed with gender dysphoria will eventually desist or come to accept their physical sex. Puberty blockers have been shown to dramatically alter natural desistance.

In a Dutch study that included seventy adolescents who took puberty blockers, all seventy decided to go on to hormones of the opposite sex (de Vries, et al. 2011). In a follow-up study, the overwhelming majority went on to have sex reassignment surgery by either vaginoplasty for males or hysterectomy with ovariectomy for females (de Vries, et al. 2014). These surgeries resulted in sterilization. This is why puberty blockers, rather than

being a "pause" to consider aspects of mental health, are instead a pathway towards future sterilizing surgeries. The surgeries were consequential in another important way. One person who had a vaginoplasty died of post-surgical complications of necrotizing fasciitis which is a rapidly progressive and very severe infection of the soft tissues beneath the skin and which has a high mortality (Id.).

e. Infertility as a result of Puberty Blockers in GAT

Dr. Antommaria states that "Florida Medicaid provides coverage for the use of puberty blockers to treat central precocious puberty, but now prohibits coverage for the use of puberty blockers to treat gender dysphoria, even though the use of puberty blockers to treat both conditions has comparable risks and is supported by comparable types of evidence" (Antommaria decl, p. 24). These statements fail to recognize the very different effects of PB medication in early childhood versus during adolescence.

Giving puberty blockers to a four year old with central precocious puberty will obviously not impair fertility, as the four year old has not yet become fertile. The child will at a later time have the puberty blocker discontinued and then normal pubertal development can proceed. Therefore when they are no longer taking the medication, they will gain natural fertility.

In contrast, puberty blocking medication given to minors in GAT occurs at precisely the time that the child will gain reproductive function. This will stop sperm production in the male and ovulation in the female (if these have already occurred, otherwise the functions will not even begin) which produces the infertile condition. Importantly, so long as the minor continues PB they will remain infertile. Should they continue on to opposite sex hormones as part of GAT then they will remain infertile. There is the additional possibility that cytotoxic effects of high dose opposite sex hormones will damage the immature gonads leading to permanent sterility.

3. Opposite Sex Hormones

The third stage of gender affirmative therapy involves using hormones of the opposite sex at high doses to attempt to create secondary sex characteristics in the person's body.

a. Testosterone

Testosterone is an anabolic steroid of high potency. It is classified as a Schedule 3 controlled substance by the DEA: "Substances in this schedule have a potential for abuse less than substances in Schedules I or II and abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2022). A licensed physician with a valid DEA registration is required to prescribe testosterone.

I prescribe testosterone to men for testosterone deficiency. The state of testosterone deficiency can cause various problems including problems of mood, sexual function, libido, and bone density. Prescription testosterone is given to correct the abnormally low levels and bring them back into balance. The dose of testosterone must be carefully considered and monitored to avoid excess levels in the male as there are a number of serious concerns when prescribing testosterone.

Regarding the potential for abuse, the labeling reads "Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication...Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions...Abuse and misuse of testosterone are seen in male and female adults and adolescents...There have been reports of misuse by men taking higher doses of legally obtained testosterone than prescribed and continuing testosterone despite adverse events or against medical advice." (Actavis Pharma, 2018)

Adverse events with respect to the nervous system include: "Increased or decreased libido, headache, anxiety, depression, and generalized paresthesia." (Actavis Pharm, 2018)

With regard to ultimate height, “[t]he following adverse reactions have been reported in male and female adolescents: premature closure of bony epiphyses with termination of growth” (Actavis Pharma, Inc., 2018). What this means is that testosterone applied to the adolescent will cause premature closure of the growth plates, stopping further gains in height in the growing individual, and ultimately making the person shorter than they otherwise would have been.

With respect to the cardiovascular system of men using ordinary doses, “Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone

replacement therapy in men" (Actavis Pharma, 2018). No clinical safety trials have been performed for women or adolescent girls to my knowledge.

"There have been postmarketing reports of venous thromboembolic events [blood clots], including deep vein thrombosis (DVT) [blood clot of the extremity such as the lef] and pulmonary embolism (PE) [blood clot of the lung which may be deadly], in patients using testosterone products, such as testosterone cypionate" (Actavis Pharma, 2018).

A very recently published study of adverse drug reactions (ADRs) as part of gender affirming hormone therapies in France states that "[o]ur data show a previously unreported, non-negligible proportion of cases indicating cardiovascular ADRs in transgender men younger than 40 years… In transgender men taking testosterone enanthate, all reported ADRs were cardiovascular events, with pulmonary embolism in 50% of cases" (Yelehe et al., 2022).

There are also serious concerns regarding liver dysfunction: "Prolonged use of high doses of androgens ... has been associated with development of hepatic adenomas [benign tumors], hepatocellular carcinoma [cancer], and peliosis hepatis [generation of blood-filled cavities in the liver that may rupture] —all potentially life-threatening complications" (Actavis Pharma, 2018).

In GAT, what is termed "cross sex hormones" is the use of hormones of the opposite sex to attempt to create secondary sex characteristics. To do so, very high doses of these hormones are administered. When hormone levels climb above normal levels they are termed supraphysiologic.

b. Opposite Sex Hormones - Supraphysiologic Doses of Testosterone for Females

The female person does produce some smaller amount of testosterone relative to the male. The normal reference range for adult females depending on the lab is about 10 to 50 ng/dL. However, in female disease conditions these levels can be much higher. For example, in polycystic ovarian syndrome levels may range from 50 to 150 ng/dL. PCOS has been associated with insulin resistance (Dunaif, 1989), metabolic syndrome (Apridonidze, 2005) and diabetes (Joham, 2014).

In certain endocrine tumors such as adrenal carcinoma these levels may be substantially higher in the 300 to 1000 ng/dl range. Adrenal carcinoma is a serious medical condition and may be treated by surgery and potent endocrine medications.

Recommendations from the Endocrine Society's clinical guidelines related to GAT are to ultimately raise female levels of testosterone to 320 to 1000 ng/dL[4] which is on the same order as dangerous endocrine tumors for women as described above (Hembree, 2017). A simple calculation shows this level for the adult may be anywhere from 6 to 100 times higher than native female testosterone levels. In doing so they are creating a hormone imbalance known as hyperandrogenism. These extraordinarily high levels of testosterone are associated with multiple risks to the physical and mental health of the patient.

“"Studies of transgender males taking testosterone have shown up to a nearly 5-fold increased risk of myocardial infarction relative to females not receiving testosterone” (Laidlaw et al.,2021; Alzahrani et al., 2019). A female can also develop unhealthy, high levels of red blood cells referred to as erythrocytosis. These high red blood cell counts in young women have been shown to be an independent risk factor for cardiovascular disease, coronary heart disease and death due to both (Gagnon, 1994).

Other permanent effects of testosterone therapy involve irreversible changes to the vocal cords. Abnormal amounts of hair growth which may occur on the face, chest, abdomen, back and other areas is known as hirsutism. Should the female eventually regret her decision to take testosterone, this body hair can be very difficult to remove. Male pattern balding of the scalp may also occur. Common sense suggests that changes of voice and hair growth could be psychologically troubling should the patient attempt to reintegrate into society as a female.

Changes to the genitourinary system include polycystic ovaries and atrophy of the lining of the uterus. The breasts have been shown to have an increase in fibrous breast tissue and a decrease in normal glandular tissue (Grynberg et al., 2010). Potential cancer risks from high dose testosterone include ovarian and breast cancer (Hembree, 2017).

---

[4] In the Endocrine Society's Guidelines there is no grading of evidence for the rationale of using such high supraphysiologic doses of opposite sex hormones for the female or male. There seems to be an underlying assumption that because the person believes to be the opposite sex then they acquire the sex specific laboratory ranges of the opposite sex. "The root cause of this flaw in thinking about diagnostic ranges was exemplified in a response letter by Rosenthal et al claiming that gender identity determines the ideal physiologic range of cross-sex hormone levels (5). Thus, a psychological construct, the ‘gender identity’, is imagined to affect physical reality and change a person’s sex-specific laboratory reference ranges. This is clearly not the case, otherwise there would be no serious complications of high-dose androgen treatment in transgender males" (Laidlaw et al., 2021).

According to research regarding testosterone abuse, high doses of testosterone have been shown to predispose individuals towards mood disorders, psychosis, and psychiatric disorders. The "most prominent psychiatric features associated with AAS [anabolic androgenic steroids, i.e. testosterone] abuse are manic-like presentations defined by irritability, aggressiveness, euphoria, grandiose beliefs, hyperactivity, and reckless or dangerous behavior. Other psychiatric presentations include the development of acute psychoses, exacerbation of tics and depression, and the development of acute confusional/delirious states" (Hall, 2005). Moreover, "[s]tudies... of medium steroid use (between 300 and 1000 mg/week of any AAS) and high use (more than 1000 mg/week of any AAS) have demonstrated that 23% of subjects using these doses of steroids met the DSM-III-R criteria for a major mood syndrome (mania, hypomania, and major depression) and that 3.4% — 12% developed psychotic symptoms" (Hall, 2005).

c. Estrogen

Estrogen is the primary sex hormone of the female. Prescription estrogen may be used if a woman has low estrogen levels due to premature failure of her ovaries. Estrogen is prescribed to bring these levels back into a normal range for the patient's age. Another labeled use of estrogen is to treat menopausal symptoms.

d. Opposite Sex Hormones - Supraphysiologic Estrogen for Males

For the male, estrogen is being used at supraphysiologic doses. The high doses are used in an attempt to primarily affect an increase of male breast tissue development known as gynecomastia. Gynecomastia is the abnormal growth of breast tissue in the male. The occurrence of gynecomastia in the male is sometimes corrected by medication or more commonly by surgery if needed. Other changes of secondary sex characteristics may develop such as softening of the skin and changes in fat deposition and muscle development.

The doses of estrogen given to males for GAT are high and may vary from two to eight or more times higher than normal adult male levels. This produces the endocrine condition called hyperestrogenemia. Long-term consequences include increased risk of myocardial infarction and death due to cardiovascular disease (Irwig, 2018). Also "[t]here is strong

evidence that estrogen therapy for trans women increases their risk for venous thromboembolism[5] over 5 fold" (Irwig, 2018).

Breast cancer is a relatively uncommon problem of the male. However the risk of a male developing breast cancer has been shown to be 46 times higher with high dose estrogen (Christel et al., 2019).

It is clear that supraphysiologic doses of either testosterone for the female or estrogen for the male can have detrimental health consequences. This is only now being borne out in the literature for adults. However as more children and adolescents are put on these medications one would expect these consequences to become more frequent and to occur earlier in their lives.

4. Surgeries

The fourth stage of gender affirmative therapy is surgical alterations of the body of various kinds in an attempt to somehow mimic features of the opposite sex.

Individual surgical procedures can be a complex topic. It is helpful to first step back and consider conceptually what any surgery can and cannot accomplish.

In its basic form surgery is subtractive. In other words, a portion of tissue, an organ or organs are removed in order to restore health. For example, a diseased gallbladder may be surgically removed to help the patient get back to wellness. An infected appendix may be surgically removed to prevent worsening infection or even death. In both of these cases an unhealthy body part is surgically removed in order to restore health.

In some cases a diseased tissue or organ is removed so that a foreign replacement part may be substituted for an unhealthy organ or tissue. For example, a diseased heart valve may be replaced with a pig valve or a prosthetic heart valve. Another example is a failed liver may be replaced by liver transplant.

Though modern surgical techniques and procedures are astounding, there are very noteworthy limitations. Importantly, surgery cannot de novo create new organs. If a person's kidneys fail, the surgeon has no scientific method for creating a new set of kidneys

[5] Venous thromboembolism is a blood clot that develops in a deep vein and “can cause serious illness, disability, and in some cases, death” (CDC, 2022).

that can be implanted or grown within the patient. This conceptual background is helpful when considering various gender affirming surgeries.

There are a variety of gender affirming surgeries for females. These may include mastectomies, metoidioplasty, and phalloplasty.

a. Mastectomy

Mastectomies are the surgical removal of the breasts. The procedure is used in GAT in an attempt to make the chest appear more masculine. The surgery results in a permanent loss of the ability to breastfeed and significant scarring of 7 to 10 inches. The scars are prone to widening and thickening due to the stresses of breathing and arm movement. Other potential complications include the loss of normal nipple sensation and difficulties with wound healing (American Cancer Society, 2022).

It is important to note that this operation cannot be reversed. The female will never regain healthy breasts capable of producing milk to feed a child (Mayo Clinic, Top Surgery, 2022).

Another important consideration is that compared to the removal of an unhealthy gallbladder or appendix, in the case of gender dysphoria the breasts are perfectly healthy and there is no organic disease process such as a cancer warranting their removal. The future woman who later desists is left with regret about what happened to her at an age before she could provide true informed consent. Functioning breasts cannot be created by a surgeon and restored to a patient in case of regret. She is left with permanent injury and loss of function with respect to her breasts.

b. GAT Surgeries on the Male

GAT surgeries for the male include removal of the testicles alone to permanently lower testosterone levels. This is by nature a sterilizing procedure. Further surgeries may be done in an attempt to create a pseudo-vagina which is called vaginoplasty. In this procedure, the penis is surgically opened and the erectile tissue is removed. The skin is then closed and inverted into a newly created cavity in order to simulate a vagina. A dilator must be placed in the new cavity for some time so that it does not naturally close.

Potential surgical complications may include urethral strictures, infection, prolapse, fistulas and injury to the sensory nerves with partial or complete loss of erotic sensation (Mayo Clinic, Feminizing Surgery, 2022).

c. GAT Surgeries of the Female Pelvis and Genitalia

Other types of surgery for females include those of the genitalia and reproductive tract. For example, the ovaries, uterus, fallopian tubes, cervix and the vagina may be surgically removed. Removal of the ovaries results in sterilization.

Importantly, removing female body parts does not produce a male. Rather, the female has had sex specific organs permanently destroyed with no hope of replacement, while remaining biologically female.

There have also been attempts to create a pseudo-penis. This procedure is known as phalloplasty. It is not possible to de novo create a new human penis. Instead, a roll of skin and subcutaneous tissue is removed from one area of the body, say the thigh or the forearm, and transplanted to the pelvis. An attempt is made to extend the urethra or urinary tract for urination through the structure. This transplanted tissue lacks the structures inherent in the male penis which allow for erection, therefore erectile devices such as rods or inflatable devices are placed within the tube of transplanted tissue in order to simulate erection (Hembree, 2017). The labia may also be expanded to create a simulated scrotum containing prosthetic objects to provide the appearance of testicles.

Complications may include urinary stricture, problems with blood supply to the transplanted roll of tissue, large scarring to the forearm or thigh, infections including peritonitis, and possible injury to the sensory nerve of the clitoris (Mayo Clinic, Masculinizing Surgery, 2022). A recent systematic review and meta-analysis of 1731 patients who underwent phalloplasty found very high rates of complications (76.5%) including a urethral fistula rate of 34.1% and urethral stricture rate of 25.4% (Wang, 2022).

H. Life Threatening Physical Medical Conditions Versus Suicidal Ideation

Any child or adolescent who has suicidal ideation or has attempted suicide should receive immediate, appropriate psychiatric care. Psychologists and psychiatrists are trained in the recognition and treatment of suicidal ideation and prevention of suicide. A child or adolescent with gender dysphoria who also has suicidal ideation should not be treated any

differently. They require compassionate care and a full psychological evaluation of comorbidities such as depression, anxiety, and self-harming behaviors.

However, suicidal ideation or attempts are categorically different than other life-threatening situations, such as a rapidly expanding brain tumor or a severe infection. In these situations, a medication or a surgery is used to stop the progression of an organic physical condition. In contrast, the danger to the self with suicidal ideation relates to a condition of the mind.

Gender affirmative therapy does not treat any life-threatening physical condition. In fact, it creates a number of new medical conditions as described above. It is also not an appropriate treatment for suicidal ideation. Neither puberty blocking medications, nor testosterone, nor estrogen have been FDA approved for suicide prevention. Moreover, as noted above, the hormone imbalances generated by the medications used in GAT actually increase psychological conditions that lead to suicidal ideation and completed suicide.

I. Informed Consent

Any person who is to take a medication, undergo a surgical procedure, or have a psychological intervention should understand the risks and benefits before proceeding. A discussion of these risks and benefits should be provided by medical professionals and then the person of sufficient intellectual capacity and maturity can consent to the treatment.

Naturally difficulties arise when a minor is involved in the process of medical decision-making. Their intellect, emotions, and judgment are not fully developed and they are not capable of fully appreciating permanent, life altering changes such as described above. Therefore, they cannot provide informed consent. They may sometimes "assent" to a procedure or medication with a parent or guardian making the final decision.

With respect to GAT, in my opinion, it 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 long-term 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.

Because this age group is still undergoing brain development and they are immature with respect to intellect, emotion, judgment, and self-control, in my professional opinion there is a significant chance a young person may later regret the irreversible bodily changes that result from hormones or from removing an organ or organs that will no longer function and cannot be replaced.

I would also note that adolescents are more prone to high-risk behavior and less likely to fathom the risks and consequences of these decisions (Steinberg, 2008).

J. The WPATH and The Endocrine Society

According to their declarations, the experts Dr. Johanna Olson-Kennedy, Dr. Loren Schechter, and Dr. Dan H. Karasic are members of WPATH. Dr. Schechter was "co-lead author of the surgical and postoperative care chapter" for SOC 8 (Schechter decl, p 4). Dr. Karasic was a lead author of the Mental Health chapter for SOC 8 (Karasic decl, p. 3).

WPATH's Standards of Care 7 were produced over a decade ago in 2011. They were prepared within their advocacy organization and are purported to be a "professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria" (WPATH, 2022). However, the "professional consensus" exists only within the confines of its organization. Furthermore, their Standards of Care 7, unlike the Endocrine Society's guidelines, do not have a grading system for either the strength of their recommendations or the quality of the evidence presented.

While the Endocrine Society has issued "Endocrine Treatment of Gender-Dysphoric / Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline," these are only "guidelines." The Endocrine Society's guidelines (ESG) specifically state that their "guidelines cannot guarantee any specific outcome, <u>nor do they establish a standard of care</u>" (Hembree at al, 2017, p. 3895).

With respect to the makeup of authors of the ESG, nine out of ten authors were members of WPATH or worked on WPATH's scientific committees. Seven of those nine had at some time been in WPATH leadership including the WPATH presidency and board of directors (File: WPATH - Endocrine Society 2017 guidelines.pdf).

In the Endocrine Society's guidelines, the quality of evidence for the treatment of adolescents is rated "very low-quality evidence" and "low quality evidence". "The quality

of evidence for [puberty blocking agents] is noted to be low. In fact, all of the evidence in the guidelines with regard to treating children/adolescents by [gender affirmative therapy] is low to very low because of the absence of proper studies" (Laidlaw et al., 2019).

Unlike some other recommendations for adolescent GAT, the Endocrine Society's guidelines do not include any grading of the quality of evidence specifically for their justification of laboratory ranges of testosterone or estrogen or for adolescent mastectomy or other surgeries.

Endocrinologists W. Malone and P. Hruz and colleagues have written critically of the Endocrine Society's (ES) guidelines: "Unlike standards of care, which should be authoritative, unbiased consensus positions designed to produce optimal outcomes, practice guidelines are suggestions or recommendations to improve care that, depending on their sponsor, may be biased. In addition, the ES claim of effectiveness of these interventions is at odds with several systematic reviews, including a recent Cochrane review of evidence (5), and a now corrected population-based study that found no evidence that hormones or surgery improve long-term psychological well-being (6). Lastly, the claim of relative safety of these interventions ignores the growing body of evidence of adverse effects on bone growth, cardiovascular health, and fertility, as well as transition regret" (Malone et al., 2021).

In June of 2022, the Endocrine Society published "Enhancing the Trustworthiness of the Endocrine Society's Clinical Practice Guidelines" (McCartney et al., 2022). They wrote "In an effort to enhance the trustworthiness of its clinical practice guidelines, the Endocrine Society has recently adopted new policies and more rigorous methodologies for its guideline program." (Id.) They relate that in 2019, the ECRI Guidelines Trust "asked the Society for permission to include its guidelines in the ECRI Guidelines Trust database". However, after an evaluation by ECRI, the guideline related to osteoporosis "was the only guideline for which all recommendations were based on verifiable systematic evidence review with explicit descriptions of search strategy, study selection, and evidence summaries" (Id.). Therefore we can conclude that with regard to the recommendations from the ESG 2017 on Gender Dysphoria/Gender Incongruence not all recommendations were "based on verifiable systematic evidence review with explicit descriptions of search strategy, study selection, and evidence summaries". Furthermore, these ESG 2017 were highly subject to conflicts of interest. As related earlier, nine out of the 10 authors were members or worked on the scientific committees of the advocacy group WPATH. Additionally, the ESG 2017 document was endorsed by WPATH. The "Enhancing

Trustworthiness" article recommends the opposite composition of authors for guidelines: "A majority (>50%) of non-Chair GDP members must be free of relevant C/DOI [conflict/duality of interest]" (McCartney et al., 2022).

WPATH Standards of Care 8 (SOC 8) were just published Sep. 6, 2022 (Coleman et al., 2022) . In a correction to the SOC 8, all guidelines for minimum age of surgery were removed, meaning a minor of any age could be referred for any of the GAT surgeries listed previously (Correction IJTH, 2022). All guidelines for minimum age of oppposite sex hormones were also removed.

The correction reads: "On page S258, the following text was removed:
'The following are suggested minimal ages when considering the factors unique to the adolescent treatment time frame for gender-affirming medical and surgical treatment for adolescents, who fulfil all of the other criteria listed above.
– Hormonal treatment: 14 years
– Chest masculinization: 15 years
– Breast augmentation, Facial Surgery: 16 years
– Metoidioplasty, Orchiectomy, Vaginoplasty,
– Hysterectomy, Fronto-orbital remodeling: 17 years
– Phalloplasty: 18 years'" (WPATH SOC 8 Correction, p. S261).

Of great concern is that the minimum age recommendations were retracted, it appears, in contradiction to the recommendation of their own expert consensus:
"On page S66, the following text was removed:
'Age recommendations for irreversible surgical procedures were determined by a review of existing literature and the expert consensus of mental health providers, medical providers, and surgeons highly experienced in providing care to TGD adolescents.'" (WPATH SOC 8 Correction, p. S260).

Additionally, a chapter regarding eunuchs was inserted into SOC 8 that gives recommendations for how to induce hypogonadism in men who have the eunuch "gender identity"[6] by either orchiectomy [testicle removal] or chemical castration such as with GnRH analogues (Coleman et al., 2022)[7].

[6] The notion that there is a "eunuch gender identity" further invalidates the gender identity as a serious biological property of human beings: "Many eunuch individuals see their status as eunuch as their distinct gender identity with no other gender or transgender affiliation" (Coleman et al., 2022, p. S88).

[7] "Treatment options for eunuchs to consider include:

The SOC8 also used an aberrant form of the GRADE approach for systematic reviews that removed the grading of quality of evidence (which should be categorized as very low, low, moderate, and high quality).[8] Instead any recommendation of "recommend" is automatically assigned as high quality of evidence. SOC 8 also failed to provide evidence profile tables which should include “an explicit judgment of each factor that determines the quality of evidence for each outcome" (Guyatt et al., 2021).

Such a modification of GRADE is explicitly recommended against in the referenced GRADE document[9] and in so doing, in my opinion, invalidates all of the SOC 8 recommendations as being evidence-based.

For at least the reasons above, in my 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.

K. Harms of off-label treatments in GAT

Dr. Antommaria makes a faulty comparison between migraine headaches and gender dysphoria (Antommaria decl, p. 7). First, migraine headaches are a neurological condition with a potential vascular component and not a condition of the mind, nor found as a psychological diagnosis in the DSM-5. Second the treament of migraine headaches

---

• Hormone suppression to explore the effects of androgen deficiency for eunuch individuals wishing to become asexual, nonsexual,
or androgynous;
• Orchiectomy [testicle removal] to stop testicular production
of testosterone;
• Orchiectomy with or without penectomy to
alter their body to match their self-image;
• Orchiectomy followed by hormone replacement with testosterone or estrogen. " (Id.)

[8] From SOC 8 "The [recommendation] statements were classified as:
• Strong recommendations (“we recommend”) are for
those interventions/therapy/strategies where:
• the evidence is of high quality" (Id., p. S250).

[9]From the GRADE guidelines: "Some organizations have used modified versions of the GRADE approach. We recommend against such modifications because the elements of the GRADE process are interlinked because modifications may confuse some users of evidence summaries and guidelines, and because such changes compromise the goal of a single system with which clinicians, policy makers, and patients can become familiar" (Guyatt et al., 2011).

with a medication such as sumitriptan or similar are labled indications for the condition unlike GnRH agonists and opposite sex hormones in GAT (FDA.gov sumitriptan). Third, the side effects of medications like sumitriptan do not alter or block normal human development such as the case with puberty blocking medication, or cause permanent alterations of the body such as with sex hormones, or lead to the permanent loss of healthy functioning organs such as occurs with surgeries which alter sex as a part of GAT.

Dr. Olson-Kennedy also draws a faulty comparison when she compares the off-label use of antibiotics or anti-histamines to blocking normal puberty, administering high-dose opposite sex hormones, or the permanent removal of healthy organs as part of GAT (Olson-Kennedy decl, p. 38). The health consequences are categorically different and the lifelong potential for permanent injury are extremely high in GAT.

L. The Lack of Evidence of Effectiveness of GAT

There is much additional evidence that questions the long-term benefits of opposite sex hormones and gender reassignment surgery and in fact suggests serious harms.

1. Sweden's Long-term study of 30 years of data by Dhejne

The most comprehensive study of its kind is from Sweden in 2011. The authors examined data over a 30-year time period (Dhejne, 2011). The Dhejne team made extensive use of numerous Swedish database registries and examined data from 324 patients in Sweden over 30 years who had taken opposite sex hormones and had undergone sex reassignment surgery. They used population controls matched by birth year, birth sex, and reassigned sex. When followed out beyond ten years, the sex-reassigned group had nineteen times the rate of completed suicides and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to the general population of Sweden.

2. The Branstrom and Pachankis Retraction

Other published studies of GAT have been shown to have serious errors. For example, a major correction was issued by the American Journal of Psychiatry. The authors and editors of a 2020 study, titled "Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: a total population study" (Bränström study, 2020) retracted their original primary conclusion. Letters to the editor by twelve authors

including myself led to a reanalysis of the data and a corrected conclusion stating that in fact the data showed no improvement in mental health for transgender identified individuals after surgical treatment nor was there improvement with opposite sex hormones ("Correction", 2020; Van Mol et al., 2020).

The initial reports of this study claimed that the authors found treatment benefits with surgery, and this was shared widely in the media. For example, ABC News posted an article titled "Transgender surgery linked with better long-term mental health, study shows" (Weitzer, 2019). An NBC news/Reuters headline reads "Sex-reassignment surgery yields long-term mental health benefits, study finds" (Reuters, 2019).

However, after twelve authors from around the world including our team investigated the study in detail, a number of serious errors were exposed leading to a retraction (Kalin, 2020; Anckarsäter et al., 2020).

In our letter to the editor which I co-wrote with former Chairman of Psychiatry at Johns Hopkins Medical School, Paul McHugh, MD, we noted key missing evidence in the original Branstrom report when compared to the previous body of knowledge yielded from the Swedish Dhejne study. We wrote that "[t]he study supports only weak conclusions about psychiatric medication usage and nothing decisive about suicidality. In overlooking so much available data, this study lacks the evidence to support its pro gender-affirmation surgery conclusion" (Van Mol, Laidlaw, et al., 2020).

In another letter, Professor Mikael Landen writes that "the authors miss the one conclusion that can be drawn: that the perioperative transition period seems to be associated with high risk for suicide attempt. Future research should use properly designed observational studies to answer the important question as to whether gender-affirming treatment affects psychiatric outcomes" (Landen, 2020).

In another letter to the editor, psychiatrist David Curtis noted that "[t]he study confirms the strong association between psychiatric morbidity and the experience of incongruity between gender identity and biological sex. However, the Branstrom study does not demonstrate that either hormonal treatment or surgery has any effect on this morbidity. It seems that the main message of this article is that the incidence of mental health problems and suicide attempts is especially high in the year after the completion of gender-affirming surgery" (Curtis, 2020).

In yet another critical letter, Dr. Agnes Wold states that "[w]hether these factors involve a causal relationship (i.e., that surgery actually worsens the poor mental health in individuals with gender dysphoria) cannot be determined from such a study. Nevertheless, the data presented in the article do not support the conclusion that such surgery is beneficial to mental health in individuals with gender dysphoria" (Wold, 2020).

3. Flawed studies based on the problematic 2015 US Transgender Survey

A 2021 study by Almazan and Keurghlian attempted to address mental health outcomes in relation to surgery as a part of GAT (Almazan & Keurghlian, 2021). This was not a randomized controlled study nor a prospective observational study. Rather the study relied upon the 2015 US Transgender Survey (USTS), which has been severely criticized for its serious limitations and weaknesses.

D'Angelo et al. have written about the 2015 USTS survey as part of the criticism of another flawed study in the journal Pediatrics by Jack Turban in 2020 titled "Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation" (Turban, 2020). They write in their critique of the USTS that it is "a convenience sampling, a methodology which generates low-quality, unreliable data." (Bornstein, Jager, & Putnick, 2013). Specifically, the participants were recruited through transgender advocacy organizations and subjects were asked to 'pledge' to promote the survey among friends and family. This recruiting method yielded a large but highly skewed sample...Their analysis is compromised by serious methodological flaws, including the use of a biased data sample, reliance on survey questions with poor validity, and the omission of a key control variable, namely subjects' baseline mental health status." They also state that "[s]tigmatizing non-'affirmative' psychotherapy for GD [gender dysphoria] as 'conversion' will reduce access to treatment alternatives for patients seeking non-biomedical solutions to their distress" (D'Angelo et al., 2021).

4. Mastectomy Surgery for Minors

Any serious look at long-term effects at surgical treatment would follow subjects out at least ten years. For example, an article was published recently examining patients who had mild calcium disorders due to a gland called the parathyroid. They compared a group of patients who had surgical removal of the parathyroid to a control group who had not. They examined data ten years after surgery was completed and concluded that parathyroid

surgery in this group "did not appear to reduce morbidity or mortality" in that patient group (Pretorius, 2022).

To my knowledge there exists no comparable studies of minors with gender dysphoria comparing those who had mastectomy surgery to a control group who had not. There are also no known studies of minors followed for 10 years or more to determine the long-term risks and benefits of mastectomy for gender dysphoria.

Good quality studies specifically showing that mastectomy surgery is safe, effective, and optimal for treating minors with gender dysphoria do not exist. For example, there is a study titled "Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults Comparisons of Nonsurgical and Postsurgical Cohorts" (Olson-Kennedy, 2018). The study authors conclude that "[c]hest dysphoria was high among presurgical transmasculine youth, and surgical intervention positively affected both minors and young adults." However, there are a number of problems with this study. First, the term "chest dysphoria" is a creation of the study authors and is not found as a diagnosis or even referenced in the DSM-5. Second the "chest dysphoria scale" is a measuring tool created by the authors, but which the authors state "is not yet validated." (*Id*., p. 435) Third, the mastectomies were performed on girls as young as 13 and 14 years old and who thereby lacked the maturity and capacity of good judgment for truly informed consent for this life altering procedure. For this reason, in my professional opinion, the research and surgeries performed were flawed and unethical.

There exists another poorly designed study which suffers from similar methodological and ethical problems as the Olson-Kennedy study. A 2021 study published in Pediatrics examined females aged 13-21 recruited from a gender clinic. Thirty young females had mastectomy procedures and sixteen had not. The average age at surgery was 16.4 years (Mehringer, 2021). The follow up time after surgery was only 19 months and no data is provided or analyzed about key psychiatric information such as comorbid psychological illnesses, self-harming behaviors, psychiatric hospitalizations, psychiatric medication use, or suicide attempts.

Information returned from the study surveys were all qualitative and included responses such as "[My chest dysphoria] made me feel like shit, honestly. It made me suicidal. I would have breakdowns". Another respondent stated, "I've been suicidal quite a few times over just looking at myself in the mirror and seeing [my chest]. That's not something that I should have been born with" (Mehringer, 2021). The omission of psychiatric data is a

major flaw in the study and also irresponsible given the obviously dangerous psychological states that some of these young people were in.

Since such a high proportion of subjects were using testosterone (83%), some of the responses could be attributed to adverse effects of testosterone. For example, as related earlier, high dose testosterone can manifest in irritability and aggressiveness. One study subject responded, “I get tingly and stuff and it kind of makes me want to punch something" (Mehringer, 2022).

The testosterone labeling also indicates nausea and depression as adverse reactions which are described by another study subject “There’s a feeling of hopelessness, of desperation, of—almost makes me feel physically sick" (Actavis Pharma, Inc., 2018; Mehringer, 2022).

The study appears to have been designed, at least in part, to justify insurance companies paying for mastectomy procedure for minors with GD, even though they have provided no long-term statistical evidence of benefit: "These findings...underscore the importance of insurance coverage not being restricted by age" (Mehrniger, 2021). This also appears to be part of the aim of the flawed Olson-Kennedy study which stated “changes in clinical practice and in insurance plans’ requirements for youth with gender dysphoria who are seeking surgery seem essential” (Olson-Kennedy, 2018). So these two studies, rather than being a thorough examination of the psychological and physical risks and benefits of mastectomy surgery over the long-term appear instead to exist, at least in part, to validate the need for insurance companies to insure the costs of these dubious procedures for minors.

5. Centers for Medicare and Medicaid Services

The Centers for Medicare and Medicaid Services (“CMS”) has found “inconclusive” clinical evidence regarding gender reassignment surgery. Specifically, the CMS Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N) (June 19, 2019) states: “The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.”

Dr. Schecter states: "The result of CMS’s review of the evidence is not applicable to other population groups" (Schecter decl, p. 39). However it does not make the converse true as

Dr. Schecter seems to imply. In other words, the CMS review does not therefore mean that there is conclusive evidence of benefit and lack of harm for the under 65 population. On the contrary, evidence of benefit is lacking and the risks and harms due to GAT are very high as I have described.

6. Nations and States Question and Reverse Course on GAT

Also noteworthy is that other nations are questioning and reversing course regarding gender affirmative therapy. For example in the *Bell v. Tavistock* Judgment in the UK, regarding puberty blockers in GAT, they concluded that "there is real uncertainty over the short and long-term consequences of the treatment with very limited evidence as to its efficacy, or indeed quite what it is seeking to achieve. This means it is, in our view, properly described as experimental treatment" (*Bell v. Tavistock* Judgment, 2020).

The case was appealed and although the medical decision making was returned to clinicians (rather than the courts), it was noted that great pains should be taken to ensure that the child and parents are properly informed before embarking on such treatments. In its conclusion the appeals court stated that "[c]linicians will inevitably take great care before recommending treatment to a child and be astute to ensure that the consent obtained from both child and parents is properly informed by the advantages and disadvantages of the proposed course of treatment and in the light of evolving research and understanding of the implications and long-term consequences of such treatment. Great care is needed to ensure that the necessary consents are properly obtained " (*Bell v. Tavistock* Appeal, Judgment, 2021).

In the bulletin of the Royal College of Psychiatrists in 2021, in a reevaluation of the evidence, Griffin and co-authors write, "As there is evidence that many psychiatric disorders persist despite positive affirmation and medical transition, it is puzzling why transition would come to be seen as a key goal rather than other outcomes, such as improved quality of life and reduced morbidity. When the phenomena related to identity disorders and the evidence base are uncertain, it might be wiser for the profession to admit the uncertainties. Taking a supportive, exploratory approach with gender-questioning patients should not be considered conversion therapy" (Griffin et al., 2021).

In 2020, Finland recognized that "[r]esearch data on the treatment of dysphoria due to gender identity conflicts in minors is limited," and recommended prioritizing psychotherapy for gender dysphoria and mental health comorbidities over medical gender

affirmation (Council for Choices in Healthcare in Finland, 2020). Additionally, "[s]urgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors".

In 2021, Sweden's largest adolescent gender clinic announced that it would no longer prescribe puberty blockers or cross-sex hormones to youth under 18 years outside clinical trials (SEGM, 2021). "In December 2019, the SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) published an overview of the knowledge base which showed a lack of evidence for both the long-term consequences of the treatments, and the reasons for the large influx of patients in recent years. These treatments are potentially fraught with extensive and irreversible adverse consequences such as cardiovascular disease, osteoporosis, infertility, increased cancer risk, and thrombosis. This makes it challenging to assess the risk / benefit for the individual patient, and even more challenging for the minors or their guardians to be in a position of an informed stance regarding these treatments" (Gauffen and Norgren, 2021).

Dr Hilary Cass "was appointed by NHS England and NHS Improvement to chair the Independent Review of Gender Identity Services for children and young people in late 2020" (The Cass Review website, 2022). In her interim report dated February 2022, it states that "[e]vidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally" (Cass, 2022).

M. Assessment of the patient with gender dysphoria

In light of the very serious medical concerns and potential harms of gender affirmative therapy, there are several criteria that I believe would be important to fulfill before applying the GAT model to a patient.

1. Minors should be evaluated to determine if they will follow the natural pattern of desistance which 50 to 98% of pediatric age children will follow[10].
2. Patients, parents and guardians should be made aware of other options for treatment of gender dysphoria including active psychosocial treatment or watching and waiting with support in order to help with natural desistance.

[10] From the DSM-5: "Rates of persistence of gender dysphoria from childhood into adolescence or adulthood vary…In natal males, persistence has ranged from 2.2% to 30%. In natal females, persistence has ranged from 12% to 50%" (American Psychiatric Association, 2013).

REMAINDER OMITTED

EXHIBIT 4

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.,	)
	)
Plaintiffs,	) Case No: 4:22cv325
	)
v.	) Tallahassee, Florida
	) October 12, 2022
SIMONE MARSTILLER, et al.,	)
	) 9:33 AM
Defendants.	)
_____	)

TRANSCRIPT OF PRELIMINARY INJUNCTION PROCEEDINGS
BEFORE THE HONORABLE ROBERT L. HINKLE
UNITED STATES CHIEF DISTRICT JUDGE
(Pages 1 through 120)

Court Reporter: MEGAN A. HAGUE, RPR, FCRR, CSR
111 North Adams Street
Tallahassee, Florida 32301
megan.a.hague@gmail.com

Proceedings reported by stenotype reporter.
Transcript produced by Computer-Aided Transcription.

APPEARANCES:

For Plaintiffs:

Lambda Legal
By: OMAR GONZALEZ-PAGAN
Attorney at Law
ogonzalez-pagan@lambdalegal.com
120 Wall Street
19th Floor
New York, New York 10005

Pillsbury, Winthrop, Shaw, Pittman, LLP
By: JENNIFER ALTMAN
Attorney at Law
jennifer.altman@pillsburylaw.com
600 Brickell Avenue
Suite 3100
Miami, Florida 33131

Lambda Legal
By: CARL S. CHARLES
Attorney at Law
ccharles@lambdalegal.org
1 West Court Square
Suite 105
Decatur, Georgia 30030

Southern Legal Counsel Inc
By: SIMONE M. CHRISS
CHELSEA LEE DUNN
Attorney at Law
simone.chriss@southernlegal.org
chelsea.dunn@southernlegal.org
1229 NW 12th Avenue
Gainesville, Florida 32601

Florida Health Justice Project
By: KATHERINE JEAN ANN DEBRIERE
Attorney at Law
debriere@floridahealthjustice.org
3900 Richmond Street
Jacksonville, Florida 32205

National Health Law Program
By: CATHERINE ANNE MCKEE
Attorney at Law
mckee@healthlaw.org
1512 East Franklin Street
Chapel Hill, North Carolina 27514

APPEARANCES (continued):

For Defendants: Holtzman Vogel Baren, et al.
By: MOHAMMAD OMAR JAZIL
GARY VERGIL PERKO
MICHAEL BEATO
Attorneys at Law
mjazil@holtzmanvogel.com
garyp@holtzmanvogel.com
michaelb@holtzmanvogel.com
119 South Monroe Street
Suite 500
Tallahassee, Florida 32301

PAGE BREAK

Q. Are you a member of any professional associations?
A. I am a member of the Endocrine Society.
MR. PERKO: Your Honor, at this time we'd proffer Dr. Laidlaw as an expert in endocrinology.
MR. CHARLES: Objection, Your Honor. I'd like to voir dire the witness.
THE COURT: You may certainly voir dire the witness.
MR. CHARLES: May it please the Court, Your Honor. My name is Carl Charles for the plaintiffs.

VOIR DIRE EXAMINATION

BY MR. CHARLES:
Q. Dr. Laidlaw, can you hear me?
A. Yes.
Q. Okay. Dr. Laidlaw, you wrote a declaration that was filed in this case; correct?
A. Correct.
Q. And as a part of that declaration, you submitted a CV entitled "Exhibit A"?
A. Yes.
Q. And you're not a practicing psychiatrist; is that correct, Dr. Laidlaw?
A. That is correct.
Q. You are not a licensed mental health care provider; is that correct?
A. That's correct.

Q. And you're not a psychologist; is that correct?
A. That is correct.
Q. And, Dr. Laidlaw, you're not an obstetrician; is that correct?
A. That is correct.
Q. And, Dr. Laidlaw, you're not a gynecologist; is that correct?
A. That is correct.
Q. And you're not a surgeon, Dr. Laidlaw; is that correct?
A. That's correct.
Q. And you're not a pediatric endocrinologist; is that correct?
A. That is correct.
Q. Less than 5 percent of your patients are under the age of 18; is that correct?
A. Yes.
Q. And you're not a bioethicist; is that correct?
A. I have no formal training other than an IRB certification many years ago.
Q. Okay. So you don't practice as a bioethicist; is that correct?
A. That's correct.
Q. And you haven't done any primary research on fertility; is that correct?
A. No primary research on fertility; that's correct.

Q. And you haven't done any primary research on sterility; is that correct?
A. That is correct.
Q. And you haven't written any articles which have been subjected to a confirmed peer-review process about fertility; is that correct?
A. I -- specifically about fertility -- I don't know what the peer review -- I had a paper in *The American Journal of Bioethics.* I don't know what the peer-review process was.
Q. Okay. So you -- again, you have not written any articles which have been subjected to a peer review for process which you can confirm about fertility; is that correct?
A. Not that I can confirm.
Q. And you haven't written any articles that have been subjected to a confirmed peer-review process about sterility; is that correct?
A. Correct.
Q. And you haven't performed any primary research about medical ethics; is that correct?
A. That's correct.
Q. And you haven't written any confirmed peer-reviewed publications about medical ethics; is that correct?
A. I have not independent -- there is the article that I mentioned. I have not independently confirmed the peer-review process.

Q. Okay. You cannot confirm that that article has been peer reviewed?
A. I cannot confirm.
Q. And you have not performed any primary research about informed consent; is that correct?
A. That's correct.
Q. And you have not written any articles confirmed to be peer reviewed regarding parents' ability to consent for treatment for their minor children; is that correct?
A. I have not written a peer reviewed article on that topic.
Q. And none of the publications listed in your CV attached to your declaration are based on original primary research; is that correct?
A. That's correct.
Q. And you haven't done any primary research about transgender people; is that correct?
A. Just to clarify, when you say "primary research," you're talking about using human subjects in the research -- as part of the research rather than a review of the literature; is that correct?
Q. You haven't done any original primary research about transgender people; is that correct?
A. In the context of working with human subjects, that is correct.
Q. And that includes any research about children and

adolescents; isn't that correct?
A. Yes. With regard to human subjects, that is correct.
Q. And you haven't received any grants to support research into endocrine treatments for gender dysphoria; is that correct?
A. That is correct.
Q. And you have not done any original primary research about the treatment of gender dysphoria; is that correct?
A. Not with human subjects; that's correct.
Q. And you haven't performed any original primary research into the frequency of gender -- into how frequently gender dysphoria occurs; is that correct?
A. I have not done primary research involving which -- human subjects on that matter.
Q. And you haven't -- and you have not done any original primary research about the phenomenon of desistance; is that correct?
A. I have not done primary research with human subjects on that condition -- for that condition.
Q. And you've never diagnosed anyone with gender dysphoria; is that correct?
A. That is correct.
Q. And you've previously testified under oath that you've only provided care to one transgender patient related to the treatment of gender dysphoria; is that correct?
A. I have worked with patients with gender incongruence in the

1 context of my practice, but as far as providing hormones, there
2 was -- someone with gender dysphoria, there was one.
3 Q. And it was only to provide that patient with a refill of
4 estrogen; is that correct?
5 A. There was an evaluation. There was an office visit, and
6 there was necessity for a refill of estrogen in that case.
7 Q. Okay. And so you did not deny the patient the refill of
8 the estrogen?
9 A. That's correct.
10 Q. So you have utilized the Endocrine Society guidelines for
11 the treatment of gender dysphoria once; is that correct?
12 A. This was -- this preceded the Endocrine Society guidelines.
13 Q. What year was the treatment of that patient?
14 A. It was in the early 2000s. It was prior to -- it was prior
15 to 2009, which is when the first Endocrine Society guidelines
16 were published.
17 Q. In your private practice, Dr. Laidlaw, you do not contract
18 with California Medicaid insurance; is that correct?
19 A. That's correct.
20 Q. And you have not spoken with any transgender Florida
21 Medicaid beneficiaries; is that correct?
22 A. Yeah, not that I'm aware of.
23 Q. And that would include the plaintiffs in this matter; is
24 that correct?
25 A. That's correct.

PAGE BREAK

CONTINUED DIRECT EXAMINATION

BY MR. PERKO:

Q. Dr. Laidlaw, you submitted a declaration in this matter, didn't you?

A. I did.

Q. And have you reviewed the declarations -- rebuttal declarations that the plaintiffs submitted in response to your declaration?

A. Yes.

Q. And do you stand by the opinions in your declaration, notwithstanding those rebuttal reports?

A. Yes, I do stand by those opinions.

Q. What were your opinions expressed in your declaration based on?

A. My opinions are based on my education and clinical experience in endocrinology, my work with gender incongruent patients in the context of my practice, including a detransitioner, my extensive evaluation of the scientific literature regarding the treatment of gender dysphoria, gender incongruence for adults and minors, and also my review of all the plaintiffs' declarations and the medical records provided to me.

Q. Dr. Laidlaw, you stated that you had limited experience with gender dysphoria. But have you reviewed the literature with regard to gender dysphoria in the gender-affirming care?

A. I have reviewed the literature extensively over the last at least four years.
Q. And why is that?
A. Well, for a few reasons. One is that these treatments that they advocate for involve hormones and raising hormone levels to sometimes very high levels or very low levels. So I've taken an interest in the risk-and-benefit ratio of these types of treatments, and this is something I do every day in endocrinology.

Furthermore, before my colleagues and I are to follow any sort of treatment protocol, I think it's essential that these studies and so forth are evaluated to determine the risk-benefit profile before any of us use these treatments.
Q. And, Dr. Laidlaw, what exactly is gender dysphoria?
A. Gender dysphoria is -- well, there's a couple of terms that would be helpful. Gender identity is a person's internal or mental sense of being male or female or perhaps some other designation, and there's an incongruence or mismatch in these cases with their physical body. For example, a person may identify as a female but have been born with a male body, and so there is resulting distress and impairment of function. There's different definitions from there on as to how long it lasts and slight differences for adults versus children and adolescents.
Q. And is gender dysphoria an endocrine disorder?
A. It's not an endocrine disorder. It's a disorder found in

PAGE BREAK

A. No.
Q. And why is that?
A. Well, I think that it's proved by the desistance, particularly with young people. Children have high desistance rates. There are many detransitioners who are adults, including one patient of mine, which proves that this gender identity is not immutable.
Q. Doctor, switching gears a little bit, you say in your declaration that hormone treatment for gender dysphoria can lead to infertility.
Is that always the case?
MR. CHARLES: Objection, Your Honor.
The witness has already stated he's not qualified to opine about this subject.
MR. PERKO: I don't believe that's the case, Your Honor. He's talking about hormone therapy, and he's an endocrinologist.
THE COURT: I'll overrule the objection. I'm going to be the finder of fact.
When Dr. Laidlaw has knowledge because of his actual medical practice, as opposed to having read some stuff over the last four years, you might want to point it out, because he's not going to persuade me very much -- he may persuade me, but he's less likely to persuade me when all he is telling me is what he has read and not what he has applied in his practice.

PAGE BREAK

Q. Psychological conditions?
A. I do not make diagnoses, but we're trained in psychology and psychiatry. It's part of our medical licensing.
Q. Okay. But you are not a practicing psychologist?
A. That's correct.
Q. And you're not a practicing psychiatrist?
A. That's correct.
Q. And you have not met with any of the plaintiffs in this matter --
THE COURT: Mr. Charles, I sat through the voir dire. I'm not going to sit through it again on cross. You get one chance to ask some questions. You've asked those. Let's ask some new ones.
MR. CHARLES: Thank you, Your Honor.
BY MR. CHARLES:
Q. Dr. Laidlaw, you stated you don't follow the WPATH standards of care; is that right?
A. Yes.
Q. But you testified earlier you don't treat gender dysphoria; is that correct?
A. I don't treat gender dysphoria with hormones and surgeries.
Q. Dr. Laidlaw, are you aware that your 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?

PAGE BREAK

Q. Yes, let's start with that one.
A. Well, I'm just reading it now for the first time, so it must be -- it was 2019 -- unless they have changed their opinion.
Q. Okay. But you don't have any --
THE COURT: Let me just back up. I'm going to exclude the exhibit. I did require things to be disclosed, and you can't come up to the hearing and bring up a new exhibit that you didn't timely disclose.
MR. CHARLES: Okay.
THE COURT: So Plaintiffs' 1 is excluded.
The scheduling order is ECF No. 32.
MR. CHARLES: Okay. Thank you, Your Honor.
Ms. Markley, you can unpublish, please. Thank you.
BY MR. CHARLES:
Q. Dr. Laidlaw, are you aware that the American Academy of Family Physicians supports gender-affirming care for youth and adults?
A. Supports gender-affirming care for youth and adults?
Q. Yes. Do you need to me to repeat? Did you hear that?
A. They probably do. I don't know their exact statement.
Q. Okay. Are you aware that the American Academy of Family Physicians published a policy statement in July of 2022, approved by their board of directors, entitled "Care for the Transgender and Gender Nonbinary Patient"?

A. I have not read that particular document -- Family Practice Document.

Q. Okay. Are you aware that the American Academy of Family Physicians supports gender-affirming care as an evidence-informed intervention that can promote permanent health equity for gender-diverse individuals?

MR. PERKO: Your Honor, I would object for the same reasons. He's essentially reading from an exhibit that was not disclosed.

THE COURT: He's now exploring the witness's knowledge of the situation in the field. The objection is overruled.

BY MR. CHARLES:

Q. Dr. Laidlaw --

A. I'm not a family practice physician, so I don't keep up with --

Q. Just a moment. Sorry. Let me start over.

A. -- the literature of that organization.

Q. I'm sorry. Can you please repeat that?

A. I said I'm not a family practice physician; I'm an endocrinologist, so I don't keep up with whatever they're publishing.

Q. Okay. So I -- let me just ask you one more question about that brief -- or policy statement. Excuse me.

Are you aware that the American Academy of Family Physicians asserts the full spectrum of gender-affirming health

1 care should be legal and should remain a treatment decision
2 between a physician and their patient?
3 A. I'm not surprised.
4 Q. Can -- so does that mean you are or are not aware?
5 A. I don't read the Family Practice documents, unless they are
6 provided to me.
7 Q. Dr. Laidlaw, are you aware the American Academy of
8 Pediatrics supports gender-affirming care for youth?
9 A. Yes.
10 Q. Dr. Laidlaw, are you aware that the American College of
11 Obstetricians and Gynecologists has recommendations and
12 conclusions that support gender-affirming care for youth and
13 adults?
14 A. I'm not -- again, I'm not surprised, but I don't read their
15 literature regularly for that purpose.
16 Q. Okay. Are you aware that the American College of
17 Obstetricians and Gynecologists has conclusions that
18 gender-affirming hormone therapy is not effective contraception?
19 A. That gender-affirming therapy is not effective
20 contraception?
21 Q. Correct.
22 A. I have read that. I'm not sure if it was theirs or someone
23 else who is publishing that. I'm aware of that concept.
24 Q. Can you repeat your answer? I didn't understand you.
25 A. I said I haven't read their statements specifically, but

I'm aware of the concept or proposition that gender-affirming hormones are not effective contraception.

Q. Okay. So you're not aware of the American College of Obstetricians and Gynecologists conclusion that it is not effective contraception?

A. I have not read their particular conclusion.

Q. Are you aware that the American College of Physicians, the largest medical specialty society in the world with 160,000 internal medicine and subspecialty members, supports public and private health care coverage of gender-affirming care?

A. I'm not aware that all 160,000 members voted to approve such a thing, but I'm aware that they have issued a statement like that.

Q. You are aware they issued such a statement?

A. Yes.

Q. Are you aware that in 2022, the American College of Physicians issued a brief supporting access to gender-affirming care and opposing discriminatory policies enforced against LGBTQ people and objected, in particular, to the interference with the physician-patient relationship and the penalization of evidence-based care?

A. I may have read that particular statement from that organization.

Q. Are you aware that the American Medical Association supports gender-affirming medical care for youth and adults?

A. Yes.
Q. Are you aware that in April of 2021, the American Medical Association wrote a letter to the National Governors Association objecting to the interference with health care of transgender children?
A. I believe I had come across that headline.
Q. Are you aware that the American Medical Association, in conjunction with GLMA, has issued a brief in support of public and private insurance coverage of gender-affirming care?
A. I'm not a member of the American Medical Association. I think only 20 percent of physicians in the nation are even a member. So I don't follow everything they say, but I do believe I read that document.
Q. Do you have evidence to support your assertion that only 20 percent of medical practitioners in the United States are members of the AMA?
A. I don't have a piece of paper with evidence, but that's my general understanding. I'm not a member.
Q. But you don't have any evidence today to point to to support that assertion?
A. No.
Q. Are you aware that in 2022, the American Medical Association reaffirmed it's resolution in support of private and public health care coverage for the treatment of gender dysphoria as recommended by a patient's physician in Resolution

Number 158.950?
A. I have not read that resolution.
Q. Are you aware, Dr. Laidlaw, that the American Psychological Association has guidelines that support access to gender-affirming care for youth and adults?
A. Yes.
Q. Are you aware that the American Psychological Association opposes gender-identity change efforts as a broad practice described as a range of techniques used by mental health professionals and nonprofessionals with the goal of changing gender identity, gender expression, or associated components of these, to be in alignment with gender role behaviors stereotypically associated with their sex assigned at birth?
A. Yes, I am aware.
Q. Are you aware that the American Psychiatric Association supports gender-affirming medical care for youth specifically?
A. Yes.
Q. Are you aware that the American Psychiatric Association has a position statement from 2018, supporting access to care for transgender and gender-variant individuals broadly?
A. Yes, I believe so.
Q. Are you aware that the Endocrine Society and the Pediatric Endocrine Society take the position that there is a durable biological underpinning to gender identity that should be considered in policy determinations?

A. I would have to read -- I have not read that particular statement from the Endocrine Society. I would like to see that before I make a -- conclude anything.
Q. Okay. Are you aware this determination was included in a position statement published in December of 2020?
A. I have read that position statement.
Q. And are you aware that the Endocrine Society and the Pediatric Endocrine Society take the position that medical intervention for transgender youth and adults is effective, relatively safe when appropriately monitored, and has been established as the standard of care?
A. Well, they wrote that it was not the standard of care in 2017, so they're contradicting themselves.
Q. Dr. Laidlaw, are you aware that that statement is contained in the transgender health position statement issued December 2020?
A. I believe I read that.
Q. And are you aware that the Endocrine Society and the Pediatric Endocrine Society take the position that 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?
A. I believe I read something along those lines.
Q. Are you aware that the Pediatric Endocrine Society supports

gender-affirming care for youth?
A. Yes.
Q. Are you aware they published a position statement to that effect in April of 2021?
A. Yes. I wrote an article describing why their conclusions are false or incorrect.
Q. Are you aware the Pediatric Endocrine Society recommends an affirmative model of care that supports one's gender identity and follows a multidisciplinary approach that includes involvement of mental health professionals, patients and their families. Puberty suppression and/or gender-affirming hormone therapy is recommended within this evidence-based approach on a case-by-case basis as medically necessary and potentially lifesaving.
Are you aware that was contained in the Pediatric Endocrine Society statement?
A. I am aware that it's contained. I don't agree with it, but, yes, I'm aware.
THE COURT: If we're leading up to something, you can go ahead with all of this. If all you're doing is publishing stuff I've already read --
MR. CHARLES: No, Your Honor.
THE COURT: You're welcome to make a closing argument later and to go through all of this, but if -- this is an incredibly inefficient way to publish material.

PAGE BREAK

example, the thyroid is a gland that makes thyroid hormone. When people have very high levels of thyroid hormone, we call that hyperthyroidism. They can have physical effects like fast heart rates, heart palpitations, tremors, but they can also have mental effects like anxiety and even psychosis. This can occur because their body develops too much thyroid hormone, or they may be taking too high of a dose of thyroid hormone.

So I have to distinguish if a mental health condition is related to a hormone imbalance versus a native psychological condition, or both sometimes.

BY MR. PERKO:

Q. Dr. Laidlaw, one final question.

How many patients a year do you treat with hormone treatments?

A. For hormone treatments?

Q. Yes.

A. Well, all of them, for the most part. I'd have to make an estimate. I see about 50 patient visits a week 50 weeks or so out of the year.

MR. PERKO: Thank you, Your Honor. No further questions.

THE COURT: Dr. Laidlaw, I want to ask you a question, and to do it, I need to define a couple of terms. These may not be the best definitions. They are my definition for purposes of my question.

I'm going to refer to natal identity as the identity at birth, and then I'm going to refer to gender identity as a person's perceived identity, the identity the person believes is the correct identity for the person.

Here's my question. In your opinion, is it ever appropriate for any medical professional in any specialty to support a person's decision to live in the person's gender identity instead of in the person's natal identity?

THE WITNESS: Ever under any circumstances, is that what you are saying?

I think my determination is that, in general, the risks of the hormones that are required and surgeries outweigh the benefits for the majority of people. I recognize there's some small degree of adults, perhaps, who are living this way. There are risks to mental health and things like that. So I'm not opposed to personal autonomy, but I am concerned about risks versus benefits, particularly for minors and youth.

THE COURT: So is the answer no?

THE WITNESS: I guess no.

THE COURT: Questions to follow up on mine?

MR. PERKO: No, Your Honor.

MR. CHARLES: No, Your Honor.

THE COURT: Thank you, Dr. Laidlaw. That concludes your testimony.

THE WITNESS: Thank you.

PAGE BREAK

irreparable harm. It's their burden to establish irreparable harm for the four individual plaintiffs. We've got declarations from the four individual plaintiffs, but we don't have any of the treating physicians for any of the four individual plaintiffs providing any opinions to this Court.

We have Dr. Laidlaw who is an endocrinologist who prescribes hormones and puberty blockers.

THE COURT: And has an opinion about sex reassignment surgery. What is his expertise to talk about these surgeries?

MR. JAZIL: Your Honor, he's someone who's tracking the literature. He is advising people who go into his clinic. And I take Your Honor's point that if it's something that he's not experienced with as a clinician, you're going to give it little weight.

THE COURT: And he's a doctor who says a person with gender dysphoria should not be treated in a way affirmative of the person's perceived gender by any medical professional. So a psychiatrist, psychologist, therapist should never say to a natal male, for example, that it's okay to live as a female.

Now, how far off the standard, the general view in the medical profession, is that?

MR. JAZIL: Your Honor, two points on that: One, his answer there was a little confusing. He -- and Your Honor asked a follow-up question to him. When he initially gave an answer, he said, I could think of possibly some instances where it would

PAGE BREAK

A. Yes.
Q. Do you know whether the report pertaining to the United Kingdom was peer-reviewed?
A. Which report are you referring to?
Q. You refer to a Kass review within your report, is that right?
A. Yes.
Q. Do you know whether that was peer-reviewed?
A. My assumption is yes.
Q. It's actually a preliminary report, is that right?
A. The one I refer to, I don't know if the final reports come out or not.
Q. Okay. Are you certain that it was peer-reviewed?
A. I'm certain that the NIH -- sorry, NHS, is involved with the reports. So, you know, then again, it depends how you define peer-reviewed. I presume if the NHS is involved then they have peers looking at the report before it's published. That's just my assumption.
Q. Peer-review has a particular meaning within the scientific literature, does it not?
A. If you're talking about publication in a scientific journal?

Q. Yes.
A. Then an article is submitted, appropriate peers are selected, have a look and decide whether, you know, the arguments are valid or, you know, the data is valid. That sort of thing.
Q. Essentially the publication goes out to external reviewers who may have some expertise in the area and may have some comments or not on the publication, is that right?
A. That's my understanding.
Q. Okay. Do you know whether it happened with the Kass review?
A. I don't know. I'm not part of the review.
Q. Do you know whether the report from Sweden was peer-reviewed?
A. Well, if it's not in a scientific publication -- and what my -- the reason that I think these are important is because peers within their public health system have looked at it and decided it should be published. So it's not a scientific --
Q. I understand that. I guess I'm asking an underlying threshold question for my edification which is --
A. It's --
Q. -- whether they were externally

1 peer-reviewed or not.
2 MS. PAYTON: Please don't talk over each
3 other.
4 A. Because it's not published in a journal it
5 would not have a journal type peer review.
6 Q. (By Mr. Gonzalez-Pagan) Does that hold true
7 also for the report pertaining to Finland?
8 A. That's my assumption.
9 Q. Do you know what the percentage of
10 desistance is among transgender adolescents?
11 A. Now, if you could -- I think that's a
12 difficult question to answer because when did they
13 come to -- when did they come to see a medical or
14 psychological health professional. When did they come
15 to seek treatment and how long had they had the
16 dysphoria.
17 So are you asking me someone who's had
18 dysphoria since age four and presents at age 13, for
19 example?
20 Q. Well, I guess what I'm asking is you made a
21 statement about desistance on your report --
22 A. Uh-huh.
23 Q. -- and you referenced particular studies --
24 A. Yes.
25 Q. -- and we've established that those studies

PAGE BREAK

Supreme Court will tell us otherwise here in the next day or two -- in the next few days. It seems to me this certainly would be an appealable order, and I'll get you a written order so that if you wish to appeal, you can.

What else, if anything, do we need to address today?

Thank you all. We are adjourned.

(Proceedings concluded at 12:57 PM on Wednesday, October 12, 2022.)

* * * * * * * *

I certify that the foregoing is a correct transcript from the record of proceedings in the above-entitled matter. Any redaction of personal data identifiers pursuant to the Judicial Conference Policy on Privacy is noted within the transcript.

/s/ Megan A. Hague 10/12/2022

Megan A. Hague, RPR, FCRR, CSR Date
Official U.S. Court Reporter

I N D E X

DEFENDANT'S WITNESSES	PAGE
DR. MICHAEL K. LAIDLAW	
Direct Examination By Mr. Perko	6
Voir Dire Examination By Mr. Charles	7
Cont. Direct Examination By Mr. Perko	15
Cross-Examination By Mr. Charles	23
Redirect Examination By Mr. Perko	38
ZOE HAWES	
Direct Examination By Mr. Beato	41
Cross-Examination	45
YAACOV SHEINFELD	
Direct Examination By Mr. Jazil	50
Cross-Examination By Ms. Altman	55

E X H I B I T S

PLAINTIFFS' EXHIBITS		OFFERED	RECEIVED
P1	American Academy of Child and Adolescent Psychiatry Statement Responding to Efforts to ban Evidence-Based Care for Transgender and Gender Diverse Youth	26	

OTHER RECORD MADE	PAGE
Closing Argument By Mr. Gonzalez-Pagan	64
Closing Argument By Mr. Jazil	82
Rebuttal Closing Argument By Mr. Gonzalez-Pagan	102

EXHIBIT 5

UNITED STATES DISTRICT COURT

WESTERN DISTRICT OF F WASHINGTON

AT TACOMA

C.P., by and through his parents,	)	
Patricia Pritchard and Nolle	)	
Pritchard and PATRICIA PRITCHARD,	)	
Plaintiffs,	)	
vs.	)	No. 3:20-cv-06145-RJB
BLUE CROSS BLUE SHIELD OF	)	
ILLINOIS,	)	
Defendant.	)	

ZOOM VIDEO DEPOSITION UPON ORAL EXAMINATION

OF

MICHAEL LAIDLAW

9:00 a.m.

September 2, 2022

REPORTED BY: Pat Lessard, CCR #2104

A P P E A R A N C E S

FOR THE PLAINTIFFS:

MS. ELEANOR HAMBURGER
Sirianni, Youtz, Spoonemore & Hamburger
3101 Western Avenue, Suite 350
Seattle, Washington 98121
206.223.0303
ele@sylaw.com
MR. OMAR GONZALEZ-PAGAN, pro hac vice
Lamda Legal Defense and Education Fund
120 Wall Street, 19th Floor
New York, NY 1005
212.809.9585
ogonzalez-pagan@lambdalegal.org

FOR THE DEFENDANT:

MS. GWENDOLYN PAYTON
Kilpatrick Townsend
1420 Fifth Avenue, Ste. 3700
Seattle, WA 98101
206.467.9600
gpayton@kilpatricktownsend.com

ALSO PRESENT:

MR. PATRICK NORTON, Videographer

E X H I B I T I N D E X

No.	DESCRIPTION	PAGE
Exhibit 1	Declaration of Michael Laidlaw.	9
Exhibit 2	Michael Laidlaw CV.	11
Exhibit 3	Notice of Deposition of Michael K. Laidlaw, M.D.	19
Exhibit 4	Our Mission - Public Discourse.	38
Exhibit 5	Subpoena to Produce Documents.	62
Exhibit 6	Understanding the Well-Being of LGBTQI Populations (2020)	104
Exhibit 7	Formal comment on: Parent reports of adolescents and young adults...	122
Exhibit 8	Gender nonconforming youth: current perspectives.	128
Exhibit 9	Position Statement on Conversion Therapy and LGBTQ Patients.	139
Exhibit 10	Resolution by the American Psychological Association.	140
Exhibit 11	Treatment of Central Precocious Puberty.	148
Exhibit 12	Notice in Federal Register.	161
Exhibit 13	Understanding Unapproved Use of Approved Drugs "Off Label."	162
Exhibit 15	Removing Financial Barriers to Care for Transgender Patients.	171

E X H I B I T I N D E X

No.	DESCRIPTION	PAGE
Exhibit 16	Health insurance coverage for gender-affirming care of transgender patients.	172
Exhibit 17	Hormonal Therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes.	179
Exhibit 18	American Psychiatric Association Ethics Committee Opinion.	191
Exhibit 19	Neurobiology of gender identity and sexual orientation.	93

E X A M I N A T I O N

ATTORNEY	PAGE
BY MR. GONZALEZ-PAGAN:	6
BY MR. GONZALEZ-PAGAN:	115

PAGE BREAK

on existing publications and preexisting data.
I think that's the distinction that you were drawing in your answer as well, is that correct?
A. Yes.
Q. So would you be comfortable with that understanding, that shared understanding of -- do you know what I mean by primary research?
A. Yes, I understand your meaning.
Q. Have you performed any primary research?
A. Yes.
Q. On what? On what matters?
A. There were two studies. One was a magnesium study that had to -- we're looking for an association of low magnesium leading to osteoporosis.
And the other study was regarding thyroid cancer where we were looking at thyroid globulin tumor markers and how they correlated with ultrasound findings of the neck.
Q. And when did you perform this research?
A. This was during my -- it may have begun during my -- I think it began during my residency and then I continued into fellowship.
Q. Have you performed any primary research regarding gender dysphoria?
A. No.

Q. Have you performed any primary research relating to transgender people?
A. No.
Q. Have you performed any primary research relating to gender identity?
A. No.
Q. Do you have any peer-reviewed publications?
A. Yes.
Q. Do you have a copy of your CV with you?
A. No.
Q. I will show you what's been marked as Exhibit 2.
A. Okay.
Q. And this is a copy of your CV, right?
Well, it's not showing yet. This is a copy of your CV, right?
A. Yes. It's the one we looked at earlier.
Q. And you have here a section titled "Research, Publications, and Expert Witness Work," is that right?
A. Yes.
Q. And we can scroll through it but just go area by area.
Can you tell me which the -- within the screen showing right now which of these publications

listed here are peer-reviewed?
MS. PAYTON: Object to the form of the question. And the blue print on the question on the screen here, I'm not sure that's easy to follow.
But go ahead and answer.
THE WITNESS: Understood.
Q. (By Mr. Gonzalez-Pagan) Dr. Laidlaw, you have marked in your CV some of these as expert witness --
A. Yes.
Q. -- brief of Amicus Curiae, Expert Witness, et cetera, is that correct?
A. Yes.
Q. Okay. So there's a publication listed for 2021 --
A. Uh-huh.
Q. -- it's a Letter to the Editor --
A. Uh-huh.
Q. -- titled "Erythrocytosis in a Large Cohort of Trans Men Using Testosterone: A Long-Term Follow-Up Study on Prevalence, Determinants and Exposure Years," is that right?
A. Yes.
Q. It's a Letter to the Editor pertaining to that separate article, is that correct?

A. That's right.
Q. And is a Letter to the Editor a peer reviewed publication?
A. I don't know. It has to be accepted before they publish it, so I don't know what process they go through. It may be or it may not be.
Q. There's another listing or a publication in 2020 titled "Correction Transgender Surgery Provides No Mental Health Benefit," is that right?
A. Yes.
Q. And you're a coauthor of this piece, is that right?
A. Yes.
Q. It was published in the Public Discourse, is that correct?
A. That's correct.
Q. Is this a peer-reviewed publication?
A. Not to my knowledge.
Q. There's another publication just below it, in 2020, titled Gender-Affirmation surgery conclusion lacks evidence (letter)."
And you're a coauthor of this publication, is that right?
A. That's right.
Q. This was another letter, is that correct?

A. Yes, it's a Letter to the Editor.
Q. Okay. Is this peer-reviewed?
A. I don't know. It has to be accepted for publication, like I said, so I don't know what process they go through.
Q. Below that there's another publication titled "The Pediatric Endocrine Society's Statement on Puberty Blockers isn't just Deceptive. It's Dangerous."
And you're the sole author of this publication, is that right?
A. Yes.
Q. And it was published in Public Discourse, is that correct?
A. That's correct.
Q. And the next page, the next publication listed is "The Right to Best Care for Children does Not Include the Right to Medical Transition," is that right?
A. Yes.
Q. And you're a coauthor of this piece?
A. Yes.
Q. And this is an opinion piece, is that correct?
MS. PAYTON: Object to the form.

A. My understanding is it's a peer-reviewed piece, but that's the one I would say has to be peer-reviewed to be published but I don't know their process.

Q. (By Mr. Gonzalez-Pagan) But is it an opinion piece or is it a research piece?

MS. PAYTON: Object to the form.

A. I mean it's the Journal of Bioethics, so it's not -- if you're asking is it based on primary research? Because there's two different things. You could have a peer-reviewed -- peer review doesn't necessarily mean it's primary research, to my understanding.

Q. No. Understood.

I'm asking the question is the Journal of Bioethics a peer-reviewed publication?

A. That's my understanding, yes. I mean all the medical journals that you have listed are peer reviewed publications. The exact process they use, I don't know.

Q. And this piece in 2019 for which you are a coauthor in the American Journal of Bioethics is not a piece of original research, is that correct?

A. When you say that, do you mean did we have patients doing -- collecting data on individual

patients? Is that what you mean by that?
Q. Yes. Do you have an understanding of what primary research meant? So I guess I would ask it that way.
Is this article based on primary research you conducted?
A. It's not based on primary research I conducted.
Q. Thank you. There's another publication. It's a Letter to the Editor, "Endocrine Treatment of Gender-Dysphoric/Gender Incongruent Persons: An Endocrine Society Clinical Practice Guideline," is that correct?
A. Correct.
Q. And you're a coauthor of this piece?
A. Yes.
Q. And this is another Letter to the Editor, correct?
A. Yes.
Q. Just below that there's a publication titled "The Gender Identity Phantom," and you are the sole author, is that right?
A. Correct.
Q. And it appears to be published in the gdworkinggroup.org, is that right?

A. Yes, I think so.
Q. What's the gdworkinggroup.org?
A. They're a collection of different psychologists, psychiatrists and other mental health professionals, and there may have been other physicians, but who were writing pieces with concerns or criticisms about the care of people with gender identity conditions.
Q. Is this a publication posting on a discussion board?
A. Could you repeat that?
Q. Is this a publication posting within a discussion board?
A. No. Are you asking me like can you just post something as part of a discussion or are you asking can people discuss the topic below your article? Is that what you're asking?
Q. I'm asking if it's a discussion forum for professionals where you are set up, made a post, or whether it's an article.
A. Oh, it's an article against -- each author can write -- you have to be a member to be an author and you have to be an author to put something up there.
So not just any general member of the public

could write something, if that clarifies it.
Q. Okay. Is this peer-reviewed?
A. No.
Q. The next publication is titled "Gender Dysphoria and Children: An Endocrinologist's evaluation of 'I am Jazz,'" and you're the sole author, is that right?
A. That's correct.
Q. And it was published in Public Discourse, is that correct?
A. Yes.
Q. Are there any other publications that you have in relation to gender dysphoria or transgender issues?
A. Not that I can think of. I did have this -- I think I put it somewhere with my subpoena response, but there's gendersanity.org where I explained myself and coauthors explained the most recent Letter to the Editor.
Q. Sorry? What is that?
A. Gendersanity.org I believe is the name.
Q. And is that a self-published website?
A. Yes.
Q. We've established that three of your publications are for Public Discourse, is that

correct?
MS. PAYTON: Object to the form.
A. Yeah. Three -- I think it was three, yeah, three publications for Public Discourse.
Q. (By Mr. Gonzalez-Pagan) Who publishes, Public Discourse?
A. I believe at the time I submitted my articles that -- I don't know who the publisher is but the editor was Ryan Anderson, I believe.
Q. Are you familiar with the Witherspoon Institute?
A. Only that I saw their name associated with Public Discourse.
Q. I'm going to show you what's been marked as Exhibit 4.
A. Okay.
(Marked Deposition Exhibit No. 4.)
Q. (By Mr. Gonzalez-Pagan) Do you see the document in front of you?
A. Yes.
Q. This is the Mission Statement for Public Discourse, is that right?
A. It says "Our Mission," so I suppose it is.
Q. Okay. And just to clarify, this is a printout on September 2nd, 2022, 8:30 a.m., off the

website www.the public discourse.com/our mission, is that correct?

MS. PAYTON: Object to the form, foundation.

A. You are posting -- or I can see on the screen a mission statement from Public Discourse as of today. Today is the first time I've ever seen it.

Q. (By Mr. Gonzalez-Pagan) Yes. On the screen?

A. Yeah.

Q. And do you understand Public Discourse to be an online journal?

A. Yes.

Q. And are you aware that their mission is to enhance public understanding of the moral foundations of free society?

MS. PAYTON: Object to the form.

A. You know, I'm looking at it now and I can say you just read what is on there. But I don't have any affiliation with them in particular.

I think, but I don't recall exactly, that anything I publish at the bottom, I think, says something like "This does not necessarily represent the views of the Public Discourse," so --

Q. Is there any reason why you chose to publish in the Public Discourse?

PAGE BREAK

THE VIDEOGRAPHER: We're going off the record at 10:00 a.m.

(Recess.)

THE VIDEOGRAPHER: We're back on the record at 10:07 a.m.

Q. (By Mr. Gonzalez-Pagan) We left off discussing your publications. Do you recall that, Dr. Laidlaw?

A. Yes, I do.

Q. Just to sum up, none of your publications pertaining to gender dysphoria are based on original primary research, is that correct?

A. That's correct.

Q. And with the exception of the piece in the Journal of Bioethics none of your publications pertaining to gender dysphoria are peer-reviewed?

A. Well, a number are published in peer-reduced journals.

Q. Sorry. The Letters to the Editor, is that right?

A. The Letters to the Editors are in peer-reviewed journals, yes.

Q. We've established that you have a private practice dedicated to endocrinology, is that correct?

A. That's correct.

Q. As part of your practice do you treat any pediatric patients?

A. I have some patients who are under the age of 18, so later teens or mid teens.

Q. What percentage of your practice are patients under the age of 18?

A. Probably, like, less than five percent.

Q. Have you ever provided care to a transgender patient?

A. Yes.

Q. Have you provided them with care relating to their gender dysphoria?

A. Only once.

Q. What care did you provide that one patient?

A. The patient needed a refill of estrogen.

Q. Did you provide them with the refill?

A. Yes.

Q. About how many transgender patients have you treated for other conditions besides this one patient for gender dysphoria?

A. So I would say that in my practice I have patients with, I would use a more general term and say "gender incongruence," who I'm seeing for other conditions.

For example, they may have a pituitary

PAGE BREAK

A. Or there would be one who had -- well, I would say two because the detransition person I am treating as a consequence of gender dysphoria. So I would say two.

Q. Okay. So there's the one person who has detransitioned and then the one person who you provided a refill for estrogen, is that correct?

A. Those are two patients who received hormones related to a gender incongruence condition.

Q. How old was the patient that detransitioned?

A. In his 20s. He was diagnosed in his early teens.

Q. Do you know how this patient came about connecting with you?

A. He has had a very difficult time finding an endocrinologist who will treat him. He had an orchiectomy or testicles removed and vaginal plasty.

He had a difficult time finding a physician who would prescribe testosterone so he had made a search and somehow found me.

Q. Have you ever diagnosed any patient with gender dysphoria?

A. Being that it's a psychological diagnosis, I do not make psychological diagnoses, so no.

Q. Have you ever diagnosed a person with gender

1 identity disorder?
2 A. The same answer. A psychological, you know,
3 diagnosis that I do not make.
4 Q. Just to clarify, for the patient who
5 detransitioned, you're not providing care for
6 treatment of gender dysphoria, is that correct?
7 A. Well, I guess it depends how you define
8 treatment for gender dysphoria.
9 Q. Well, what do you understand gender
10 dysphoria to be?
11 A. Well, this would be a discomfort arising
12 from a person's, you know, true feeling of their
13 gender identity versus their physical body.
14 So I don't think this person has fully
15 resolved that issue within himself, but he feels very
16 poorly not receiving testosterone so I'm treating him.
17 So in a sense I am treating his gender -- I mean he
18 feels better. He's doing better.
19 So I believe I am treating his gender
20 dysphoria. That's not my primary purpose but it's a
21 secondary consequence.
22 Q. Are you working in conjunction with a mental
23 health therapist or mental health provider in
24 providing this care to this individual?
25 A. He just moved to Southern California and in

PAGE BREAK

1 last two sentences. It states "WPATH claims to be a
2 scientific organization while explicitly acting as an
3 advocacy group. These are incompatible goals."
4 A. Yes.
5 Q. What is the basis for your opinion that a
6 scientific organization cannot engage in advocacy?
7 A. I think a scientific organization can -- for
8 example, the American Cancer Society, which we talked
9 about earlier, they can advocate for eliminating
10 cancer or better treatments for cancer. But they
11 would not -- one would expect them not to exclusively
12 follow one, say, politically based point of view.
13 There could be a variety of points of view
14 within the American Cancer Society, I'm just giving
15 you an example, or Endocrine Society. Whatever the
16 society is should be open to a variety of points of
17 view.
18 And what I've seen is that the WPATH is not.
19 Q. You're not a member of WPATH, is that right?
20 A. That's correct.
21 Q. Do you know, are you privy to the debates
22 that occur within WPATH?
23 A. I've seen some online debates. I've spoken
24 to a psychologist who was a member and quit basically
25 because of this problem.

Q. But you're not privy to the actual internal conversations of WPATH, is that correct?

A. I've spent time looking at the WPATH standards of care.

Q. That wasn't my question, though. Have you participated in any WPATH conferences?

A. I do not participate in WPATH conferences. I'm not a member.

Q. Have you participated in internal discussion forums?

A. I do not participate with WPATH. I'm not a member.

Q. So what is the basis for your opinion that there are no diverse -- no differences of opinion within WPATH?

A. I'm basing it on their standards of care.

Q. The Endocrine Society has a variety of clinical practice guidelines, is that not correct?

A. They do.

Q. Some people disagree with many of those variety of clinical practice guidelines, is that not correct?

A. Are you saying that the members of the Endocrine Society disagree with practice guidelines?

Q. Yes.

PAGE BREAK

allowed for a variety of viewpoints in my opinion.
Q. (By Mr. Gonzalez-Pagan) And I'm asking whether you know whether, know from a first hand basis whether WPATH allows for a variety of opinions?
A. My impression is that they do not.
Q. What's the basis for your impression?
A. Their standards of care and my conversation with the psychologist that I mentioned.
Q. So the standards of care itself is proof there's no debate?
A. Right. Because it doesn't offer any alternatives.
Q. Let's turn to page 31 -- sorry, paragraph 31 of your report.
A. Okay.
Q. There you state -- is there an echo? There you state that the assertion by Dr. Etner that a growing assemblage of research documents that gender identity is immutable and biologically based lacks scientific support and therefore impairs the credibility of Dr. Etner's opinions?
A. Yes.
Q. Okay. Are you saying that gender identity is not biologically based?
A. I'm saying there's no evidence of it at this

PAGE BREAK

A. I'm not sure. I think some of the earlier studies were in the United States but I'm not a hundred percent sure.

Q. Are you aware that the desistance studies only involve youth that were diagnosed or were sub threshold for gender identity disorder rather than gender dysphoria?

A. Well, the gender dysphoria diagnosis was not, you know, hadn't been published at that point, so.

Q. It didn't exist at that time, is that correct?

A. Well, I mean it may have existed but it didn't exist as a term in the DSM.

Q. Sure. What I'm trying to say, the gender dysphoria diagnosis as contained within the DSM-5 did not exist at the time that these studies were conducted?

A. Yes.

Q. Okay. And the diagnostic criteria of gender identity disorder contained in the DSM-3 and 4 is different than the diagnostic criteria for gender dysphoria in the DSM-5, is that correct?

A. At that time I believe they had a term gender identity disorder.

Q. Yes. And I'm asking whether the diagnostic criteria are different.

A. There were different diagnostic criteria, to my knowledge.

Q. I'm going to show you what's been marked as Plaintiffs' Exhibit 6.

(Marked Deposition Exhibit No. 6.)

Q. (By Mr. Gonzalez-Pagan) I apologize. This is actually a pretty enormous PDF.

Can you see my screen?

A. Yes.

This is a publication titled "Understanding the Well-Being of LGBTQI Populations," from 2020, published by the National Academies of Sciences, Engineering and Medicine.

Do you see that?

A. I see it.

Q. Are you familiar with this document?

A. Only briefly looking at it this morning but I had not heard of it before.

Q. Okay. And in your report you relied on reported reviews from the United kingdom, Sweden and Finland relating to the scientific evidence of the care of gender dysphoria, is that right?

A. Yes.

PAGE BREAK

1 looked at primarily up to age twelve population.
2 So I'm asking if you know any desistance
3 rates or studies pertaining to desistance rates, you
4 know, above age twelve?
5 A. Well, I don't -- well, let's say from the
6 age of 13 to 18 I'm not aware of any study that looks
7 at desistance.
8 Q. Do you know of any study that looks at
9 desistance above age 18?
10 A. I don't know if there's any published study.
11 I know there was a professor in the UK who wanted to
12 publish something and he was obstructed from doing
13 that. I don't remember his name, Caspin, I think.
14 So I'm not aware that there's any out there.
15 Q. (By Mr. Gonzalez-Pagan) I'm going to refer
16 you again to Exhibit 6. This is the National
17 Academies study report. I'm on page 302 of the
18 document.
19 And it states that while interest in the
20 so-called desistance of transgender identity has been
21 informed by studies suggesting that as high as 80
22 percent of prepubertal youth presenting to pediatric
23 gender clinics ultimately do not identify as
24 transgender, many of the youth included in the studies
25 did not meet full DSM criteria for a gender

PAGE BREAK

on minor C.P."

That's a mode of treatment. And I'm asking how is that consistent with your critique on paragraph 180?

A. Well, my critique was of Dr. Karasic.

Q. Did that apply to you?

A. No.

Q. You're not a mental health provider, right?

A. I'm sorry?

Q. You're not a mental health provider, right?

A. No.

Q. And you're not a surgeon, right?

A. Correct.

Q. Look at paragraph 195. You conclude "Therefore, it appears that Dr. Hatfield had begun pubertal suppression at Tanner Stage 1, which was not advised by either the ESG or even the WPATH's SOC."

Did I read that correctly?

A. Yes.

Q. That is not something you know, that is speculation based on some gaps you appear to have found in the medical records, is that right?

A. No. I'm basing my opinion on the medical record.

Q. Okay. So are you saying that with

PAGE BREAK

that question, do you consider a person to be transgendered to be troubling?

MS. PAYTON: I'll object to the form.

A. I'm not sure what you mean by that. Are you saying medically or are they troubled, you know, at risk for hormones? Is that what you're saying?

Q. (By Mr. Gonzalez-Pagan) I am making reference to your own publication.

A. Well, you'd have to show me exactly what it is. I'm not sure what you're referencing.

MR. Gonzalez-Pagan: Okay. Those are all my questions.

MS. PAYTON: No questions. We'll reserve. No video, please.

THE VIDEOGRAPHER: Did Ele have some questions?

MS. HAMBURGER: No. I have no questions.

THE VIDEOGRAPHER: Okay. I thought she said hold on a few minutes.

This concludes the video-recorded deposition of Dr. Michael Laidlaw.

We are off the record at 3:21 p.m.

(Deposition recessed at 3:21 p.m.)

S I G N A T U R E

I declare under penalty of perjury under the laws of the State of Washington that I have read my within deposition, and the same is true and accurate, save and except for changes and/or corrections, if any, as indicated by me on the CHANGE SHEET flyleaf page hereof.

Signed in _____, Washington, this _____ day of _____, 2022.

MICHAEL LAIDLAW

Taken: September 2, 2022

Re: C.P. versus Blue Cross Blue Shield
Cause No.: 3:20-cv-06145-RJB
Pat Lessard, CCR 2104

C E R T I F I C A T E

STATE OF WASHINGTON)
) ss.
COUNTY OF KING)

I, the undersigned Washington Certified Court Reporter, hereby certify that the foregoing deposition upon oral examination of MICHAEL LAIDLAW was taken stenographically by me on September 2, 2022, and transcribed under my direction;

That the witness was duly sworn by me pursuant to RCW 5.28.010 to testify truthfully; that the transcript of the deposition is a full, true, and correct transcript to the best of my ability; that I am neither attorney for nor relative or employee of any of the parties to the action or any attorney or counsel employed by the parties hereto, nor am I financially interested in its outcome.

I further certify that in accordance with CR 30(e) the witness was given the opportunity to examine, read and sign the deposition within 30 days upon its completion and submission, unless waiver of signature was indicated in the record.

IN WITNESS WHEREOF, I have hereunto set my hand this 12th day of September, 2022.

Pat Lessard,
pat@court-reporter.com

CHANGE SHEET

PLEASE MAKE ALL CHANGES OR CORRECTIONS ON THIS SHEET, SHOWING PAGE, LINE AND REASON.

PAGE	LINE	CORRECTION AND REASON

_____

MICHAEL LAIDLAW
Taken: September 2, 2022
Re: C.P. versus Blue Cross Blue Shield
Cause No.: 3:20-cv-06145-RJB
Pat Lessard, CCR 2104.

EXHIBIT 6

OPEN ACCESS Freely available online PLoS one

Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden

Cecilia Dhejne[1], Paul Lichtenstein[2], Marcus Boman[2], Anna L. V. Johansson[2], Niklas Långström[2,3], Mikael Landén[1,2,4]*

1 Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden, **2** Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, **3** Centre for Violence Prevention, Karolinska Institutet, Stockholm, Sweden, **4** Institute of Neuroscience and Physiology, The Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

Abstract

Context: The treatment for transsexualism is sex reassignment, including hormonal treatment and surgery aimed at making the person's body as congruent with the opposite sex as possible. There is a dearth of long term, follow-up studies after sex reassignment.

Objective: To estimate mortality, morbidity, and criminal rate after surgical sex reassignment of transsexual persons.

Design: A population-based matched cohort study.

Setting: Sweden, 1973-2003.

Participants: All 324 sex-reassigned persons (191 male-to-females, 133 female-to-males) in Sweden, 1973–2003. Random population controls (10:1) were matched by birth year and birth sex or reassigned (final) sex, respectively.

Main Outcome Measures: Hazard ratios (HR) with 95% confidence intervals (CI) for mortality and psychiatric morbidity were obtained with Cox regression models, which were adjusted for immigrant status and psychiatric morbidity prior to sex reassignment (adjusted HR [aHR]).

Results: The overall mortality for sex-reassigned persons was higher during follow-up (aHR 2.8; 95% CI 1.8–4.3) than for controls of the same birth sex, particularly death from suicide (aHR 19.1; 95% CI 5.8–62.9). Sex-reassigned persons also had an increased risk for suicide attempts (aHR 4.9; 95% CI 2.9–8.5) and psychiatric inpatient care (aHR 2.8; 95% CI 2.0–3.9). Comparisons with controls matched on reassigned sex yielded similar results. Female-to-males, but not male-to-females, had a higher risk for criminal convictions than their respective birth sex controls.

Conclusions: Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population. Our findings suggest that sex reassignment, although alleviating gender dysphoria, may not suffice as treatment for transsexualism, and should inspire improved psychiatric and somatic care after sex reassignment for this patient group.

Citation: Dhejne C, Lichtenstein P, Boman M, Johansson ALV, Långström N, et al. (2011) Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden. PLoS ONE 6(2): e16885. doi:10.1371/journal.pone.0016885

Editor: James Scott, The University of Queensland, Australia

Received September 30, 2010; **Accepted** January 9, 2011; **Published** February 22, 2011

Copyright: © 2011 Dhejne et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: Financial support was provided through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and the Karolinska Institutet, and through grants from the Swedish Medical Research Council (K2008-62x-14647-06-3) and the Royal Swedish Academy of Sciences (Torsten Amundson's Foundation). The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and the final responsibility for the decision to submit for publication was made by the corresponding author.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: mikael.landen@neuro.gu.se

Introduction

Transsexualism (ICD-10),[1] or gender identity disorder (DSM-IV),[2] is a condition in which a person's gender identity - the sense of being a man or a woman - contradicts his or her bodily sex characteristics. The individual experiences gender dysphoria and desires to live and be accepted as a member of the opposite sex.

The treatment for transsexualism includes removal of body hair, vocal training, and cross-sex hormonal treatment aimed at making the person's body as congruent with the opposite sex as possible to alleviate the gender dysphoria. Sex reassignment also involves the surgical removal of body parts to make external sexual characteristics resemble those of the opposite sex, so called sex reassignment/confirmation surgery (SRS). This is a unique

intervention not only in psychiatry but in all of medicine. The present form of sex reassignment has been practised for more than half a century and is the internationally recognized treatment to ease gender dysphoria in transsexual persons.[3,4]

Despite the long history of this treatment, however, outcome data regarding mortality and psychiatric morbidity are scant. With respect to suicide and deaths from other causes after sex reassignment, an early Swedish study followed 24 transsexual persons for an average of six years and reported one suicide.[5] A subsequent Swedish study recorded three suicides after sex reassignment surgery of 175 patients.[6] A recent Swedish follow-up study reported no suicides in 60 transsexual patients, but one death due to complications after the sex reassignment surgery.[7] A Danish study reported death by suicide in 3 out of 29 operated male-to-female transsexual persons followed for an average of six years.[8] By contrast, a Belgian study of 107 transsexual persons followed for 4–6 years found no suicides or deaths from other causes.[9] A large Dutch single-centre study (N = 1,109), focusing on adverse events following hormonal treatment, compared the outcome after cross-sex hormone treatment with national Dutch standardized mortality and morbidity rates and found no increased mortality, with the exception of death from suicide and AIDS in male-to-females 25–39 years of age.[10] The same research group concluded in a recent report that treatment with cross-sex hormones seems acceptably safe, but with the reservation that solid clinical data are missing.[11] A limitation with respect to the Dutch cohort is that the proportion of patients treated with cross-sex hormones who also had surgical sex-reassignment is not accounted for.[10]

Data is inconsistent with respect to psychiatric morbidity post sex reassignment. Although many studies have reported psychiatric and psychological improvement after hormonal and/or surgical treatment,[7,12,13,14,15,16] other have reported on regrets,[17] psychiatric morbidity, and suicide attempts after SRS.[9,18] A recent systematic review and meta-analysis concluded that approximately 80% reported subjective improvement in terms of gender dysphoria, quality of life, and psychological symptoms, but also that there are studies reporting high psychiatric morbidity and suicide rates after sex reassignment.[19] The authors concluded though that the evidence base for sex reassignment "is of very low quality due to the serious methodological limitations of included studies."

The methodological shortcomings have many reasons. First, the nature of sex reassignment precludes double blind randomized controlled studies of the result. Second, transsexualism is rare [20] and many follow-ups are hampered by small numbers of subjects.[5,8,21,22,23,24,25,26,27,28] Third, many sex reassigned persons decline to participate in follow-up studies, or relocate after surgery, resulting in high drop-out rates and consequent selection bias.[6,9,12,21,24,28,29,30] Forth, several follow-up studies are hampered by limited follow-up periods.[7,9,21,22,26,30] Taken together, these limitations preclude solid and generalisable conclusions. A long-term population-based controlled study is one way to address these methodological shortcomings.

Here, we assessed mortality, psychiatric morbidity, and psychosocial integration expressed in criminal behaviour after sex reassignment in transsexual persons, in a total population cohort study with long-term follow-up information obtained from Swedish registers. The cohort was compared with randomly selected population controls matched for age and gender. We adjusted for premorbid differences regarding psychiatric morbidity and immigrant status. This study design sheds new light on transsexual persons' health after sex reassignment. It does not, however, address whether sex reassignment is an effective treatment or not.

Methods

National registers

The study population was identified by the linkage of several Swedish national registers, which contained a total of 13.8 million unique individuals. The Hospital Discharge Register (HDR, held by the National Board of Health and Welfare) contains discharge diagnoses, up to seven contributory diagnoses, external causes of morbidity or mortality, surgical procedure codes, and discharge date. Discharge diagnoses are coded according to the 8th (1969-1986), 9th (1987–1996), and 10th editions (1997-) of the International Classification of Diseases (ICD). The register covers virtually all psychiatric inpatient episodes in Sweden since 1973. Discharges that occurred up to 31 December 2003 were included. Surgical procedure codes could not be used for this study due to the lack of a specific code for sex reassignment surgery. The Total Population Register (TPR, held by Statistics Sweden) is comprised of data about the entire Swedish population. Through linkage with the Total Population Register it was possible to identify birth date and birth gender for all study subjects. The register is updated every year and gender information was available up to 2004/2005. The Medical Birth Register (MBR) was established in 1973 and contains birth data, including gender of the child at birth. National censuses based on mandatory self-report questionnaires completed by all adult citizens in 1960, 1970, 1980, and 1990 provided information on individuals, households, and dwellings, including gender, living area, and highest educational level. Complete migration data, including country of birth for immigrants for 1969–2003, were obtained from the TPR. In addition to educational information from the censuses, we also obtained highest educational level data for 1990 and 2000 from the Register of Education. The Cause of Death Register (CDR, Statistics Sweden) records all deaths in Sweden since 1952 and provided information on date of death and causes of death. Death events occurring up to 31 December 2003 are included in the study. The Crime Register (held by the National Council of Crime Prevention) provided information regarding crime type and date on all criminal convictions in Sweden during the period 1973–2004. Attempted and aggravated forms of all offences were also included. All crimes in Sweden are registered regardless of insanity at the time of perpetration; for example, for individuals who suffered from psychosis at the time of the offence. Moreover, conviction data include individuals who received custodial or non-custodial sentences and cases where the prosecutor decided to caution or fine without court proceedings. Finally, Sweden does not differ considerably from other members of the European Union regarding rates of violent crime and their resolution.[31]

Study population, identification of sex-reassigned persons (exposure assessment)

The study was designed as a population-based matched cohort study. We used the individual national registration number, assigned to all Swedish residents, including immigrants on arrival, as the primary key through all linkages. The registration number consists of 10 digits; the first six provide information of the birth date, whereas the ninth digit indicates the gender. In Sweden, a person presenting with gender dysphoria is referred to one of six specialised gender teams that evaluate and treat patients principally according to international consensus guidelines: Standards of Care.[3] With a medical certificate, the person applies to the National Board of Health and Welfare to receive permission for sex reassignment surgery and a change of legal sex status. A new national registration number signifying the new gender is assigned after sex reassignment surgery. The National

Board of Health and Welfare maintains a link between old and new national registration numbers, making it possible to follow individuals undergoing sex reassignment across registers and over time. Hence, sex reassignment surgery in Sweden requires (i) a transsexualism diagnosis and (ii) permission from the National Board of Health and Welfare.

A person was defined as exposed to sex reassignment surgery if two criteria were met: (i) at least one inpatient diagnosis of gender identity disorder diagnosis without concomitant psychiatric diagnoses in the Hospital Discharge Register, and (ii) at least one discrepancy between gender variables in the Medical Birth Register (from 1973 and onwards) or the National Censuses from 1960, 1970, 1980, or 1990 and the latest gender designation in the Total Population Register. The first criterion was employed to capture the hospitalization for sex reassignment surgery that serves to secure the diagnosis and provide a time point for sex reassignment surgery; the plastic surgeons namely record the reason for sex reassignment surgery, i.e., transsexualism, but not any co-occurring psychiatric morbidity. The second criterion was used to ensure that the person went through all steps in sex-reassignment and also changed sex legally.

The date of sex reassignment (start of follow-up) was defined as the first occurrence of a gender identity disorder diagnosis, without any other concomitant psychiatric disorder, in the Hospital Discharge Register after the patient changed sex status (any discordance in sex designation across the Censuses, Medical Birth, and Total Population registers). If this information was missing, we used instead the closest date in the Hospital Discharge Register on which the patient was diagnosed with gender identity disorder without concomitant psychiatric disorder prior to change in sex status. The reason for prioritizing the use of a gender identity disorder diagnosis *after* changed sex status over *before* was to avoid overestimating person-years at risk of sex-reassigned person.

Using these criteria, a total of 804 patients with gender identity disorder were identified, whereof 324 displayed a shift in the gender variable during the period 1973–2003. The 480 persons that did not shift gender variable comprise persons who either did not apply, or were not approved, for sex reassignment surgery. Moreover, the ICD 9 code 302 is a non specific code for sexual disorders. Hence, this group might also comprise persons that were hospitalized for sexual disorders other than transsexualism. Therefore, they were omitted from further analyses. Of the remaining 324 persons, 288 were identified with the gender identity diagnosis *after* and 36 *before* change of sex status. Out of the 288 persons identified *after* changed sex status, 185 could also be identified *before* change in sex status. The median time lag between the hospitalization *before* and *after* sex change for these 185 persons was 0.96 years (mean 2.2 years, SD 3.3).

Gender identity disorder was coded according to ICD-8: 302.3 (transsexualism) and 302.9 (sexual deviation NOS); ICD-9: 302 (overall code for sexual deviations and disorders, more specific codes were not available in ICD-9); and ICD-10: F64.0 (transsexualism), F64.1 (dual-role transvestism), F64.8 (other gender identity disorder), and F64.9 (gender identity disorder NOS). Other psychiatric disorders were coded as ICD-8: 290-301 and 303-315; ICD-9: 290-301 and 303-319; and ICD-10: F00-F63 as well as F65-F99.

Identification of population-based controls (unexposed group)

For each exposed person (N = 324), we randomly selected 10 unexposed controls. A person was defined as unexposed if there were no discrepancies in sex designation across the Censuses, Medical Birth, and Total Population registers *and* no gender identity disorder diagnosis according to the Hospital Discharge Register. Control persons were matched by sex and birth year and had to be alive and residing in Sweden at the estimated sex reassignment date of the case person. To study possible gender-specific effects on outcomes of interest, we used two different control groups: one with the same sex as the case individual at birth (birth sex matching) and the other with the sex that the case individual had been reassigned to (final sex matching).

Outcome measures

We studied mortality, psychiatric morbidity, accidents, and crime following sex reassignment. More specifically, we investigated: (1) all-cause mortality, (2) death by definite/uncertain suicide, (3) death by cardiovascular disease, and (4) death by tumour. Morbidity included (5) any psychiatric disorder (gender identity disorders excluded), (6) alcohol/drug misuse and dependence, (7) definite/uncertain suicide attempt, and (8) accidents. Finally, we addressed court convictions for (9) any criminal offence and (10) any violent offence. Each individual could contribute with several outcomes, but only one event per outcome. Causes of death (Cause of Death Registry from 1952 and onwards) were defined according to ICD as suicide (ICD-8 and ICD-9 codes E950-E959 and E980-E989, ICD-10 codes X60-X84 and Y10-Y34); cardiovascular disease (ICD-8 codes 390-458, ICD-9 codes 390-459, ICD-10 codes I00-I99); neoplasms (ICD-8 and ICD-9 codes 140-239, ICD-10 codes C00-D48), any psychiatric disorder (gender identity disorders excluded); (ICD-8 codes 290-301 and 303-315, ICD-9 codes 290-301 and 303-319, ICD-10 codes F00-F63 and F65-F99); alcohol/drug abuse and dependence (ICD-8 codes 303-304, ICD-9 codes 303-305 (tobacco use disorder excluded), ICD-10 codes F10-F16 and F18-F19 (x5 excluded); and accidents (ICD-8 and ICD-9 codes E800-E929, ICD-10 codes V01-X59).

Any criminal conviction during follow-up was counted; specifically, violent crime was defined as homicide and attempted homicide, aggravated assault and assault, robbery, threatening behaviour, harassment, arson, or any sexual offense.[32]

Covariates

Severe psychiatric morbidity was defined as inpatient care according to ICD-8 codes 291, 295-301, 303-304, and 307; ICD-9 codes 291-292, 295-298, 300-301, 303-305 (tobacco use disorder excluded), 307.1, 307.5, 308-309, and 311; ICD-10 codes F10-F16, F18-F25, F28-F45, F48, F50, and F60-F62. Immigrant status, defined as individuals born abroad, was obtained from the Total Population Register. All outcome/covariate variables were dichotomized (i.e., affected or unaffected) and without missing values.

Statistical analyses

Each individual contributed person-time from study entry (for exposed: date of sex reassignment; for unexposed: date of sex reassignment of matched case) until date of outcome event, death, emigration, or end of study period (31 December 2003), whichever came first. The association between exposure (sex reassignment) and outcome (mortality, morbidity, crime) was measured by hazard ratios (HR) with 95% CIs, taking follow-up time into account. HRs were estimated from Cox proportional hazard regression models, stratified on matched sets (1:10) to account for the matching by sex, age, and calendar time (birth year). We present crude HRs (though adjusted for sex and age through matching) and confounder-adjusted HRs [aHRs] for all outcomes. The two potential confounders, immigrant status (yes/no) and history of severe psychiatric morbidity (yes/no) prior to sex

reassignment, were chosen based on previous research[18,33] and different prevalence across cases and controls (Table 1).

Gender-separated analyses were performed and a Kaplan-Meier survival plot graphically illustrates the survival of the sex reassigned cohort and matched controls (all-cause mortality) over time. The significance level was set at 0.05 (all tests were two-sided). All outcome/covariate variables were without missing values, since they are generated from register data, which are either present (affected) or missing (unaffected). The data were analysed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Ethics

The data linking of national registers required for this study was approved by the IRB at Karolinska Institutet, Stockholm. All data were analyzed anonymously; therefore, informed consent for each individual was neither necessary nor possible.

Results

We identified 324 transsexual persons (exposed cohort) who underwent sex reassignment surgery and were assigned a new legal sex between 1973 and 2003. These constituted the sex-reassigned (exposed) group. Fifty-nine percent (N = 191) of sex-reassigned persons were male-to-females and 41% (N = 133) female-to-males, yielding a sex ratio of 1.4:1 (Table 1).

The average follow-up time for all-cause mortality was 11.4 (median 9.1) years. The average follow-up time for the risk of being hospitalized for any psychiatric disorder was 10.4 (median 8.1).

Characteristics prior to sex reassignment

Table 1 displays demographic characteristics of sex-reassigned and control persons prior to study entry (sex reassignment). There were no substantial differences between female-to-males and male-to-females regarding measured baseline characteristics. Immigrant status was twice as common among transsexual individuals compared to controls, living in an urban area somewhat more common, and higher education about equally prevalent. Transsexual individuals had been hospitalized for psychiatric morbidity other than gender identity disorder prior to sex reassignment about four times more often than controls. To adjust for these baseline discrepancies, hazard ratios adjusted for immigrant status and psychiatric morbidity prior to baseline are presented for all outcomes [aHRs].

Mortality

Table 2 describes the risks for selected outcomes during follow-up among sex-reassigned persons, compared to same-age controls of the same birth sex. Sex-reassigned transsexual persons of both genders had approximately a three times higher risk of all-cause mortality than controls, also after adjustment for covariates. Table 2

Table 1. Baseline characteristics among sex-reassigned subjects in Sweden (N = 324) and population controls matched for birth year and sex.

Characteristic at baseline	Sex-reassigned subjects (N = 324)	Birth-sex matched controls (N = 3,240)	Final-sex matched controls (N = 3,240)
Gender			
Female at birth, male after sex change	133 (41%)	1,330 (41%)	1,330 (41%)
Male at birth, female after sex change	191 (59%)	1,910 (59%)	1,910 (59%)
Average age at study entry [years] (SD, min-max)			
Female at birth, male after sex change	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)	33.3 (8.7, 20–62)
Male at birth, female after sex change	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)	36.3 (10.1, 21–69)
Both genders	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)	35.1 (9.7, 20–69)
Immigrant status			
Female at birth, male after sex change	28 (21%)	118 (9%)	100 (8%)
Male at birth, female after sex change	42 (22%)	176 (9%)	164 (9%)
Both genders	70 (22%)	294 (9%)	264 (8%)
Less than 10 years of schooling prior to entry vs. 10 years or more			
Females at birth, males after sex change	49 (44%); 62 (56%)	414 (37%); 714 (63%)	407 (36%); 713 (64%)
Males at birth, females after sex change	61 (41%); 89 (59%)	665 (40%); 1,011 (60%)	595 (35%); 1,091 (65%)
All individuals with data	110 (42%); 151 (58%)	1,079 (38%); 1,725 (62%)	1,002 (36%); 1,804 (64%)
Psychiatric morbidity* prior to study entry			
Female at birth, male after sex change	22 (17%)	47 (4%)	42 (3%)
Male at birth, female after sex change	36 (19%)	76 (4%)	72 (4%)
Both genders	58 (18%)	123 (4%)	114 (4%)
Rural [vs. urban] living area prior to entry			
Female at birth, male after sex change	13 (10%)	180 (14%)	195 (15%)
Male at birth, female after sex change	20 (10%)	319 (17%)	272 (14%)
Both genders	33 (10%)	499 (15%)	467 (14%)

Note:
*Hospitalizations for gender identity disorder were not included.
doi:10.1371/journal.pone.0016885.t001

Table 2. Risk of various outcomes among sex-reassigned subjects in Sweden (N = 324) compared to population controls matched for birth year and birth sex.

	Number of events cases/ controls 1973–2003	Outcome incidence rate per 1000 person-years 1973–2003 (95% CI)		Crude hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–2003	Adjusted* hazard ratio (95% CI) 1973–1988	Adjusted* hazard ratio (95% CI) 1989–2003
		Cases	Controls				
Any death	27/99	7.3 (5.0–10.6)	2.5 (2.0–3.0)	2.9 (1.9–4.5)	2.8 (1.8–4.3)	3.1 (1.9–5.0)	1.9 (0.7–5.0)
Death by suicide	10/5	2.7 (1.5–5.0)	0.1 (0.1–0.3)	19.1 (6.5–55.9)	19.1 (5.8–62.9)	N/A	N/A
Death by cardiovascular disease	9/42	2.4 (1.3–4.7)	1.1 (0.8–1.4)	2.6 (1.2–5.4)	2.5 (1.2–5.3)	N/A	N/A
Death by neoplasm	8/38	2.2 (1.1–4.3)	1.0 (0.7–1.3)	2.1 (1.0–4.6)	2.1 (1.0–4.6)	N/A	N/A
Any psychiatric hospitalisation‡	64/173	19.0 (14.8–24.2)	4.2 (3.6–4.9)	4.2 (3.1–5.6)	2.8 (2.0–3.9)	3.0 (1.9–4.6)	2.5 (1.4–4.2)
Substance misuse	22/78	5.9 (3.9–8.9)	1.8 (1.5–2.3)	3.0 (1.9–4.9)	1.7 (1.0–3.1)	N/A	N/A
Suicide attempt	29/44	7.9 (5.5–11.4)	1.0 (0.8–1.4)	7.6 (4.7–12.4)	4.9 (2.9–8.5)	7.9 (4.1–15.3)	2.0 (0.7–5.3)
Any accident	32/233	9.0 (6.3–12.7)	5.7 (5.0–6.5)	1.6 (1.1–2.3)	1.4 (1.0–2.1)	1.6 (1.0–2.5)	1.1 (0.5–2.2)
Any crime	60/350	18.5 (14.3–23.8)	9.0 (8.1–10.0)	1.9 (1.4–2.5)	1.3 (1.0–1.8)	1.6 (1.1–2.4)	0.9 (0.6–1.5)
Violent crime	14/61	3.6 (2.1–6.1)	1.4 (1.1–1.8)	2.7 (1.5–4.9)	1.5 (0.8–3.0)	N/A	N/A

Notes:
*Adjusted for psychiatric morbidity prior to baseline and immigrant status.
‡Hospitalisations for gender identity disorder were excluded.
N/A Not applicable due to sparse data.
doi:10.1371/journal.pone.0016885.t002

separately lists the outcomes depending on when sex reassignment was performed: during the period 1973-1988 or 1989–2003. Even though the overall mortality was increased across both time periods, it did not reach statistical significance for the period 1989–2003. The Kaplan-Meier curve (Figure 1) suggests that survival of transsexual persons started to diverge from that of matched controls after about 10 years of follow-up. The cause-specific mortality from suicide was much higher in sex-reassigned persons, compared to matched controls. Mortality due to cardiovascular disease was moderately increased among the sex-reassigned, whereas the numerically increased risk for malignancies was borderline statistically significant. The malignancies were lung cancer (N = 3), tongue cancer (N = 1), pharyngeal cancer (N = 1), pancreas cancer (N = 1), liver cancer (N = 1), and unknown origin (N = 1).

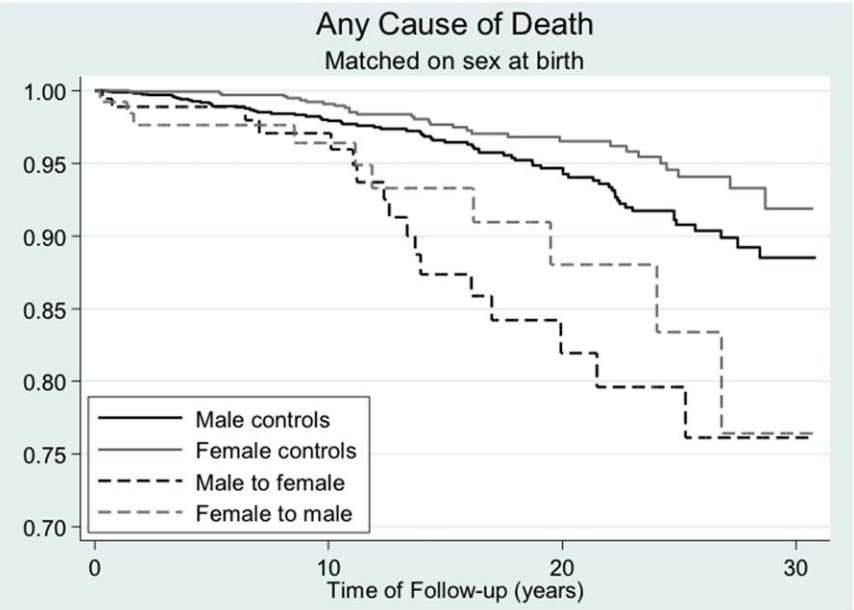


Figure 1. Death from any cause as a function of time after sex reassignment among 324 transsexual persons in Sweden (male-to-female: N = 191, female-to-male: N = 133), and population controls matched on birth year.
doi:10.1371/journal.pone.0016885.g001

Psychiatric morbidity, substance misuse, and accidents

Sex-reassigned persons had a higher risk of inpatient care for a psychiatric disorder other than gender identity disorder than controls matched on birth year and birth sex (Table 2). This held after adjustment for prior psychiatric morbidity, and was true regardless of whether sex reassignment occurred before or after 1989. In line with the increased mortality from suicide, sex-reassigned individuals were also at a higher risk for suicide attempts, though this was not statistically significant for the time period 1989–2003. The risks of being hospitalised for substance misuse or accidents were not significantly increased after adjusting for covariates (Table 2).

Crime rate

Transsexual individuals were at increased risk of being convicted for any crime or violent crime after sex reassignment (Table 2); this was, however, only significant in the group who underwent sex reassignment before 1989.

Gender differences

Comparisons of female-to-males and male-to-females, although hampered by low statistical power and associated wide confidence intervals, suggested mostly similar risks for adverse outcomes (Tables S1 and S2). However, violence against self (suicidal behaviour) and others ([violent] crime) constituted important exceptions. First, male-to-females had significantly increased risks for suicide attempts compared to both female (aHR 9.3; 95% CI 4.4–19.9) and male (aHR 10.4; 95% CI 4.9–22.1) controls. By contrast, female-to-males had significantly increased risk of suicide attempts only compared to male controls (aHR 6.8; 95% CI 2.1–21.6) but not compared to female controls (aHR 1.9; 95% CI 0.7–4.8). This suggests that male-to-females are at higher risk for suicide attempts after sex reassignment, whereas female-to-males maintain a female pattern of suicide attempts after sex reassignment (Tables S1 and S2).

Second, regarding any crime, male-to-females had a significantly increased risk for crime compared to female controls (aHR 6.6; 95% CI 4.1–10.8) but not compared to males (aHR 0.8; 95% CI 0.5–1.2). This indicates that they retained a male pattern regarding criminality. The same was true regarding violent crime. By contrast, female-to-males had higher crime rates than female controls (aHR 4.1; 95% CI 2.5–6.9) but did not differ from male controls. This indicates a shift to a male pattern regarding criminality and that sex reassignment is coupled to increased crime rate in female-to-males. The same was true regarding violent crime.

Discussion

Principal findings and comparison with previous research

We report on the first nationwide population-based, long-term follow-up of sex-reassigned transsexual persons. We compared our cohort with randomly selected population controls matched for age and gender. The most striking result was the high mortality rate in both male-to-females and female-to males, compared to the general population. This contrasts with previous reports (with one exception[8]) that did not find an increased mortality rate after sex reassignment, or only noted an increased risk in certain subgroups.[7,9,10,11] Previous clinical studies might have been biased since people who regard their sex reassignment as a failure are more likely to be lost to follow-up. Likewise, it is cumbersome to track deceased persons in clinical follow-up studies. Hence, population-based register studies like the present are needed to improve representativity.[19,34]

The poorer outcome in the present study might also be explained by longer follow-up period (median >10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards. In accordance, the overall mortality rate was only significantly increased for the group operated before 1989. However, the latter might also be explained by improved health care for transsexual persons during 1990s, along with altered societal attitudes towards persons with different gender expressions.[35]

Mortality due to cardiovascular disease was significantly increased among sex reassigned individuals, albeit these results should be interpreted with caution due to the low number of events. This contrasts, however, a Dutch follow-up study that reported no increased risk for cardiovascular events.[10,11] A recent meta-analysis concluded, however, that data on cardiovascular outcome after cross-sex steroid use are sparse, inconclusive, and of very low quality.[34]

With respect to neoplasms, prolonged hormonal treatment might increase the risk for malignancies,[36] but no previous study has tested this possibility. Our data suggested that the cause-specific risk of death from neoplasms was increased about twice (borderline statistical significance). These malignancies (see Results), however, are unlikely to be related to cross-hormonal treatment.

There might be other explanations to increased cardiovascular death and malignancies. Smoking was in one study reported in almost 50% by the male-to females and almost 20% by female-to-males.[9] It is also possible that transsexual persons avoid the health care system due to a presumed risk of being discriminated.

Mortality from suicide was strikingly high among sex-reassigned persons, also after adjustment for prior psychiatric morbidity. In line with this, sex-reassigned persons were at increased risk for suicide attempts. Previous reports [6,8,10,11] suggest that transsexualism is a strong risk factor for suicide, also after sex reassignment, and our long-term findings support the need for continued psychiatric follow-up for persons at risk to prevent this.

Inpatient care for psychiatric disorders was significantly more common among sex-reassigned persons than among matched controls, both before and after sex reassignment. It is generally accepted that transsexuals have more psychiatric ill-health than the general population prior to the sex reassignment.[18,21,22,33] It should therefore come as no surprise that studies have found high rates of depression,[9] and low quality of life[16,25] also after sex reassignment. Notably, however, in this study the increased risk for psychiatric hospitalisation persisted even after adjusting for psychiatric hospitalisation prior to sex reassignment. This suggests that even though sex reassignment alleviates gender dysphoria, there is a need to identify and treat co-occurring psychiatric morbidity in transsexual persons not only before but also after sex reassignment.

Criminal activity, particularly violent crime, is much more common among men than women in the general population. A previous study of all applications for sex reassignment in Sweden up to 1992 found that 9.7% of male-to-female and 6.1% of female-to-male applicants had been prosecuted for a crime.[33] Crime after sex reassignment, however, has not previously been studied. In this study, male-to-female individuals had a higher risk for criminal convictions compared to female controls but not compared to male controls. This suggests that the sex reassignment procedure neither increased nor decreased the risk for criminal offending in male-to-females. By contrast, female-to-males were at a higher risk for criminal convictions compared to female controls and did not differ from male controls, which suggests increased crime proneness in female-to-males after sex reassignment.

Strengths and limitations of the study

Strengths of this study include nationwide representativity over more than 30 years, extensive follow-up time, and minimal loss to follow-up. Many previous studies suffer from low outcome ascertainment,[6,9,21,29] whereas this study has captured almost the entire population of sex-reassigned transsexual individuals in Sweden from 1973–2003. Moreover, previous outcome studies have mixed pre-operative and post-operative transsexual persons,[22,37] while we included only post-operative transsexual persons that also legally changed sex. Finally, whereas previous studies either lack a control group or use standardised mortality rates or standardised incidence rates as comparisons,[9,10,11] we selected random population controls matched by birth year, and either birth or final sex.

Given the nature of sex reassignment, a double blind randomized controlled study of the result after sex reassignment is not feasible. We therefore have to rely on other study designs. For the purpose of evaluating whether sex reassignment is an effective treatment for gender dysphoria, it is reasonable to compare reported gender dysphoria pre and post treatment. Such studies have been conducted either prospectively[7,12] or retrospectively,[5,6,9,22,25,26,29,38] and suggest that sex reassignment of transsexual persons improves quality of life and gender dysphoria. The limitation is of course that the treatment has not been assigned randomly and has not been carried out blindly.

For the purpose of evaluating the safety of sex reassignment in terms of morbidity and mortality, however, it is reasonable to compare sex reassigned persons with matched population controls. The caveat with this design is that transsexual persons before sex reassignment might differ from healthy controls (although this bias can be statistically corrected for by adjusting for baseline differences). It is therefore important to note that the current study is only informative with respect to transsexuals persons health after sex reassignment; no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism. In other words, the results should not be interpreted such as sex reassignment *per se* increases morbidity and mortality. Things might have been even worse without sex reassignment. As an analogy, similar studies have found increased somatic morbidity, suicide rate, and overall mortality for patients treated for bipolar disorder and schizophrenia.[39,40] This is important information, but it does not follow that mood stabilizing treatment or antipsychotic treatment is the culprit.

Other facets to consider are first that this study reflects the outcome of psychiatric and somatic treatment for transsexualism provided in Sweden during the 1970s and 1980s. Since then, treatment has evolved with improved sex reassignment surgery, refined hormonal treatment,[11,41] and more attention to psychosocial care that might have improved the outcome. Second, transsexualism is a rare condition and Sweden is a small country (9.2 million inhabitants in 2008). Hence, despite being based on a comparatively large national cohort and long-term follow-up, the statistical power was limited. Third, regarding psychiatric morbidity after sex reassignment, we assessed inpatient psychiatric care. Since most psychiatric care is provided in outpatient settings (for which no reliable data were available), underestimation of the *absolute* prevalences was inevitable. However, there is no reason to believe that this would change the *relative risks* for psychiatric morbidity unless sex-reassigned transsexual individuals were more likely than matched controls to be admitted to hospital for any given psychiatric condition.

Finally, to estimate start of follow-up, we prioritized using the date of a gender identity disorder diagnosis *after* changed sex status over *before* changed sex status, in order to avoid overestimating person-years at risk after sex-reassignment. This means that adverse outcomes might have been underestimated. However, given that the median time lag between the hospitalization before and after change of sex status was less than a year (see Methods), this maneuver is unlikely to have influenced the results significantly. Moreover, all deaths will be recorded regardless of this exercise and mortality hence correctly estimated.

Conclusion

This study found substantially higher rates of overall mortality, death from cardiovascular disease and suicide, suicide attempts, and psychiatric hospitalisations in sex-reassigned transsexual individuals compared to a healthy control population. This highlights that post surgical transsexuals are a risk group that need long-term psychiatric and somatic follow-up. Even though surgery and hormonal therapy alleviates gender dysphoria, it is apparently not sufficient to remedy the high rates of morbidity and mortality found among transsexual persons. Improved care for the transsexual group after the sex reassignment should therefore be considered.

Supporting Information

Table S1 Risk of various outcomes in sex-reassigned persons in Sweden compared to population controls matched for birth year and *birth sex*.
(DOCX)

Table S2 Risk of various outcomes in sex-reassigned persons in Sweden compared to controls matched for birth year and *final sex*.
(DOCX)

Author Contributions

Conceived and designed the experiments: CD PL AJ NL ML. Performed the experiments: MB AJ. Analyzed the data: CD PL MB AJ NL ML. Contributed reagents/materials/analysis tools: PL NL AJ. Wrote the paper: CD PL MB AJ NL ML.

References

1. World Health Organization (1993) The ICD-10 Classification of Mental and Behavioural Disorders. Diagnostic criteria for research. Geneva: WHO.
2. American Psychiatric Association, ed (1994) Diagnostic and Statistical Manual of Mental Disorders. Washington, DC: APA.
3. Meyer W, Bockting W, Cohen-Kettenis P, Coleman E, DiCeglie D, et al. (2002) The Harry Benjamin International Gender Dysphoria Association's Standards of Care for Gender Identity Disorders, Sixth Version. Journal of Psychology & Human Sexuality 13: 1–30.
4. Cohen-Kettenis PT, Gooren LJG (1999) Transsexualism: A review of etiology, diagnosis and treatment. J Psychosom Res 46: 315–333.
5. Wålinder J, Thuwe I (1975) A social-psychiatric follow-up study of 24 sex-reassigned transsexuals. Göteborg, Sweden: Scandinavian University Books.
6. Eldh J, Berg A, Gustafsson M (1997) Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg 31: 39–45.
7. Johansson A, Sundbom E, Höjerback T, Bodlund O (2010) A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav 39: 1429–1437.
8. Sørensen T, Hertoft P (1982) Male and female transsexualism: the Danish experience with 37 patients. ArchSex Behav 11: 133–155.
9. De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, et al. (2005) Sexual and physical health after sex reassignment surgery. Arch Sex Behav 34: 679–690.
10. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ (1997) Mortality and morbidity in transsexual subjects treated with cross-sex hormones. Clin Endocrinol Oxf 47: 337–342.

11. Gooren LJ, Giltay EJ, Bunck MC (2008) Long-term treatment of transsexuals with cross-sex hormones: extensive personal experience. J Clin Endocrinol Metab 93: 19–25.
12. Smith YL, van Goozen SH, Cohen-Kettenis PT (2001) Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. J Am Acad Child Adolesc Psychiatry 40: 472–481.
13. Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT (2005) Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med 35: 89–99.
14. Leavitt F, Berger JC, Hoeppner JA, Northrop G (1980) Presurgical adjustment in male transsexuals with and without hormonal treatment. J Nerv Ment Dis 168: 693–697.
15. Cohen Kettenis PT, van Goozen SH (1997) Sex reassignment of adolescent transsexuals: a follow-up study. J Am Acad Child Adolesc Psychiatry 36: 263–271.
16. Newfield E, Hart S, Dibble S, Kohler L (2006) Female-to-male transgender quality of life. Qual Life Res 15: 1447–1457.
17. Landén M, Wålinder J, Hambert G, Lundström B (1998) Factors predictive of regret in sex reassignment. Acta Psychiatrica Scandinavica 97: 284–289.
18. Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A (2005) Psychiatric comorbidity in gender identity disorder. J Psychosom Res 58: 259–261.
19. Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, et al. (2010) Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 72: 214–231.
20. Landén M, Wålinder J, Lundström B (1996) Incidence and sex ratio of transsexualism in Sweden. Acta Psychiatrica Scandinavica 93: 261–263.
21. Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, et al. (2006) Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. Arch Sex Behav 35: 711–715.
22. Bodlund O, Kullgren G (1996) Transsexualism-General outcome and prognostic factors. A five year follow-up study of 19 transsexuals in the process of changing sex. Arch Sex Behav 25: 303–316.
23. Lindemalm G, Körlin D, Uddenberg N (1986) Long-term follow-up of "sex change" in 13 male-to-female transsexuals. Arch Sex Behav 15: 187–210.
24. Rauchfleisch U, Barth D, Battegay R (1998) [Results of long-term follow-up of transsexual patients]. Nervenarzt 69: 799–805.
25. Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller MD, et al. (2009) Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril 92: 1685–1689 e1683.
26. Zimmermann A, Zimmer R, Kovacs L, Einodshofer S, Herschbach P, et al. (2006) [Transsexuals' life satisfaction after gender transformation operations]. Chirurg 77: 432–438.
27. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to- female transsexual patients. Arch Sex Behav 28: 71–89.
28. Hepp U, Klaghofer R, Burkhard-Kubler R, Buddeberg C (2002) [Treatment follow-up of transsexual patients. A catamnestic study]. Nervenarzt 73: 283–288.
29. Lawrence AA (2003) Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. Arch Sex Behav 32: 299–315.
30. Kaube H, Biemer E (1991) [Results of sex change operations in 30 transsexual patients: psychosocial and sexual adaptation–surgical complications]. Handchir Mikrochir Plast Chir 23: 276–278.
31. Dolmén L (2001) Brottsligheten i olika länder (Criminality in different countries). Stockholm: Brottsförebyggande rådet (the Swedish National Council for Crime Prevention).
32. Fazel S, Grann M (2006) The population impact of severe mental illness on violent crime. Am J Psychiatry 163: 1397–1403.
33. Landén M, Wålinder J, Lundström B (1998) Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatrica Scandinavica 97: 189–194.
34. Elamin MB, Garcia MZ, Murad MH, Erwin PJ, Montori VM (2010) Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. Clin Endocrinol (Oxf) 72: 1–10.
35. Landén M, Innala S (2000) Attitudes toward transsexualism in a Swedish national survey. Archives of Sexual Behavior 29: 375–388.
36. Mueller A, Gooren L (2008) Hormone-related tumors in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol 159: 197–202.
37. Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L (2009) Transsexualism in Serbia: a twenty-year follow-up study. J Sex Med 6: 1018–1023.
38. Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A (1999) The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. Arch Sex Behav 28: 71–89.
39. Ösby U, Brandt L, Correia N, Ekbom A, Sparén P (2001) Excess mortality in bipolar and unipolar disorder in Sweden. Arch Gen Psychiatry 58: 844–850.
40. Tidemalm D, Langstrom N, Lichtenstein P, Runeson B (2008) Risk of suicide after suicide attempt according to coexisting psychiatric disorder: Swedish cohort study with long term follow-up. Bmj 337: a2205.
41. Toorians AW, Thomassen MC, Zweegman S, Magdeleyns EJ, Tans G, et al. (2003) Venous thrombosis and changes of hemostatic variables during cross-sex hormone treatment in transsexual people. J Clin Endocrinol Metab 88: 5723–5729.

EXHIBIT 7

Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study

Richard Bränström, Ph.D., John E. Pachankis, Ph.D.

Objective: Despite professional recommendations to consider gender-affirming hormone and surgical interventions for transgender individuals experiencing gender incongruence, the long-term effect of such interventions on mental health is largely unknown. The aim of this study was to ascertain the prevalence of mood and anxiety disorder health care visits and antidepressant and anxiolytic prescriptions in 2015 as a function of gender incongruence diagnosis and gender-affirming hormone and surgical treatment in the entire Swedish population.

Methods: This study used the Swedish Total Population Register (N=9,747,324), linked to the National Patient Register and the Prescribed Drug Register. Among individuals who received a diagnosis of gender incongruence (i.e., transsexualism or gender identity disorder) between 2005 and 2015 (N=2,679), mental health treatment in 2015 was examined as a function of length of time since gender-affirming hormone and surgical treatment. Outcome measures were mood and anxiety disorder health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after a suicide attempt.

Results: Compared with the general population, individuals with a gender incongruence diagnosis were about six times as likely to have had a mood and anxiety disorder health care visit, more than three times as likely to have received prescriptions for antidepressants and anxiolytics, and more than six times as likely to have been hospitalized after a suicide attempt. Years since initiating hormone treatment was not significantly related to likelihood of mental health treatment (adjusted odds ratio=1.01, 95% CI=0.98, 1.03). However, increased time since last gender-affirming surgery was associated with reduced mental health treatment (adjusted odds ratio=0.92, 95% CI=0.87, 0.98).

Conclusions: In this first total population study of transgender individuals with a gender incongruence diagnosis, 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.

Am J Psychiatry 2020; 177:727–734; doi: 10.1176/appi.ajp.2019.19010080

Numerous studies indicate that transgender individuals—that is, individuals who experience incongruity between their sex assigned at birth and their current gender identity—are at particular risk of psychological distress and associated impairment (e.g., suicidality) (1–3). This elevated risk is hypothesized to stem at least in part from transgender individuals' elevated exposure to stigma-related stress, also known as minority stress (4, 5), and it can also result from the stress associated with a lack of gender affirmation (i.e., the accurate recognition and validation of one's gender identity) (6). ICD-11 (7) specifies that individuals experiencing persistent discordance between their experienced gender and their assigned sex meet diagnostic criteria for gender incongruence.

To alleviate the stress of persistent discordance between experienced gender and assigned sex, an increasing number of transgender individuals who experience gender incongruence seek gender-affirming medical interventions, including hormone replacement therapy and gender-affirming surgeries (8). The World Professional Association for Transgender Health's *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People* recommends consideration of these interventions for affirming transgender individuals' gender and alleviating gender-related stress (9).

Despite professional recommendations to consider gender-affirming medical interventions for transgender individuals who experience gender incongruence, the effect of such interventions on long-term mental health is largely unknown. Available evidence stems mainly from small samples utilizing cross-sectional designs and self-reported treatment exposures and mental health outcomes (2, 10, 11). A meta-analysis

See related feature: **Editorial** *by Dr. Mueller (p. 657)*

that aggregated data across nearly two dozen small-sample studies (10), mostly relying on cross-sectional designs, found positive associations between self-reports of receiving both hormone therapy and gender-affirming surgery and mental health. Several more recent uncontrolled studies of the effects of hormone replacement therapy on transgender individuals' mental health have found that transgender individuals' mental health improved for up to 24 months after initiating hormone therapy (11, 12).

Because of previous studies' limitations, including short assessment periods and the fact that existing probability-based surveys do not routinely assess transgender status or other aspects of gender diversity, insufficient evidence exists regarding associations between length of time since receiving gender-affirming interventions and treatment for psychiatric disorders among the transgender population. In fact, no probability-based evidence exists regarding even the prevalence of mood and anxiety disorder treatment among transgender individuals compared with the general population (1).

The limitations of previous research in terms of nonrepresentative sampling, self-reported measurement, and limited follow-up periods can be overcome with national health registry data sets that include clinician-derived assessment of gender incongruence and complete records of psychiatric and gender-affirming treatment and utilization data in an entire population. In the one known study to use a population-based design to investigate psychiatric morbidity among transgender individuals (N=324), individuals who had legally changed their gender and had a diagnosis of gender incongruence associated with an inpatient hospital visit in Sweden between 1973 and 2003 were at higher risk of suicide attempts, suicide-related mortality, and psychiatric hospitalization compared with age- and reassigned-gender-matched controls (13). The study did not report the prevalence of mood and anxiety disorder treatment among those receiving gender-affirming treatment compared with the total population or as a function of length of time since receiving gender-affirming treatment. Furthermore, the proportion of individuals receiving gender-affirming treatments in Sweden has increased nearly exponentially since 2003 (8, 14). Similar recent increases in referrals for gender-affirming treatments have been reported in other countries around the world (15–18).

In this study, we took advantage of the Swedish Total Population Register (19), linked to the Swedish National Patient Register and the Swedish Prescribed Drug Register, to ascertain the prevalence of mood and anxiety disorder health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after a suicide attempt among the entire Swedish population as a function of gender incongruence diagnosis, gender-affirming hormone and surgery utilization, and length of time since receiving gender-affirming treatments. This data set permitted identification of all individuals in Sweden seeking gender-affirming treatments between January 1, 2005, and December 31, 2015. Although not all transgender individuals seek gender-affirming treatments and not all treatment-seeking transgender individuals meet diagnostic criteria for gender incongruence, findings from this unique data opportunity have timely implications for documenting the mental health of transgender individuals seeking gender-affirmative treatment and ways in which the medical profession can support this increasingly visible population.

METHODS

This total population prospective study included all individuals living in Sweden on December 31, 2014, as identified in the Swedish Total Population Register. Using de-identified personal identification numbers (a unique number assigned to all Swedish residents), we linked sociodemographic information with National Patient Register information on health care usage between January 1, 2005, and December 31, 2015, and Prescribed Drug Register information on prescribed and purchased medication between July 1, 2005, and December 31, 2015. The study was approved by the Regional Ethics Committee in Stockholm (no. 2017/1736–31).

Gender Incongruence Diagnosis

Using the Swedish National Patient Register, we classified all individuals in Sweden according to whether they had received a diagnosis of gender incongruence, as defined by the diagnostic system applied in Sweden during the study period (i.e., a diagnosis of either transsexualism [ICD-10 code F64.0] or gender identity disorder [ICD-10 codes F64.8, F64.9]) during an inpatient or specialized outpatient visit between January 1, 2005, and December 31, 2015. The two diagnoses used to define gender incongruence at the time of the study are not fully equivalent but capture largely overlapping populations (20). In Sweden during the study period, a diagnosis of either transsexualism or gender identity disorder was required for accessing gender-affirming treatment (e.g., gender-affirming hormone treatment, hormone-suppressing or -blocking medication treatment, mastectomy with chest contouring, hair removal, vocal cord surgery, speech therapy, genital surgery) and was given after an approximately yearlong evaluation, following a national consensus program (14, 21). Adolescents could receive the same gender-affirming treatments as adults but could not receive genital surgery before age 18 (22).

Outcome Measures

This study's outcome measures were psychiatric outpatient health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after a suicide attempt between January 1, 2015, and December 31, 2015. Restricting the outcome assessment period to one year, 2015, the most recent available, removes potential confounding by secular trends in treatment utilization and transgender acceptance and visibility. Each psychiatric outpatient visit was coded by the treating physician with a primary diagnosis from ICD-10 (23)

and up to 20 supplementary ICD-10 diagnostic codes. Using these codes, we classified all individuals as having received treatment for any or no mood disorders (codes F30–F39) or anxiety disorders (codes F40–F42). Prescribed medication use was obtained from the Swedish Prescribed Drug Register, which contains information regarding all prescribed and purchased medications nationwide for all individuals. Individuals were categorized into any use or no use of antidepressant and anxiolytic medication according to the Anatomical Therapeutic Chemical (ATC) Classification system (codes N06A and N05B). All inpatient health care visits were similarly coded by the treating physician using ICD-10, indicating a primary cause of hospitalization and up to 30 supplementary causes. Using these codes, we classified all individuals as having been hospitalized after a suicide attempt (versus not) using the ICD-10 codes for intentional self-harm (codes X60–X84).

TABLE 1. Demographic characteristics of the Swedish population, by gender incongruence diagnosis, December 31, 2014

Measure	Individuals Diagnosed With Gender Incongruence (N=2,679)		General Population[a] (N=9,744,645)	
	Mean	SD	Mean	SD
Age (years)	31.5	14.0	40.7	23.8
Mean yearly household income (Swedish kronor, 000s)	298.4	301.0	464.8	800.6
	N	%	N	%
Legal gender				
Male	1,284	47.9	4,870,930	50.0
Female	1,395	52.1	4,873,715	50.0
University education	809	30.2	2,643,505	27.1
Urbanicity				
Larger city	1,102	41.1	3,364,003	34.5
Smaller city	867	32.4	3,238,223	33.2
Rural community	710	26.5	3,142,419	32.2
Country of birth				
Sweden	2,214	82.6	8,141,590	83.5
Other European country	164	6.1	801,227	8.2
Outside of Europe	301	11.2	800,800	8.2
No information about country of birth	0	0.0	1,028	0.01

[a] The N for general population excludes those with a diagnosis of gender incongruence.

Covariates

Sociodemographic information was drawn from the Swedish Total Population Register in December 2014 and included current legal gender, age, country of birth, level of education, urbanicity, and household income.

Gender-Affirming Treatment Utilization

For individuals with a gender incongruence diagnosis at any visit, we assessed the type and year of gender-affirming treatment, both hormone treatment and surgery. Information about hormone treatment, including androgen-suppressing and -blocking medication, was obtained from the Swedish Prescribed Drug Register between July 1, 2005, and December 31, 2015. All medications prescribed to individuals who had received a gender incongruence diagnosis were coded as gender-affirming if they were feminizing hormone medication (i.e., estrogens [ATC codes G03C, L02AA], progestogen [G03D]), masculinizing hormone medication (i.e., androgens [G03B]), or androgen-suppression or -blocking medication (i.e., testosterone-5-alpha reductase inhibitors [G04CB], antiandrogens [G03H], gonadotropin-releasing hormone analogues [G03GA, L02AE, H01CA], antigonadotropin-releasing hormones [H01CC], and spironolactone [C03DA01]). For each individual with a gender incongruence diagnosis who received prescriptions for any of these medications, we calculated the number of years since initiation.

Gender-affirming surgery was coded using information about all inpatient surgical procedures received by individuals with a gender incongruence diagnosis in the National Patient Register between January 1, 2005, and December 31, 2015. All surgical procedures associated with a gender incongruence diagnosis performed during this period were coded by type of surgery using the Nordic Medico-Statistical Committee Classification of Surgical Procedures (16): breast or dermatological chest surgery (codes H and QB), surgery of the reproductive organs (codes K and L), dermatological surgery (code Q), and laryngeal surgery (code DQ).

Statistical Analysis

We first examined sociodemographic differences between individuals with a gender incongruence diagnosis and the rest of the population in Sweden. We then compared the prevalence of any mood and anxiety disorder treatments (i.e., psychiatric outpatient health care visits and prescribed psychiatric medication) between individuals receiving gender-affirming treatments and the rest of the population in Sweden during 2015, using logistic regression. Among individuals with a gender incongruence diagnosis, we then investigated the odds of mood and anxiety disorder treatment and hospitalization following a suicide attempt (occurring in 2015) as a function of years since initiation of hormone or hormone-suppressing treatment and since last gender-affirming surgery. We examined years since *last* gender-affirming surgery because gender-affirming surgery is often a lengthy process involving several distinct procedures before gender affirmation is attained.

All analyses were conducted using SPSS, version 24 (IBM, Armonk, N.Y.), and adjusted for current legal gender, age, country of birth, level of education, urbanicity, and household income.

TABLE 2. Association between gender incongruence diagnosis and mood- and anxiety-related health care visits, antidepressant and anxiolytic prescriptions, and hospitalization after suicide attempt in the total Swedish population, 2015[a]

	Individuals Diagnosed With Gender Incongruence (N=2,679)		General Population[b] (N=9,744,645)		Unadjusted		Adjusted	
Measure	N	%	N	%	Odds Ratio	95% CI	Odds Ratio	95% CI
Psychiatric outpatient visits, 2015								
Any mood disorder	250	9.3	95,137	1.0	10.44	9.16, 11.89	6.07	5.32, 6.93
Any anxiety disorder	197	7.4	63,200	0.6	12.16	10.52, 14.06	5.92	5.10, 6.86
Prescribed medication treatment, 2015								
Any antidepressant use	771	28.8	377,043	9.4	3.90	3.58, 4.24	3.95	3.62, 4.31
Any anxiolytic treatment	449	16.8	566,678	5.8	3.26	2.95, 3.61	3.43	3.09, 3.81
Inpatient visits, 2015								
Hospitalization after suicide attempt	22	0.8	7,104	0.1	11.35	7.46, 17.28	6.79	4.45, 10.35

[a] All analyses were conducted using logistic regression and adjusted for age, gender, education, income, urbanity, and country of birth.
[b] The N for general population excludes those with a diagnosis of gender incongruence.

RESULTS

Of the total Swedish population on December 31, 2014 (N=9,747,324), 2,679 had received a diagnosis of gender incongruence between January 1, 2005, and December 31, 2015 (Table 1). Those diagnosed with gender incongruence were significantly younger on average than the rest of the population (t=19.94, $p<0.001$), and they were more likely to have a current legal female gender than male gender (χ^2=4.54, p=0.03). Individuals with a gender incongruence diagnosis were more likely to have a university education (χ^2=12.77, $p<0.001$), to have a lower household income (t=30.61, $p<0.001$), to live in a larger city (χ^2=61.95, $p<0.001$), and to have been born outside of Europe (χ^2=32.33, $p<0.001$).

Mood and Anxiety Disorder Treatment Among Individuals Diagnosed With Gender Incongruence

Table 2 compares the prevalence of health care visits and medication treatment for mood and anxiety disorders between individuals diagnosed with gender incongruence and those not. In analyses adjusted for sociodemographic factors, those diagnosed with gender incongruence were about six times as likely to have had a health care visit due to a mood or anxiety disorder in 2015, more than three times as likely to have received prescriptions for antidepressant and anxiolytic medication in 2015, and more than six times as likely to have been hospitalized after a suicide attempt.

Gender-Affirming Treatments Among Individuals Diagnosed With Gender Incongruence

Just over 70% of individuals diagnosed with gender incongruence during the follow-up period (2005–2015) had received prescriptions for hormone treatment, including androgen-suppressing and -blocking medication, during this period. Half of those treated with hormones had initiated their hormone treatment within the past 5 years (Table 3).

Nearly 40% of those with a diagnosis of gender incongruence had received gender-affirming surgical treatments during the follow-up period. Table 3 presents the types of surgical treatments and the distribution of individuals by number of years since last gender-affirming surgery. The most common types of surgical procedures were mastectomy with chest contouring, surgery of the reproductive organs, dermatological surgeries, and laryngeal surgery.

Less than a third (29%) of those diagnosed with gender incongruence had received neither hormone treatment nor gender-affirming surgery. Among those who had received gender-affirming surgery, 97% had also been treated with hormones.

Changes in Likelihood of Mood and Anxiety Disorder Treatment After Gender-Affirming Hormone and Surgical Treatment

We examined the effect of years since hormone treatment initiation and years since last gender-affirming surgery on likelihood of having received mood or anxiety disorder treatment in 2015 among individuals with a diagnosis of gender incongruence. Among those with a gender incongruence diagnosis receiving hormone treatment, years since initiation of hormone treatment was not significantly related to likelihood of mental health treatment (i.e., psychiatric outpatient health care visits and prescribed psychiatric medication; adjusted odds ratio=1.01, 95% CI=0.98, 1.03). However, among those receiving gender-affirming surgical treatment, the risk of mental health treatment was significantly reduced with increased time since last surgical treatment (adjusted odds ratio=0.92, 95% CI=0.87, 0.97). Specifically, the likelihood of being treated for a mood or anxiety disorder was reduced by 8% for each year since last gender-affirming surgery. The number of individuals with a gender incongruence diagnosis who had been hospitalized after a suicide attempt in 2015 was low (N=22) but was also

reduced as a function of time since last surgical treatment. The association between time since gender-affirming hormone and surgical treatments and hospitalization after a suicide attempt did not reach significance (hormone treatment: adjusted odds ratio=1.12, 95% CI=0.97, 1.30; surgical treatment: adjusted odds ratio=0.87, 95% CI=0.61, 1.24). Figure 1 presents the prevalence of mental health treatment (either health care visits for depression and anxiety, antidepressant and anxiolytic prescriptions, or both) and hospitalization after a suicide attempt in 2015 by years since last gender-affirming surgical treatment.

To assess the potentially interrelated and therefore confounding effect of gender-affirming hormone and surgical treatments on each other, a sensitivity analyses was conducted, entering both years since initiation of hormone treatment and years since last surgical treatment simultaneously into the same model predicting odds of mood and anxiety disorder treatment (i.e., psychiatric outpatient health care visits and prescribed psychiatric medication). The results of this analysis were similar to those presented above, with a nonsignificant effect of time since initiation of hormone treatment (adjusted odds ratio=1.03, 95% CI=0.97, 1.08) and a significant effect of years since last gender-affirming surgical treatment (adjusted odds ratio=0.91, 95% CI=0.86, 0.97).

TABLE 3. Type of, and years since, gender-affirming hormone and surgery treatment in December 31, 2015, among individuals with a gender incongruence diagnosis in Sweden, January 1, 2005, to December 31, 2015

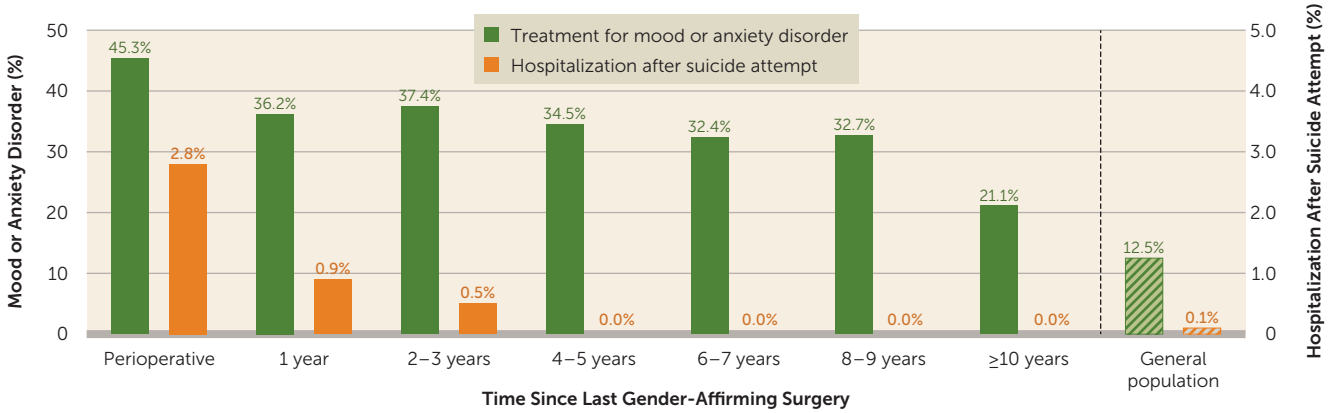
Measure	N	%
Time since first gender-affirming hormone treatment	Individuals with gender incongruence diagnosis (N=2,679)	
No hormone treatment	794	29.6
<1 year	359	13.4
1 year	226	8.4
2–3 years	367	13.7
4–5 years	330	12.3
6–7 years	176	6.6
8–9 years	193	7.2
≥10 years	234	8.7
Type of hormone treatment (more than one type is possible)	All individuals receiving gender-affirming hormone treatment (N=1,885)	
Estrogen or progesterone	1,066	56.6
Androgen	916	48.6
Androgen-suppressing or -blocking medication	808	42.9
Time since last gender-affirming surgical treatment	All individuals with gender incongruence diagnosis (N=2,679)	
No surgical treatment	1,661	62.0
<1 year	353	13.2
1 year	221	8.2
2–3 years	198	7.4
4–5 years	110	4.1
6–7 years	68	2.5
8–9 years	49	1.8
≥10 years	19	0.7
Type of surgical procedures (more than one type is possible)	All individuals receiving gender-affirming surgical treatment (N=1,018)	
Breast or dermatological chest surgery	788	77.4
Surgery of the reproductive organs	540	53.0
Dermatological surgery	315	30.9
Laryngeal surgery	70	6.9

DISCUSSION

Taking advantage of total population registers containing diagnoses of gender incongruence, gender-related hormone and surgical treatment codes, and mental health treatment utilization, we examined the potential impact of gender-affirming hormone and surgical treatment on later mental health treatment utilization. The results also present the first known population prevalence of mood and anxiety disorder treatment and suicide attempts among transgender individuals compared with the general population. Overall, our results show that transgender individuals, here defined as those with a diagnosis of gender incongruence, are about six times as likely as the general population to have had a health care visit for any mood or anxiety disorder, between three and four times as likely to have received prescriptions for antidepressant or anxiolytic medication, and more than six times as likely to have been hospitalized after a suicide attempt. Time since initiating gender-affirming hormone treatment was not associated with these mental health treatment outcomes, whereas time since receiving gender-affirming surgery was significantly associated with a decrease in mental health treatment.

These findings begin to answer the call for population-based documentation of transgender health (1) and extend earlier evidence of associations between gender-affirming treatment and improved mental health mostly derived from studies utilizing cross-sectional designs or short follow-up periods, self-reported exposures and outcomes, and small nonprobability samples (2, 10, 11). In addition to showing that transgender individuals are more likely to utilize mental health treatments than the general population, the results suggest that gender-affirming treatments may reduce this risk. Specifically, the odds of receiving mental health treatment in 2015 were reduced by 8% for every year since

FIGURE 1. Prevalence of treatment for mood or anxiety disorders (health care visit or antidepressant or anxiolytic prescription) and hospitalization after suicide attempt in 2015 among individuals with a gender incongruence diagnosis, by number of years since last gender-affirming surgery



receiving gender-affirming surgery over the 10-year follow-up period. Despite this linear decrease, even 10 years after receiving such treatments, the prevalence of mental health treatment utilization continued to exceed that of the general Swedish population (24), suggesting the need to address factors in addition to gender-affirming treatment availability that may strengthen transgender individuals' mental health. Such factors may include reductions in structural (e.g., economic inequality), interpersonal (e.g., victimization), and psychosocial (e.g., identity concealment) stressors to which transgender individuals are disproportionately exposed (4, 24). Ensuring access to transgender-affirming mental health care may also further reduce transgender individuals' persistent psychiatric risk (25). Although the prevalence of hospitalization after suicide attempt among those with a gender incongruence diagnosis was too small for statistical testing, the numbers who were treated after a suicide attempt decreased as a function of years since last gender-affirming surgery. Among those who received their last gender-affirming surgery more than 3 years ago, no suicide attempts were registered.

Despite the notable methodological strengths of utilizing data from a total population, the results should be interpreted in light of several limitations. First, the criterion used here to define the transgender population does not capture the full spectrum of those who identify as transgender. We specifically lacked information regarding gender assigned at birth, legal gender change, and gender identity at the time of data collection, preventing subgroup analyses of the transgender population (26). Recent estimates across five countries suggest that between 0.4% and 1.3% of the population may identify as transgender, including gender-nonconforming individuals who do not seek gender-affirming hormone or surgical treatment (18, 27–29). Although the transgender population in the present study is limited to individuals with a diagnosis of gender incongruence, this population is of particular concern to the medical community because of its high likelihood of seeking gender-affirming hormone and surgical treatments. Given the free availability of gender-affirming treatments in Sweden, our approach to ascertaining this particular population is likely highly sensitive. Our approach also did not include a comparison group of individuals who had sought but not yet received gender-affirming treatment. While this population might be able to serve as an important comparison group in future studies, without the ability to distinguish between those who had not received treatment because they are waiting for it and those not seeking it in the first place, the current data structure cannot provide this comparison. Longitudinal designs assessing within-person changes in treatment seeking, treatment receipt, and ultimate mental health outcomes would be essential for tracking mental health before and immediately after treatment. Because our approach could only ascertain suicide attempts among living individuals, longitudinal designs that allow for tracking completed suicide among decedents remains an important future direction.

Second, mental health treatment utilization is an imperfect proxy for mental health itself. Transgender people receiving treatment for gender incongruence are by definition exposed to treatment settings, which may disproportionately expose them to mental health treatment opportunities. Although the Swedish context of universal health care coverage removes financial barriers to treatment seeking, other unmeasured factors, such as general tendency toward treatment seeking or perceived discrimination in treatment settings, may influence the associations examined here. Third, because we derived information about outpatient psychiatric health care visits from national health care databases, we had limited information about the type of mental health treatment patients received, and we could not differentiate among individuals receiving psychotropic medication, psychotherapy, or both. Fourth, this study was conducted in a single high-income national context with legal protections for transgender individuals and universal health coverage, including for gender-affirming treatments. While this context makes the present study possible,

it also may constrain the generalizability of findings to low- and middle-income countries and to countries that lack transgender protections or universal health care coverage.

Overall, this study provides timely support for policies that ensure coverage of gender-affirming treatments. Although gender-affirming treatments are recommended as a medical necessity for appropriately selected individuals experiencing gender incongruence and are a covered health benefit in most developed countries, uncertainty exists, such as in the United States, regarding federal protections of transgender employees from transgender-related exclusions in employee benefits (30). In the context of such uncertainty, some U.S. states deny use of state funds to cover costs for gender-affirming treatments, and the Veterans Health Administration specifically prohibits gender-affirming surgery within Veterans Affairs (VA) facilities or use of VA funding for gender-affirming treatments (31, 32). To the extent that gender-affirmative medical interventions are interpreted as sterilization, many hospitals can refuse to provide such care, citing religious directives (33). Debates regarding the provision of gender-affirming health care are global, and in much of the world, such care is unavailable or largely unaffordable (29). Therefore, in many contexts around the world, lack of coverage for gender-affirming treatments drives the use of non–medically supervised hormones and surgeries, thereby exacerbating physical health risks (34) and the other epidemics disproportionately borne by the global transgender population, including suicide and HIV infection. The longitudinal association found in the present study between gender-affirming surgery and reduced mental health treatment utilization, combined with the physical and mental health risks of surgery denial, supports policies that provide gender-affirming surgeries to transgender individuals who seek such treatments.

ADDENDUM

After this article was published online on October 4, 2019, some letters containing questions on the statistical methodology employed led the *Journal* to seek statistical consultations. The results of these consultations were presented to us and we concurred with many of the points raised. The letters (35-41) and our response to them (42) appear in the Letters to the Editor section of the August 2020 issue of the *Journal*.

AUTHOR AND ARTICLE INFORMATION

Department of Social and Behavioral Sciences, Yale School of Public Health, New Haven, Conn. (Bränström, Pachankis); and the Department of Clinical Neuroscience, Karolinska Institutet, Stockholm (Bränström).

Send correspondence to Dr. Bränström (richard.branstrom@ki.se).

Supported by the Swedish Research Council (no. 2016-01707) and the Swedish Research Council for Health, Working Life, and Welfare (no. 2018-01628).

The authors report no financial relationships with commercial interests.

Received January 25, 2019; revisions received May 7 and June 14, 2019; accepted July 16, 2019; published online Oct. 4, 2019.

REFERENCES

1. Reisner SL, Poteat T, Keatley J, et al: Global health burden and needs of transgender populations: a review. Lancet 2016; 388: 412–436
2. Dhejne C, Van Vlerken R, Heylens G, et al: Mental health and gender dysphoria: a review of the literature. Int Rev Psychiatry 2016; 28: 44–57
3. Connolly MD, Zervos MJ, Barone CJ 2nd, et al: The mental health of transgender youth: advances in understanding. J Adolesc Health 2016; 59:489–495
4. White Hughto JM, Reisner SL, Pachankis JE: Transgender stigma and health: a critical review of stigma determinants, mechanisms, and interventions. Soc Sci Med 2015; 147:222–231
5. Hatzenbuehler ML, Pachankis JE: Stigma and minority stress as social determinants of health among lesbian, gay, bisexual, and transgender youth: research evidence and clinical implications. Pediatr Clin North Am 2016; 63:985–997
6. Sevelius JM: Gender affirmation: a framework for conceptualizing risk behavior among transgender women of color. Sex Roles 2013; 68:675–689
7. World Health Organization: International Classification of Diseases, 11th Revision (ICD-11). Geneva, World Health Organization, 2018
8. Dhejne C, Öberg K, Arver S, et al: An analysis of all applications for sex reassignment surgery in Sweden, 1960–2010: prevalence, incidence, and regrets. Arch Sex Behav 2014; 43:1535–1545
9. Coleman E, Bockting W, Botzer M, et al: Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People, 7th Version. Int J Transgenderism 2012; 13:165–232
10. Murad MH, Elamin MB, Garcia MZ, et al: Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 2010; 72: 214–231
11. White Hughto JM, Reisner SL: A systematic review of the effects of hormone therapy on psychological functioning and quality of life in transgender individuals. Transgend Health 2016; 1:21–31
12. Fisher AD, Castellini G, Ristori J, et al: Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. J Clin Endocrinol Metab 2016; 101: 4260–4269
13. Dhejne C, Lichtenstein P, Boman M, et al: Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011; 6:e16885
14. Swedish National Board of Health and Welfare: Good Care of Adults With Gender Dysphoria. Stockholm, Swedish National Board of Health and Welfare, 2015
15. Torjesen I: Trans health needs more and better services: increasing capacity, expertise, and integration. BMJ 2018; 362:k3371
16. Wood H, Sasaki S, Bradley SJ, et al: Patterns of referral to a gender identity service for children and adolescents (1976–2011): age, sex ratio, and sexual orientation. J Sex Marital Ther 2013; 39:1–6
17. Chen M, Fuqua J, Eugster EA: Characteristics of referrals for gender dysphoria over a 13-year period. J Adolesc Health 2016; 58:369–371
18. Zucker KJ: Epidemiology of gender dysphoria and transgender identity. Sex Health 2017; 14:404–411
19. Ludvigsson JF, Andersson E, Ekbom A, et al: External review and validation of the Swedish national inpatient register. BMC Public Health 2011; 11:450
20. Drescher J: Queer diagnoses revisited: the past and future of homosexuality and gender diagnoses in DSM and ICD. Int Rev Psychiatry 2015; 27:386–395
21. Lundgren TK, Isung J, Rinder J, et al: Moving transgender care forward within public health organizations: inclusion of facial

feminizing surgery in the Swedish National Treatment Recommendations. Arch Sex Behav 2016; 45:1879–1880
22. The Swedish National Board of Health and Welfare: Good Care of Children and Adolescents With Gender Dysphoria. Stockholm, Swedish National Board of Health and Welfare, 2015
23. World Health Organization: International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Geneva, World Health Organization, 1993
24. Sundquist J, Ohlsson H, Sundquist K, et al: Common adult psychiatric disorders in Swedish primary care where most mental health patients are treated. BMC Psychiatry 2017; 17:235
25. Bockting WO, Knudson G, Goldberg JM: Counseling and mental health care for transgender adults and loved ones. Int J Transgenderism 2006; 9:35–82
26. Nieder TO, Herff M, Cerwenka S, et al: Age of onset and sexual orientation in transsexual males and females. J Sex Med 2011; 8:783–791
27. Flores AR, Herman JL, Gates GJ, et al: How many adults identify as transgender in the United States? Los Angeles, Williams Institute, June 2016
28. Collin L, Reisner SL, Tangpricha V, et al: Prevalence of transgender depends on the "case" definition: a systematic review. J Sex Med 2016; 13:613–626
29. Winter S, Diamond M, Green J, et al: Transgender people: health at the margins of society. Lancet 2016; 388:390–400
30. Baker KE: The future of transgender coverage. N Engl J Med 2017; 376:1801–1804
31. Kuzon WM Jr, Sluiter E, Gast KM: Exclusion of medically necessary gender-affirming surgery for America's armed services veterans. AMA J Ethics 2018; 20:403–413
32. Veterans Health Administration: Providing Health Care for Transgender and Intersex Veterans; Directive 1341. Washington, DC, Veterans Health Administration, 2018
33. United States Conference of Catholic Bishops: Ethical and Religious Directives for Catholic Health Care Services, 5th ed. Washington, DC, United States Conference of Catholic Bishops, November 17, 2009
34. Sanchez NF, Sanchez JP, Danoff A: Health care utilization, barriers to care, and hormone usage among male-to-female transgender persons in New York City. Am J Public Health 2009; 99:713–719
35. Anckarsäter H, Gillberg C: Methodological shortcomings undercut statement in support of gender-affirming surgery. Am J Psychiatry 2020; 177:764–765
36. Van Mol A, Laidlaw M, Grossman M, et al: Gender affirmation surgery conclusion lacks evidence. Am J Psychiatry 2020; 177:765–766
37. Curtis D: Study of transgender patients: conclusions are not supported by findings. Am J Psychiatry 2020; 177:766
38. Malone W, Roman S: Calling into question whether gender affirming surgery relieves psychological distress. Am J Psychiatry 2020; 177:766–767
39. Landén M: The effect of gender-affirming treatment on psychiatric morbidity is still undecided. Am J Psychiatry 2020; 177:767–768
40. Wold A: Gender corrective surgery promoting mental health in persons with gender dysphoria not supported by data presented in paper. Am J Psychiatry 2020; 177:768
41. Ring A, Malone M: Confounding effects on mental health observations after sex reassignment surgery. Am J Psychiatry 2020; 177:768–769
42. Bränström R, Pachankis JE: Toward rigorous methodologies for strengthening causal inference in the association between gender-affirming care and transgender individuals' mental health. Am J Psychiatry 2020; 177:769–772

Correction to Bränström and Pachankis

After the article "Reduction in Mental Health Treatment Utilization Among Transgender Individuals After Gender-Affirming Surgeries: A Total Population Study" by Richard Bränström, Ph.D., and John E. Pachankis, Ph.D. (doi: 10.1176/appi.ajp.2019.19010080), was published online on October 4, 2019, some letters containing questions on the statistical methodology employed in the study led the *Journal* to seek statistical consultations. The results of these consultations were presented to the study authors, who concurred with many of the points raised. Upon request, the authors reanalyzed the data to compare outcomes between individuals diagnosed with gender incongruence who had received gender-affirming surgical treatments and those diagnosed with gender incongruence who had not. While this comparison was performed retrospectively and was not part of the original research question given that several other factors may differ between the groups, the results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related health care visits or prescriptions or hospitalizations following suicide attempts in that comparison. Given that the study used neither a prospective cohort design nor a randomized controlled trial design, the conclusion that "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" is too strong. Finally, although the percentage of individuals with a gender incongruence diagnosis who had received gender-affirming surgical treatments during the follow-up period is correctly reported in Table 3 (37.9%), the text incorrectly refers to this percentage as 48%. The article was reposted on August 1, 2020, correcting this percentage and including an addendum referencing the postpublication discussion captured in the Letters to the Editor section of the August 2020 issue of the Journal (1).

1. Kalin NH: Reassessing mental health treatment utilization reduction in transgender individuals after gender-affirming surgeries: a comment by the editor on the process (letter). Am J Psychiatry 2020; 177:765

EXHIBIT 8

TRANS IN AMERICA

Most trans adults say transitioning made them more satisfied with their lives

The Washington Post and KFF surveyed one of the largest randomized samples of U.S. transgender adults to date about their childhoods, feelings and lives

By Casey Parks, Emily Guskin and Scott Clement
March 23, 2023 at 6:00 a.m. EDT

Transgender Americans experience stigma and systemic inequality in many aspects of their lives, including education, work and health-care access, a wide-ranging Washington Post-KFF poll finds.

Many have been harassed or verbally abused. They've been kicked out of their homes, denied health care and accosted in bathrooms. A quarter have been physically attacked, and about 1 in 5 have been fired or lost out on a promotion because of their gender identity. They are more than twice as likely as the population at large to have experienced serious mental health struggles such as depression.

Yet most trans adults say transitioning has made them more satisfied with their lives.

"Living doesn't hurt anymore," said TC Caldwell, a 37-year-old Black nonbinary person from Montgomery, Ala. "It feels good to just breathe and be myself."

How we conducted this survey

The Trans Survey was conducted in English and Spanish from Nov. 10-Dec. 1, 2022, among 515 U.S. adults who identify as trans and 823 cisgender U.S. adults. Sampling, data collection, weighting and tabulation were managed by SSRS.

Random sampling methods help ensure results are representative of the trans population overall, with respondents reached through probability-based survey panels by Gallup, NORC and SSRS.

The Post-KFF poll is the largest nongovernmental survey of U.S. transgender adults to rely on random sampling methods. More than 500 people who identify as trans answered questions about their childhoods, their feelings and their lives post-transition.

The poll builds on a growing but limited body of research. In 2015, the National Center for Transgender Equality polled 27,715 trans people from the United States and its territories, and the nonprofit is in the middle of analyzing data from a much larger pool of respondents who filled out the volunteer survey last year. That project, along with two federal health surveys and a random-sample poll conducted by the Williams Institute, have offered significant insight into the community, but trans people say additional data is needed.

Josie Caballero, the director of the National Center for Transgender Equality's U.S. Trans Survey and a trans woman herself, said polls like it and the Post-KFF survey "provide critical tools for researchers, policymakers and advocates seeking to better understand the needs of transgender people to find ways to improve their lives."

Other studies have shown that the trans community has grown to an estimated 1.3 million adults, and surveys by the Centers for Disease Control and Prevention find that the trans adult population is younger than the cisgender adult population at large. Most trans adults are younger than 35 years old.

The Post-KFF survey finds that trans adults hold widely different ideas about what it means to transition. While most trans people have socially transitioned, meaning they've changed their clothing, names or pronouns, far fewer have medically transitioned. Less than a third have used hormone treatments or puberty blockers, and about 1 in 6 have undergone gender-affirming surgery or other surgical treatment to change their physical appearance.

A 62 percent majority of trans adults identify as "trans, gender non-conforming" or "trans, non-binary," while 33 percent identify as a "trans man" or "trans woman." Nearly half ask people to refer to them with they/them pronouns, although most say they sometimes use she/her or he/him pronouns.

"I think there's a pushback against this idea that we have to fit in one of those boxes," said Josie Nixon, a 30-year-old nonbinary person who lives in Denver. "There are certainly binary trans men and women who fit well in those boxes and love being there, but I think there is a trend, especially as more young people find themselves, to say, 'These boxes don't do me justice, and they don't represent me in a way that encompasses all of who I am, so I'd rather exist in between or outside those boxes.'"

Childhood

Most trans adults say they knew when they were young that their gender identity was different from the sex they were assigned at birth. About a third (32 percent) say they began to understand their own gender identity when they were 10 or younger, and another third (34 percent) realized it between the ages of 11 and 17.

Alyssa Rogers, a White 26-year-old trans woman who lives in Austin, said she first knew when she was around 5 years old. Her mother had been arrested for drug use, and Rogers was sent to live in an orphanage. While she was there, Rogers tried on a pink princess dress for the first time, and she immediately felt "right."

"It was the first time I got to do something like that," Rogers said. "It was nice. I wanted to share it, but I was scared to because I knew it wouldn't be accepted."

Rogers eventually moved in with her grandparents, and like other trans people in the Post-KFF survey, she struggled with depression and loneliness in her childhood.

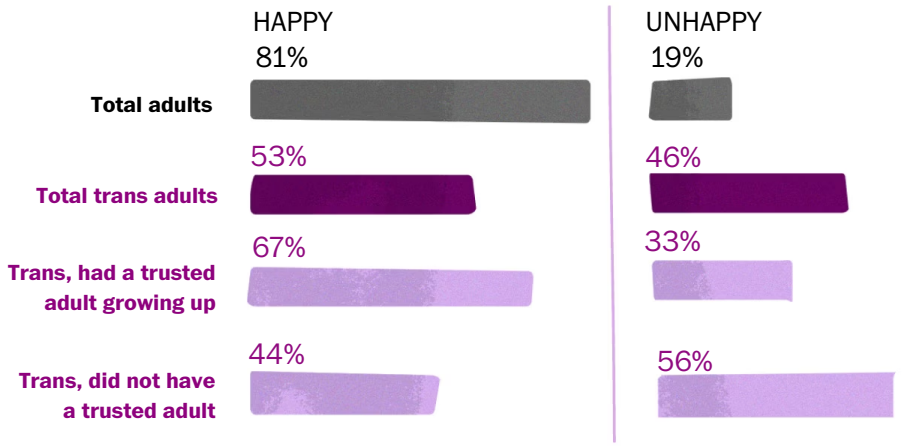
Compared with Americans as a whole, trans adults are more than twice as likely to say they experienced serious mental health problems such as depression or anxiety growing up (78 percent versus 32 percent for the U.S. overall).

Just over half of trans adults say they had a happy childhood (53 percent), but that rate is far lower than the 81 percent of Americans overall who say their childhood was happy.

Most trans people (59 percent) say they lacked a trusted adult to talk to while growing up, including 64 percent of trans people of color. Those who did have a trusted adult were much more likely to report feeling safe in their childhood homes and to have a happy childhood.

School marked one of the greatest stressors for trans children. More than 4 in 10 say they felt unsafe at school, and one-quarter felt unsafe participating in sports or in other youth activities.

Would you describe your childhood as...?



"No opinion" not shown.

Source: Nov. 10-Dec. 1, 2022, Washington Post-KFF poll of 515 U.S. trans adults with an error margin of +/- 7 percentage points and 823 cisgender adults with an error margin of +/- 4 percentage points.

Rogers said she was an "outcast" at school, so few classmates commented when she began cross-dressing as a teenager. But her family grew upset, she said. Rogers said her grandparents committed her to a mental hospital and later sent her to conversion therapy in Colorado. The state has since banned the practice, but Rogers's experience was commonplace. One in 4 trans adults say they attended religious services as a child or teenager that tried to change their sexual orientation or gender identity, and about 1 in 10 say they attended conversion or reparative therapy.

"I definitely thought about killing myself," Rogers said. "I was in a terrible situation."

For years, Rogers went to bed hungry, sometimes out of necessity, and sometimes because she believed if she didn't eat, she wouldn't grow. If she didn't grow, she thought, she could pass more easily as a girl.

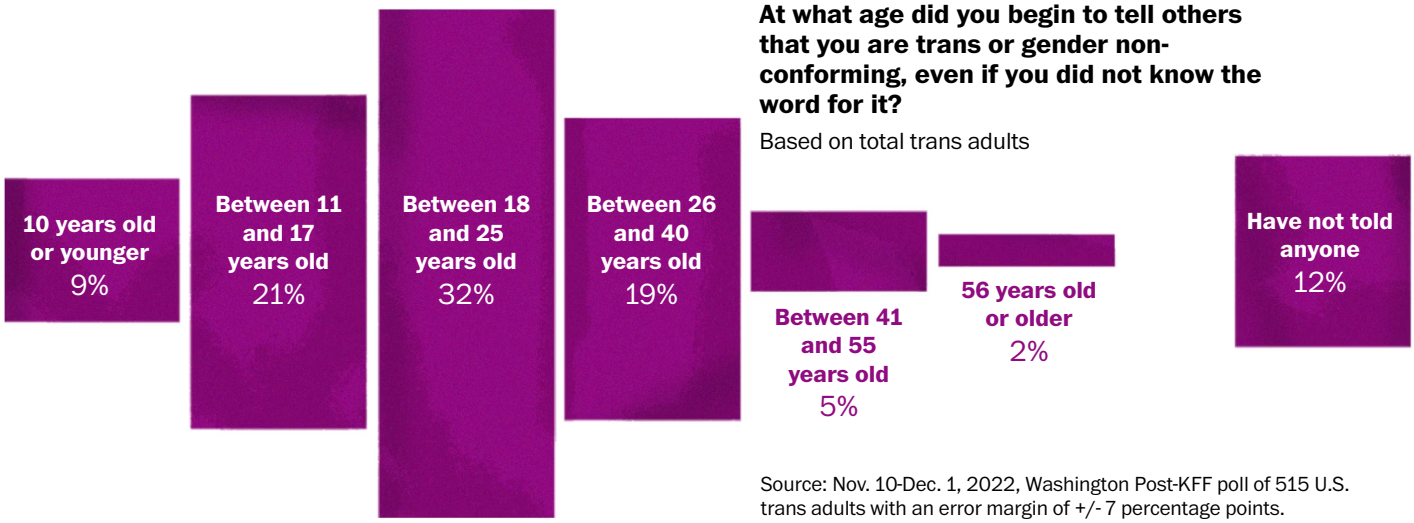
A few years after Rogers went through conversion therapy, she decided to start taking estrogen. She knew many in her family would reject her once she told them she was a woman.

Though 69 percent of trans people who are out to at least some immediate family members say their families are at least "somewhat supportive" of their gender identity, about 3 in 10 say their families are not supportive, including 13 percent who are "very unsupportive." Similarly, 29 percent of trans adults say they experienced homelessness or got kicked out of their home while they were growing up, rising to 38 percent among trans people of color.

"I knew I was going to lose some of my family," Rogers said. "It wasn't a question of if. It was a question of how many."

Transition

Poll data shows that there is no one timeline for trans people. Three in 10 say they began telling others they were trans before the age of 18, while about a third (32 percent) came out between the ages of 18 and 25. Others came out later, and 12 percent of trans adults have not told anyone.



Source: Nov. 10-Dec. 1, 2022, Washington Post-KFF poll of 515 U.S. trans adults with an error margin of +/- 7 percentage points.

For Nixon, the 30-year-old nonbinary person who lives in Denver, the process started six years ago. One night, they cried until they fell asleep, and when they woke up, they brushed their teeth, looked in the mirror and said the word for the first time.

"I just said, 'You're trans,'" Nixon recalled. "Then I crumpled on the floor, crying. I probably cried for like a week."

What a trans person does as part of their transition varies, and increasingly, younger people are opting out of a path from one binary gender to the other. The poll reveals that most adults who identify as trans or transgender prefer the terms "nonbinary" (40 percent) or "gender non-conforming" (22 percent), while 22 percent identify as a "trans woman" and 12 percent identify as a "trans man."

Nixon lived in Grand Rapids, Mich., when they decided to transition. The town felt conservative, and Nixon didn't want to live in a place where everyone knew them as a guy, so they decided to relocate. About one in 4 (27 percent) trans adults say they have moved to a different place because they thought it would be a more accepting location, including larger shares of urban (35 percent) trans adults.

"I literally Googled 'Where do trans people live,'" Nixon said, "And I found Colorado."

Nixon initially moved to Boulder. There, they changed their name, grew out their hair and started taking estrogen.

Currently, how much of the time do you physically present as a gender (such as a man, woman, or nonbinary) that is different from the one assigned to you at birth?

Based on total trans adults

Source: Nov. 10-Dec. 1, 2022, Washington Post-KFF poll of 515 U.S. trans adults with an error margin of +/- 7 percentage points.

Large majorities of trans adults have changed their physical appearance in ways that reflect their gender identity, with 77 percent changing the types of clothes they wear and 76 percent changing their hairstyle or grooming habits. Fewer have used hormone treatments (31 percent), legally changed their names (24 percent), or undergone gender-affirming surgery or other surgical treatments to change their physical appearance (16 percent).

Trans adults who identify as either a "trans man" or a "trans woman" are more than three times as likely as those who identify as nonbinary or gender non-conforming to say they have used hormone treatments (60 percent) or undergone gender-affirming surgery (31 percent).

Though Nixon experienced repeated discrimination, including in Colorado, they soon found themself feeling happy in a way they never had before. They'd always struggled to make friends as a young person, in large part, they think, because they were hiding a huge part of themself, and kids are adept at picking out inauthenticity. As Nixon's hair grew and their body changed, people sometimes harassed them in bathrooms, and a roommate "came out" as transphobic. Still, Nixon felt newly relieved.

"The worst day I've ever had as a trans person is still better than the best days I had pre-transition," Nixon said. "That's not to say that I don't look fondly on the memories of my life, but at the end of the day, not living authentically was terrible, and I would rather live authentically than hide a version of myself to appease people I don't even know."

Among those who present themselves differently from their gender assigned at birth, the Post-KFF poll finds 78 percent say that living as a different gender has made them more satisfied with their lives. More than 4 in 10 say they are "a lot" more satisfied.

Trans people don't always present as a gender other than the one they were assigned at birth.

Three in 10 trans people physically present as a different gender all of the time, while 20 percent do so "most of the time." Another 34 percent present as a different gender some of the time, and a small but significant share (16 percent) say they "never" physically present as a gender different from their sex assigned at birth.

In Colorado, Nixon said they are "visibly trans" every day, but strangers perceive them in different ways.

"When I answer the phone, I get 'Hello, sir' 100 percent of the time," Nixon said. "But when I go to the grocery store, I get 'he,' 'she' and 'they' on a daily basis. I have decided that that's where I want to be. I want to live in this androgynous space."

Hardship

Though 57 percent of trans adults say they are satisfied with their lives as a whole, that rate is lower than the U.S. adult population at large, of whom 73 percent say they are satisfied.

More than half (56 percent) of trans adults say they have felt anxious at least "often" in the past year, compared with 31 percent of cisgender adults. And they are more than twice as likely as cis people to say they felt depressed (48 percent, compared with 21 percent) or lonely (45 percent, compared with 21 percent) in the past year.

Tim McCoy, a White 72-year-old trans man who lives in Syracuse, N.Y., said he has suffered from chronic depression and anxiety since he was young. Those feelings initially dissipated after he began taking testosterone.

"I was floating on a cloud when I first transitioned," he said. "I just thought that was the answer to all my problems. I felt wonderful, but after I had transitioned for about five years, the depression came back. Transitioning has definitely made my quality of life better, but it's not the answer to everything."

That's due, he said, in large part to the discrimination trans people face. That has worsened as the political climate has turned increasingly hostile toward trans people, he said.

"You always have that fear of what's going to happen when you tell somebody you're transgender, especially these days," he said. "That definitely affects one's quality of life. It's a constant stress."

One in 4 trans adults say they have been physically attacked because of their gender identity, gender expression or sexual identity, and more than 6 in 10 (64 percent) say they have been verbally attacked.

Tessa Jelani, a 26-year-old Black trans woman from Washington, D.C., said she was harassed often before she learned the best ways to feminize her appearance.

"At the beginning of my transition, I got hit with a bat upside my head," Jelani said. "I remember him saying, 'I'm not going to hit a woman, but I'll hit you.'"

Trans adults experience discrimination in a range of day-to-day activities, according to the Post-KFF poll. About half (49 percent) say they have been asked unnecessary or invasive questions at their place of work, and 21 percent report being fired or denied a job or promotion because of their gender identity or expression or sexual identity.

Beyond the workplace, 17 percent say their identity has led them to be refused service from a health-care provider. Another 13 percent report being evicted or denied housing, including 21 percent of trans people of color.

Caldwell, the nonbinary person from Montgomery, Ala., said they went in for a coronavirus test and chest X-ray last year, and when the providers discovered Caldwell was trans, the quality of care changed.

"To me, it was a regular routine checkup, but they switched my nurse to a male nurse, and nobody would talk to me," Caldwell said. "It was an all-Black clinic, and it felt defeating to know that even your own people will treat you like 'other.' Looking back, a lot of times, I feel like it's just ignorance. They might have even thought they were helping."

Still, both Caldwell and Jelani said they have found a growing acceptance in recent years. Alabama has passed a string of anti-trans bills, but Caldwell said their fellow Alabamians often surprise them with their support. The first time Caldwell went to pick up their prescription for testosterone, for instance, they felt nervous until they met the pharmacist.

"I was shaking," Caldwell said. "But I had the most affirming pharmacist, a Black lady, who was like, 'Are you okay?' When I told her what was going on, she said, 'Oh, you're going to be great.' And she walked me through how to do the syringe, how to measure out my dosage, the difference between the drawing needle and the injection."

A majority of trans people believe people's perceptions are changing for the better. Fifty-five percent believe people in the United States are more accepting of them than they were 10 years ago, and Jelani thinks that will only improve as more people get to know their trans community members.

"The younger generation is showing how accepting they are," Jelani said. "They are willing to love people's differences, and it's definitely having an effect on the older generation and showing them to loosen up. Not everything has to be explained in order for you to agree with it. We have always been here. We're always going to be here, and y'all can't stop it."

The Washington Post-KFF Survey Project is a partnership combining survey research and reporting to better inform the public. The Trans Survey is the 36th in the series. It was conducted in English and Spanish from Nov. 10-Dec. 1, 2022, among 515 U.S. adults who identify as trans and 823 cisgender U.S. adults. Sampling, data collection, weighting and tabulation were managed by SSRS. Trans adults were reached via three survey panels recruited using random sampling methods: The Gallup Panel, NORC's AmeriSpeak Panel and the SSRS Opinion Panel. Additional trans respondents were recontacted from previous randomized telephone interviews. Random sampling methods help ensure results are representative of the trans population overall. The samples of trans adults were combined and weighted to match the demographics of the national U.S. adult trans population. Cisgender adults were recruited through the SSRS Opinion Panel. Results among the sample of trans adults have a margin of sampling error of plus or minus seven percentage points and the margin of sampling error is plus or minus four percentage points among the sample of cisgender adults. In collaboration with The Post, KFF researchers worked to design the survey sample and questionnaire, analyze and report findings. The project team from KFF included Mollyann Brodie, Ashley Kirzinger, Audrey Kearney, Alex Montero and Grace Sparks.

EXHIBIT 9

National Coverage Analysis (NCA) | Decision Memo

Gender Dysphoria and Gender Reassignment Surgery

CAG-00446N

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will 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. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

Decision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will 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. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Crips Experimental Index
CDC – Centers for Disease Control
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Exerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Korpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King's Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale
SF - Short Form
SMR - Standardized Mortality Ratio SOC – Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire
TSCS - Tennessee Self-Concept Scale
U.S. - United States

VAS - Visual Analog Scale
WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100
WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to- female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action

August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
Under §1861(s) (Definition of Medical and Other Health Services)
Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved and/or cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

(§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer- reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies for gender dysphoria. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person's knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded.

The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early termination, completed, ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. For this final decision, CMS also reviewed all evidence submitted via public comment.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

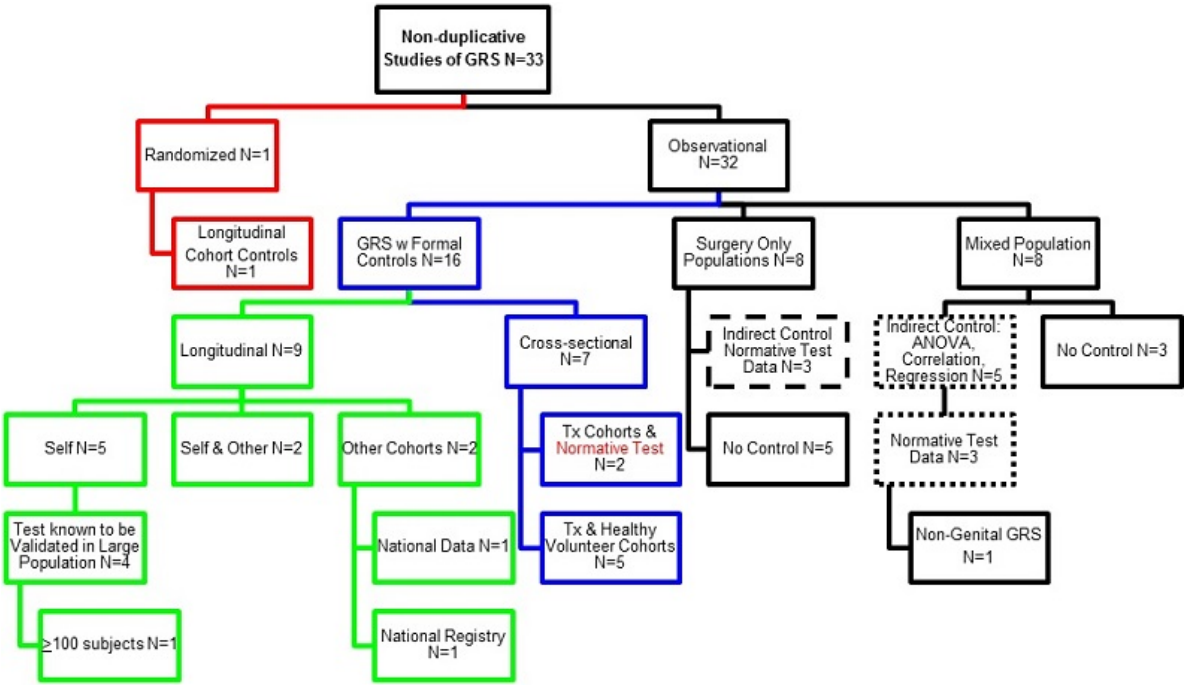
CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)



ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635-42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male- to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value p<0.0001). Later

calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female-to-male and male-to-female patients was 26.1±7.6 (range 16–56) years and 31.4±11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older (p<0.001). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8±6.3 and 19.4±7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male-to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI]) 1.47-1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87-1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients (n=18, SMR 1.64 [95% CI 1.43-1.87]), mean age [range]: 59.7 [42-79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63], p=0.01). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide (n=17, SMR 5.70 [95% CI 4.93-6.54]), AIDS (n=16, SMR 30.20 [95% CI 26.0-34.7]), and illicit drug use (n=5, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was “unknown cause” (n=21, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Overall mortality, and specifically breast cancer and cardiovascular disease, were not increased in the hormone-treated female-to-male patients. Asscheman et al. reported an elevated SMR for illicit drug use (n=1, SMR 25 [6.00-32.5]). This was the cause of one of the 12 deaths in the cohort.

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non-specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1±8.0. HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87±9.15 years (range 15-61). The current age of patients using hormones was 33.6±9.1 years (n=120) and older than the age of patients without hormone treatment (25.9±7.5) (p=0.001). The age at hormone initiation, however, was 24.6±8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone treatment. The mean scores for HAD-Anxiety, HAD- Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2±9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy n=19 (25.7%); mastectomy n=29 (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, n=47 (39.5%), followed by facial feminization, n=11 (9.2%), buttocks feminization, n=9 (7.6%), and vocal feminization (thyroid chondroplasty), n=2 (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: “Environmental” 58.81±14.89 (range 12.50-96.88), “Physical” 63.51±17.79 (range 14.29-100), “Psychological” 56.09+16.27 (range 16.67- 56.09), “Social” 60.35±21.88 (range 8.33-100), and “Global QOL and Health” 55.44+27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23±2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains and the general health and quality- of-life questions. Hormone therapy was an important element for the general questions and for all of the domains except “Environmental.” Having undergone non-genital reassignment surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2±10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre- surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64±5.03; male-to-female: 6.58±4.21) and borderline results for anxiety (female-to-male: 7.09±5.11; male-to-female: 7.74±6.13, where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study using a semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥1 year of real-life experience in preferred gender, and ≥1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre- specified except for GAF, which pre-specified a difference to mean change ≥5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female; ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male- to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) (p<0.01).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to-female patients. A ≥5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=one), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively (p<0.5). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age

and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to- female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Ghent populations studied by Heylens et al. or Weyers et al. is unknown.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross- sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6±10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had "top" surgery and 11 (2.9%) reported having "bottom" surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45±9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50±10) (p=<0.001), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63±12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50±10) (p<0.001), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12±10.2), Role Emotional (42.42±11.6), Social Functioning (43.14±10.9), and Vitality (46.22±9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub- score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22±11.9) than those with "No Testosterone Usage" (36.08±12.6) (p=0.001). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21±11.6) and those without "Top Surgery" (38.01±12.5) (p=0.067). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non- specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically (p=0.01).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 63.2% of female-to-male patients cohabitated with partners of their natal gender; 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; and no male-to-female patients with female partner preference cohabitated with partners of their natal gender.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess at al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44±9 (range 18-70) years and mean duration after surgery was 3±1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. Psychiatry Clin Neurosci. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3±8.9 (range 15-58) years with the time to follow-up being 3.8±1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec; 34(6):515-7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥6 months, and willingness to function in the life of the desired gender for ≥6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4±4.4 (range 14-36) and 27.4 ±4.0; (range 14-36); male-to-female 22.9±4.6 (range 14-36) and 24.7±4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory

adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients (p<0.001). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752-60. Epub 2008 Nov 17.

Weyers at al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient's average age was 43.1 ±10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported "sometimes" regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95±10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46±1.57, desire 3.12+1.47, arousal 2.95±2.17, lubrication 2.39±2.29, orgasm 2.82±2.29, and pain 2.21±2.46. Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx at al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self -designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30±8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ±8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oopherectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metaidoiplasty (n=9; 18.4%), phalloplasty (n=8 after metaidoiplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The "Vitality" and the "Mental Health" scales were lower than the Dutch male population: 62.1±20.7 versus 71.9±18.3 and 72.6±19.2 versus 79.3±16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oopherectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was: 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had

undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96-100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Korpers (FBeK) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0±11.3 years; post-operative 38.2±9.0 years. The mean duration after reassignment surgery was 51±25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0±3.8 versus 5.1±3.7; male-to-female 8.1±4.5 versus 4.7±3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1±2.9 versus 8.9±3.1; male-to-female 7.0±2.9 vs 9.5±2.6.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. Br J Psychiatry. 1988 Apr;152: 550-3.

Mate-Kole at al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to- female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; p=0.002); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49±0.1 SEM) than controls (7.35±0.26 SEM) ($p<0.0001$).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6±2.3 versus 20.9±1.9 ($p<0.0001$), personal limitation:

20.9±1.9 versus 11.6±0.4 (p<0.001), role limitation: 27.8+2.4 versus 34.6+1.7 (p=0.046), and general health: 31.7±2.2 versus 41.0±2.3 (p<0.02). There is a related paper by Kuhn et al. 2006.

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post–surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34±9.5 years and female-to-male 33.3±10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9±7.3 years) and 74 women (31.6±8.2) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post-reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7±1. The Global Assessment of Function was higher (better) in the gender dysphoric groups (78.0±8.9) than in the personality disorder cohort (53.0±9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67±57 and 0.56±0.45. Although they were nominally higher than the healthy normative controls (males: 0.32±0.36 and females 0.41±0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9

(28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50±10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed conditions such as, but not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [CI 5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and much of the Dhejne et al. (2014) population.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with “regret” in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the “regret rate”, was 2.2%. No one who underwent sex-reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med. 2014 Jan;11(1):119-26. Epub 2013 Oct 28.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global "psycho-neuroticism" SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global "psycho-neuroticism" normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3±32.4. The respective scores for the various gender dysphoric cohorts were 157.7±49.8 at initial presentation, 119.7±32.1 after hormone therapy, and 127.9±37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16 (6):511-22.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5±13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7±10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3±9.4 years. The age of the patients who were no longer interested in surgery was 31.8±6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with "distinct difficulties" (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with "few difficulties" (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range "few difficulties" (10-18) for the post-operative patients (13.2) and the patients no

longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between “few difficulties” (10-18) and “distinct difficulties” (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having “distinct difficulties” in psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having “few difficulties” in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not under gone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Related papers include Meyer et al. (1971), Meyer et al. (1974a-d), and Derogatis et al. (1978) along with commentary response by Fleming et al. (1980).

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the

predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ±13.4 months (range 6 months to 4 years). The age was female-to-male 27.8±5.2 (range 23-37) and male-to-female 26.4±7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2±5.78 years (female-to-male) and 52.9±10.82 years (male-to-female). The intervals for follow-up were 14.1±1.97 years and 13.7±2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oopherectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35±0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female- to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the "Interpersonal Sensitivity" scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70±0.67 to 0.26±0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher "Depression" scores for the latter.

Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. The effect size was statistically significant and large only for the "Overly Accommodating" scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64±5.99 to 7.04±4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the "Life Satisfaction" scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43±2.99 to 8.31±2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty-two (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients

who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0±40.7 (scoring range 90 to 450) and normalized after surgery 120.3±31.4. (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33±13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole at al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥2 year desire to change gender, a ≥1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator- designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic rage for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

a. CMS did not request an external technology assessment (TA) on this issue.

b. There were no AHRQ reviews on this topic.

c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

d. There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations Boehmer U. Am J Public Health. 2002; 92: 1125–30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

f. There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1). http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following:
1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document: Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists. Dec 2011, No. 512. Obstet Gyncol. 2011;118:1454-8.

"Questions [on patient visit records] should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RTCs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K.
www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf
Int J Transgend. 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly 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) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

e. American Psychological Association

Suggested citation until formally published in the American Psychologist: American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf*

"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."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and- Transgender-People.aspx

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LBGT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

ClinicalTrials.gov
There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as “clients” instead of “patients,” and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS’ experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results

a. Initial Comment Period: December 3, 2015 – January 2, 2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment

surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LBGT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that coverage is available for gender reassignment surgery when determined reasonable and necessary and not otherwise excluded by any other relevant statutory requirements by the MAC on a case-by-case basis. "The case-by-case model affords more flexibility to consider a particular individual's medical condition than is possible when the agency establishes a generally applicable rule." (78 Fed. Reg. 48165 (August 7, 2013)).

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. In this NCA, we acknowledge that gender dysphoria is a recognized Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statue and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, “We strongly caution against instituting a CED protocol.” Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, “The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment.”

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary’s physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare's reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this determination, local MACs may take into account physician's recommendations, the individual's clinical characteristics, and available clinical evidence relevant to that individual.

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment-related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community's willingness to participate. For this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Comment: One commenter noted that they thought research studies for gender reassignment surgery could not take place when the old NCD that prohibited coverage for gender reassignment surgery was in effect.

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

Response: The Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues.

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Accountable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under commercial insurers. We do not issue coverage decisions to drive policy for other health organizations' coverage in one way or the other.

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

18. Cost Barriers to Care and Effects

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that "[t]he Secretary's decision as to whether a particular medical service is 'reasonable and necessary' and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions." Heckler v. Ringer, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

Thirty-three papers were eligible based on our inclusion/exclusion criteria for the subsequent review (Figure 1). All studies reviewed had potential methodological flaws which we describe below.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se.*

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to “hard” (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, “More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria.” Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

Psychometric Tools

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co-morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

B. Health Disparities

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence 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.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: “Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate

measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We have a received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on 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. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 *Chapter: Psychosexual Disorders*	***Trans-sexualism*** *302.5x [Gender Identity Disorder of Child-hood (302.6)]*	Required A (cross-gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85

DSM III-Revised 1987 *TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence*	***Trans-sexualism*** *(TS) (302.50) [GID of C]*	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1° and 2° sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans-sexual Type • e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood, non-trans-sexual type, added			
DSM IV 1994 *Chapter: Sexual & Gender Identity Disorders*	***Gender Identity Disorder*** in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., Stated desire to be another sex • e.g., Desire to live or be treated as a member of the other sex • e.g., conviction that he/she has the typical feelings and reactions of the other sex • e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. • e.g., belief the he/she was born the wrong sex • e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex • Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions • e.g., stress related cross-dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM IV-Revised 2000 *Chapter: Sexual & Gender Identity Disorders*	***Gender Identity Disorder*** (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification • e.g., stated desire to be the other sex • e.g., desire to live or be treated as the other sex • e.g., conviction that he/she has the typical feelings & reactions of the other sex • e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex • e.g., belief the he/she was born the wrong sex • e.g., preoccupation with getting rid of 1° and 2° sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex conditions • e.g., stress related cross-dressing • e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex

DSM V 2013 *Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders*	*Gender Dysphoria (302.85)*	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	• Marked discordance between natal 1º and 2º sex characteristics* and experienced/expressed gender • Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) • Marked desire to be the other sex (or some alternative gender) • Marked desire to desire be treated as the other sex (or some alternative gender) • Marked desire to be rid of natal 1º and 2º sex characteristics** • Marked desire to acquire 1º and 2º sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2º sex characteristics ** or in young adolescents, prevent the development of the anticipated 2º sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: • Strong desire to be of the other gender or an insistence that one is of another gender. • Strong preference for cross-gender roles in make-believe play. • Strong preference for the toys, games, or activities of the other gender. • Strong preference for playmates of the other gender. • In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing • In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1º=primary 2º=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (→46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS →missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt. Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-

Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, &16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1& 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional Controlled	14 excluded for demographic matching reasons	40	10 (25%)	The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-

Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re-lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employ-ment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender iden-tity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.	119	119 (100%)	Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion

Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (→140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results→103.
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(→193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal No analysis by tx status	The number in the available patient pool was not specified.	1331	1177 (88.4%)	-
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference
B/C=because
BSRI=Bem Sex Role Inventory
F=Female
FP-R=Freiberg Personality Inventory
GD=Gender dysphoria
GID=Gender identity disorder
HADS=Hospital Anxiety & Depression Scale
IPP=Inventory of Interpersonal Problems
M=Male
NA=Not applicable
SCL-90=Symptom Checklist-90
SF-36=Short Form 36

GRS=Sex reassignment surgery
Tx=Treatment
W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery:50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3+8.7 (20–62), M to F 36.3+ 10.1(21–69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian

Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7+4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-

Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M toF; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).	W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio1:1.6.	-
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F toM: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve *Smilkstein*	Published in 1978 Initial data: 152 families in the U.S. A “friends” component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory *Beck, Ward, Mendelson, Mock, & Erbaugh*	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. Itis copyrighted and requires a fee for use
Bem Sex Role Inventory *Bem*	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire *Clement & Lowe*	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale *Lindgren & Pauly (Kuiper, Dutch adaptation 1991)*	1975 Initial data: 16 male and 16 female transsexual patients in Oregon

Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire) *Crown & Crisp*	Developed circa 1966 Manual published 1970 Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey *Anderson, Mikuliç, Vermeylen, Lyly-Yrjanainen, & Zigante,*	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index *Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino Wiegel, Meston, & Rosen*	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Korpers *Strauss*	Published 1996 (German)
Freiberg Personality Inventory *Fahrenberg, Hampel, & Selg*	7th edition published 2001, 8th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" *Smith, van Goozen, Kuiper, & Cohen-Kettenis*	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale *Altstotter-Gleich*	Published 1989 (German)
General Health Questionnaire *Goldberg & Blackwell (initial study)* *Goldberg & Williams (manual)*	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale *Zigmond & Snaith*	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1st 50 compared to 2nd 50.
Inventory of Interpersonal Problems *Horowitz*	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psycho-therapy (Kaiser Permanente-San Francisco) Proprietary test

King's Health Questionnaire *Kelleher, Cardozo, Khullar, & Salvatore*	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory *Hathaway & McKinley Butcher, Dahlstrom, Graham, & Tellegen*	Published in 1941 Updated in 1989 with new, larger, more diverse sample. MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences *Wolfradt*	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" *Cohen-Kettenis & van Goozen*	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale *Rosenberg*	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 *RAND* *Ware & Sherbourne1992* *McHorney, Ware, & Raczek 1993*	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale *Watson & Friend*	Initial publication in1969 Requires permission for use
Social Support Scale *Van Tilburg 1988*	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire *Spielberger, Gorsuch, Lushene, Vagg, & Jacobs*	Current format published in 1983 Proprietary test

Symptom Checklist-90 *Derogatis, Lipman, Covi* *Derogatis & Cleary*	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale *Fitts & Warren*	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other innformation available. Requires qualification for use
Utrecht Gender Dysphoria Scale *Cohen-Kettenis & van Goozen*	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)
WHO-Quality of Life (abbreviated version) *Harper for WHO group*	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse

Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS,STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Sub-stantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Sub-stantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscheman et al.	Yes	-	-	-	Demographic	Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)

Motmans et al.	-	SF36 EQOLS (2nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript

** From medical charts & verdicts ?=Possibly self-designed

AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)

APGAR=Family Adaptability, Partnership growth, Affection, and Resolve

BDI=Beck Depression Inventory

BIQ=Body Image Questionnaire

BIS=Body Image Scale

BSRI=Bem Sex Role Inventory

CCEI=Crown Crisp Experiential Index

Cohen-Kettenis'= Sex trait function (An author helped design)

Dorn's x2= Post-operative functioning 13 items (An author helped design)

Post-operative functioning 21 items (An author helped design)

EQOLS (2nd)=2nd European Quality of Life Survey

FBeK=Fragebogen zur Beurteilung des eigenen Korpers

FPI-R=A version of the Freiberg Personality Inventory

FSFI+Female Sexual Function Index

GHQ=General Health Questionnaire

Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)

GITS=Gender Identity Trait Scale

HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems

KHQ=King's Health Questionnaire

MMPI=Minnesota Multi-phasic Personality Inventory

SADS=Social Anxiety & Distress Scale

SCL-90 (±R)=A version of the Symptom Checklist 90

SDE=Scale for Depersonalized Experiences (An author designed)

SES=Self-Esteem Scale

SF-36 (v2)=Short Form-36(version2)

SSS=Social Support Scale (used more for predictors)

STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire

TSCS=Tennessee Self-Concept Scale

UGDS=Utrecht Gender Dysphoria Scale (An author helped design)

WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.

Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets

Author	Test	Patient and Data Loss	Results
	Psychometric Test		

Heylens et al. Belgium 2014	SCL-90R	90 applicants for SRS were recruited. • 8 (8.9%) declined participation. • 12 (13.3%) excluded b/c GID-NOS dx. • 12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical co-morbidity, personal decision for no tx, or personal decision for only hormone tx. • 1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. • 1 (12.2% of initial recruits) had not yet received SRS by study close. →**46 (51.1% of recruited) underwent serial evaluation** • The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) →**missing data for another 1.1% to 11.1%.**	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.

Ruppin,Pfafflin, Germany 2015	SCL-90R	The number in the available patient pool was not specified. 140 received recruitment letters. • 2 (1.4% of those with recruitment letters) had died. • 1 (0.7%) was institutionalized. • 5 (3.6%) were ill. • 8 (5.7%) did not have time. • 8 (5.7%) stated that GD was no longer an issue. • 8 (5.7%) provided no reason. • 28 (20.0%) declined further contact. • 9 (6.4%) were lost to follow-up. →**71 (50.7%) agreed to participate.** • **2 (1.4%) had not undergone SRS** • The test was not completed by 9. →**missing data for another 6.4%.**	At t=0, the "global severity index "SCL-90R score was 0.53±0.49. At post-SRS follow-up the score had decreased to 0.28±0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70±0.67 at t=0 and 0.26±0.34 post-SRS.
Smith et al. Holland 2005	MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. • 103 (31.7%) were not eligible to start hormone tx & real-life experience. • 34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. • **36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.**	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0±40.7. At post SRS-follow-up, the score had decreased to 120.3±31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.

Udeze, et al. 2008 Megeri, Khoosal 2007 UK	SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. • Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15. There were no statistically significant changes in the global score or for any of the subscales.
	National Databases		
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. • 480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. • All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9–8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) • 25 (3.3%) applications denied. • 61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. • All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID-NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery Tx=Treatment

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID:> 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstotter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentitat* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid- Technique as shown at the exemple of the

assessment of gender identity], Verlag fur empirische Padagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients*. 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5& 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to- male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry*. 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Gooren LJ; Eklund PL. Mortality and morbidity in transsexual patients with cross- gender hormone treatment. *Metabolism*. 1989 Sep;38(9):869-73. PMID: 2528051.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel- Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia.* 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ.* 2004 June;328(19):1490–4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA.* 2010 Summer-Fall;22 (4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med.* 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristori J, Meriggiola MC, Jannini EA, Manieri C, Corona G, Monami M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res.* 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol.* 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013 Mar;13(3):214- 22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry.* 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty.* University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal..pdf.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav.* 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav.* 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med* .2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Baumeister S, Sohn M, Domke C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. *Handchir Mikrochir Plast Chir.* 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* .1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to- female transsexualism. *Fertil Steril.* 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third> sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheoran B, Sheth L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav.* 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes.* 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), Gender dysphoria: Development, research, management (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav.* 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry.* 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med.* 2011 Jun 30;364 (26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow- up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25 (3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health*. 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am*. 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med*. 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Broderick JP. Devices and clinical trials: overview and equipoise. *Stroke.* 2013 Jun;44(6 Suppl 1):S3-6. PMID: 23709721.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev.* 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics.* 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav.* 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien).* 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav.* 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque,NM: University of New> Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth.* 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. “AskCHIS” via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self- injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med.* 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol.* 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex.* 2006;51(3):53-69. PMID: 17135115.

CMS Office of Minority Health. New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. 2015. Academy Health Annual Research Meeting, Minneapolis, Minnesota.

CMS Office of Minority Health. If You Build It, They Will Come: Accessing and Utilizing HHS LGBTI Data and Information Products. 2015. Gay and Lesbian Medical Association Meeting, Portland, Oregon.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry.* 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res.* 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT.Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress

in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology.* 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10. PMID: 25691225.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend.* 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from

a household probability sample of adults. *Am J Public Health.* 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol.* 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth.* Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther.* 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148- 53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry.* 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril.* 2010 Dec;94 (7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery.* New Zealand Health technpology Assessment. (NZHTA). The clearinghouse forhealth outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav.* 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. *J Sexol.* 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry.* 2007 Apr;22(3):137- 41. Epub 2006 Dec 26. PMID: 17188846.

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male- to-female transsexual after initiation of hormone therapy. *J Clin Neurosci.* 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull.* 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci.* 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry.* 1974;7(0):79- 110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol.* 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis.* 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gyneco*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186 (2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6 (2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav.* 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol.* 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male- to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes.* 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduin T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*.2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav.* 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol.* 2011 Jun;51 (2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis.* 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan- Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub.* 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjevic ML, Vujović S, Bizic M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal.* 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72 (1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg.* 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20 (6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikuliç B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work-Overview.* EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrc M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work.* EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The 'availability' bias: underappreciated but with major potential implications. *Crit Care.* 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefuhls: Befunde zu Reliabilitat, Validitat und Stabilitat der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica.* 1996; 42: 284–292. German. (Not in PubMed)

Ferron P, Young S, Boulanger C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med.* 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Flores A, Herman J, Gates G, Brown T. (2016) *How many adults identify as transgender in the United States?* Los Angeles, CA: The Williams Institute.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry.* 2013 Jul;203(1):1-2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexualsurgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir.* 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav.* 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl*. 2011 May;13 (3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol.* 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev.* 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol.* 2011 Oct 15;519(15):3061-84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril.* 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand.* 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165 (4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Gates GJ. How many people are lesbian, gay, bisexual, and transgender? 2011. (Not in PubMed) williamsinstitute@law.ucla.edu.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNiel D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law.* 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med.* 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int.* 2007 Sep;100(3):607- 13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J.* 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website: http://www.stat.berkeley.edu/users/hhuang/141C-2008.html. Section Website: http://www.stat.berkeley.edu/users/mgoldman.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr.* 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess.* 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav.* 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav.* 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav.* 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero- Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology.* 2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res.* 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res.* 2005;64 Suppl 2:31-6. PMID: 16286768.

Gooren L. Clinical practice. Care of transsexual persons. *N Engl J Med.* 2011 Mar 31;364(13):1251-7. PMID: 21449788.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes.* 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross- sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia.* 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med.* 2012 Feb;9 (2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self- esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis.* 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict.* 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol.* 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis.* 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment.*1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonsate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav.* 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and> strength of recommendations. *BMJ.* 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ.* 2008 May 3;336 (7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ.* 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ.* 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol.* 2011 Apr;64(4):395-400. Epub 2010 Dec 30. PMID: 21194891.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol.* 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol.* 2011 Dec;64 (12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian, gay, bisexual, and transgender populations: review and recommendations. *J Homosex*. 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery.* 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand.* 2000 Oct;102(4):276- 81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry.* 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol*. 1957 Oct;13 (4):364-8. PMID: 13463138.

Hathaway SR,Reynolds PC,Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hebbar S, Pandey H, Chawla A. Understanding King"s Health Questionnaire (KHQ) in assessment of female urinary incontinence. Int J Res Med Sci 2015;3:531-8.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am.* 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt.* 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res.* 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol.* 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol.* 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int.* 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med.* 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry.* 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services.Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology.* 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel).* 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand.* 1971;47 (1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel).* 1973;6(2):65- 80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat.* 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev.* 2009 Jan 21; (1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ.* 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials.* 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol.* 1988 Dec;56 (6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci.* 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav.* 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav.* 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B- Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha- reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013. http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry.* 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis. *J Hist Sex.* 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol.* 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS.* 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med.* 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav. 2010* Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal.* 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab.* 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co- morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XY karyotype and disorders of sex development. *Horm Behav.* 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci.* 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics.* 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav.* 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child.* 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav.* 1987 Dec;16(6):511-22. PMID:> 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav.* 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences.* Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology.* 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümmen G, Rübben H. Male-to-female transsexualism: a technique, results and long-term follow-up in 66 patients. *BJU Int.* 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry.* 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt.* 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol.* 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav.* 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hiltebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol.* 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril.* 2009 Nov;92(5):1685-1689.e3. Epub

2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ.* 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5: DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician.* 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals. *J Sex Res.* 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation.* 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet.* 2011 April 9;377: 1211. PMID:2 1481690.

A - Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand.* 1998 Apr;97(4):284-9. PMID: 9570489.

B – Landén M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatr Scand 1998: 97: 189-194.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol.* 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav.* 1999 Dec;28(6):581-3. PMID:> 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male- to-female transsexualism. *Arch Sex Behav.* 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract.* 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav.* 1993 Apr;22 (2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav.* 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand.* 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav.* 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male- to-female transsexuals. *Curr Pharm Des.* 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav.* 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav.* 1979 Sep;8 (5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav.* 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess.* 1984 Oct;48 (5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand.* 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev.* 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D,

Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grüters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5α-reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab.* 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav.* 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry.* 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry.* 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health.* 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med.* 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database.* 2009. No.3. www.birmingham.ac.uk/Documents/college-mds/haps/projects/WMHTAC/REPreports/2009/LGBThealth030409finalversion.pdf.

Medraś M, Jóźków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol.* 2010 Jul- Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy.* 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health.* 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self- prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med.* 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Jannini E, Lenzi A, Maggi M, Manieri C. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol.* 2010 May;162(5):831-3. Epub 2010 Feb 11. PMID: 20150325.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl.* 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf).* 2015 Nov;83(5):607- 15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav.* 1974 Nov;3 (6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10 (4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav.* 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am.* 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to- female transsexuals. *Horm Behav.* 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics.* 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient- subjects. *J Med Ethics.* 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol.* 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg.* 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr.* 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish. PMID: 22542505.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med.* 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav.* 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med.* 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH FY 2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities. 2015 http://edi.nih.gov/sites/default/files/EDI_Public_files/sgm-strategic-plan.pdf

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care.* 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res.* 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015.* (Portland State quantitative methods)www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter- Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med.* 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. J *Acquir Immune Defic Syndr.* 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health* 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health.* 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery.* New Zealand Health technpology Assessment. (NZHTA). The clearinghouse forhealth outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, Briel M, Nordmann AJ, Pregno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev.*2011 Apr 13; (4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J.* 1981;50 (1):46–9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res.* 2008 Jan 15;157 (1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med.* 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and surgical treatment. *Nord J Psychiatry.* 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav.* 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long- term follow-up. *Arch Sex Behav.* 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr.* 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav.* 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex.* 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med.* 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögendorfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to- male transsexuals. *J Sex Med.* 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res.* 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to- female transsexual persons. *J Voice.* 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology.* 2005 Jul;16 (4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health.* 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis.* 1968 Nov;147(5):460- 71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15 (1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril.* 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med.* 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work.* 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims.* December 2009. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To- Male Genital Reconstructive Surgery. *IJT.* 1999 Jul-Sept;3(3). (Not in PubMed) http://www.symposion.com/ijt/ijt990302.htm http://www.iiav.nl/ezines/web/ijt/97-03/numbers/symposion/ijt990302.htm

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res.* 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res.* 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2 (5164): 1448–52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):Trans-sexualism and Sex reassignment. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res.* 2006;66:195-203). *Horm Res.* 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav.* 1999 Feb;28(1):71-89. PMID: 10097806.

Reisner S, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, Holland C, Max R, Baral S. Global heath burden and needs of transgender populations: a review. *Lancet*. Epub 16 June 2016. http://dx.doi.org/10.1016/S0140-6736(16)00684-X

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav.* 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia. *Acta Psychiatr Scand.* 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav.* 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl.* 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav.* 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health.* 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract.* 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18 (88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci.* 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193–236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New women: Sexological outcomes of male-to-female gender reassignment surgery. JSET. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclaire C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab.* 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg.* 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol.* 2011 May;8 (5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol.* 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer.* 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci.* 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health.* 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law.* 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology.* 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT.* 2001 Jul-Sept; 5(3):20 pages.http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev.* 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract.* 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract.* 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2001 Apr;40(4):472-81. PMID: 11314574.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res.* 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand.* 1981 May;63 (5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand.* 1981 Jul;64 (1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav* 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):192-206Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *J Midwifery Womens Health.* 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav.* 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J.* 1972 Mar;68 (3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat.* 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBeK), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health .* 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev.* 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills.* 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol.* 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol.* 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res.* 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res.* 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female- to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand.* 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

T'Sjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry*. 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78 (4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J*. 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol.* 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol.* 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab.* 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I. T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierczak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med.* 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity inFlanders, Belgium. *Arch Sex Behav.* 2015 Jul;44 (5):1281-7. Epub 2015 Jan 15. PMID: 25588709.

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav.* 2013; 42:361–70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav.* 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf).* 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med.* 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med.* 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal.* 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow- up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry.* 1978:132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. Epub 16 June 2016 http://dx.doi.org/10.1016/S0140-6736(16)00683-8

Weigert R, Frison E, Sessiecq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med.* 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology.* 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quaility of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people.Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV.* World Health Organization. July 2015. http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther.* 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedecker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. Epub 16 June 2016. http://dx.doi.org/10.1016/S0140-6736(16)00682-6

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod.* 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross-sex hormone treatment in transsexual persons. *J Sex Med.* 2012 Oct;9(10):2641- 51. Epub 2012 Aug 20. PMID: 22906135.

C-Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav*. 2012 Oct;41(5):1069-71. PMID: 22968492.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med.* 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med.* 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction.* 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health*. 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex.* 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S.The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract*. 1999; 49 (449): 991–2. PMID: 10824346.

Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic- specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21- hydroxylase deficiency. *Mol Genet Metab.* 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab*. 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero. *Environ Health Perspect*. 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol.* 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav.* 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol.* 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav.* 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders.* (6th version) February, 2001. http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012. http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr.* 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez- Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab.* 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals*. (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5α-Reductase-2 Deficiency. *Glob. libr. women's med.*, (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg*. 2006 May;77(5):432-8. German. Erratum in *Chirurg*. 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis*. 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry.* 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res.* 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901- 14. PMID: 23868018.

EXHIBIT 10

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

---

[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**
>
> 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]

---

[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).

---

[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,"

---

[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]

---

[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

---

[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.

---

[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]

---

[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.

---

[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,

---

[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.

EXHIBIT 11

MANAGEMENT OF ENDOCRINE DISEASE

Long-term outcomes of the treatment of central precocious puberty

Federica Guaraldi, Guglielmo Beccuti, Davide Gori[1] and **Lucia Ghizzoni**

Division of Endocrinology, Diabetes, and Metabolism, Department of Medical Sciences, University of Turin, Corso Dogliotti, 14, I-10126 Turin, Italy and [1]Department of Biomedical and Neuromotor Sciences, School of Hygiene and Preventive Medicine, DIBINEM, University of Bologna, Bologna, Italy

Correspondence should be addressed to L Ghizzoni
Email
lucia.ghizzoni@unito.it

Abstract

GnRH analogues (GnRHa) are the treatment of choice for central precocious puberty (CPP), with the main objective to recover the height potential compromised by the premature fusion of growth cartilages. The aim of this review was to analyze long-term effects of GnRHa on height, body weight, reproductive function, and bone mineral density (BMD) in patients with CPP, as well as the potential predictors of outcome. Because randomized controlled trials on the effectiveness and long-term outcomes of treatment are not available, only qualified conclusions about the efficacy of interventions can be drawn. GnRHa treatment appears to improve adult height in girls with CPP, especially if diagnosed before the age of 6, whereas a real benefit in terms of adult height is still controversial in patients with the onset of puberty between 6 and 8 years of age. No height benefit was shown in patients treated after 8 years. Gonadal function is promptly restored in girls after cessation of treatment, and reproductive potential appears normal in young adulthood. Data are conflicting on the long-term risk of polycystic ovarian syndrome in both treated and untreated women. Fat mass is increased at the start of treatment but normalizes thereafter, and GnRHa itself does not seem to have any long-term effect on BMI. Similarly, analogue treatment does not appear to have a negative impact on BMD. Owing to the paucity of data available, no conclusions can be drawn on the repercussions of CPP and/or its treatment on the timing of menopause and on the health of the offspring.

European Journal of Endocrinology
(2016) **174**, R79–R87

European Journal of Endocrinology

Introduction

Puberty results from the reactivation of the hypothalamic–pituitary–gonadal (HPG) axis following the quiescent period occurring during childhood. It is characterized by an increase in the amplitude and frequency of the hypothalamic gonadotropin-releasing hormone (GnRH) pulses, which in turn promote follicle-stimulating hormone and luteinizing hormone secretion by the pituitary, leading to the activation of gonadal function (1).

Precocious puberty is clinically defined by the appearance of secondary sexual characteristics, i.e., Tanner stage II of breast development before the age of 8 in girls and the increase in testicular volume ≥4 ml before 9 years in boys (2, 3). Central precocious puberty (CPP) due to early activation of pulsatile GnRH secretion is the most common form (2). It occurs in ∼1:5000–10 000 children, with a female-to-male ratio ranging from 3:1 to 23:1 (3). Females typically present with idiopathic forms, whereas in boys CPP is mostly due to organic lesions such as hypothalamic–pituitary congenital malformations, tumors, infections, infiltrative/inflammatory disorders, and iatrogenic or traumatic injuries (3). Genetic factors (mutations of KISS1, KISS1R, and MKRN3 genes (4)), secular trend, ethnicity, nutritional status, and environmental changes have all been involved in the pathogenesis of CPP (2, 3, 5), although their exact mechanisms of action remain to be elucidated.

Short stature caused by rapid advancement of skeletal maturation driven by premature exposure to sex steroids is

www.eje-online.org
DOI: 10.1530/EJE-15-0590
© 2016 European Society of Endocrinology
Printed in Great Britain
Published by Bioscientifica Ltd.

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

the main unfavorable event associated with precocious puberty. Historical data on untreated patients with CPP show mean final heights ranging from 151 to 156 cm in boys and from 150 to 154 cm in girls, being the height loss inversely correlated with the age at the onset of puberty (2, 6).

Treatment is aimed at selectively and effectively suppressing gonadal steroid secretion through medical treatment or removing the underlying cause whenever possible to allow normal sexual maturation and statural growth (2, 3, 6). The avoidance of potential psychosocial problems derived from experiencing precocious puberty and undesirable behaviors like early sexual intercourse and substance abuse reported in some cohorts of patients may also be acknowledged as objectives of the treatment (2, 3, 7). The decision to treat depends on the age at onset of puberty, pace of pubertal development, estimated adult height, and psychological impact of the premature sexual development (2, 3). Treatment is undisputed in rapidly progressive forms, defined on the basis of clinical, radiological, and biochemical criteria (8), for the significant risk of short adult height, while it is not required in patients with nonprogressive or slowly progressive forms who were shown to achieve an adult height within the normal range without treatment (2, 3).

GnRH analogues (GnRHa) are the medical treatment of choice for progressive CPP (2, 3). They derive from a chemical substitution at position 6 and 10 of the native GnRH molecule, which increases its resistance to the enzymatic degradation and affinity to the GnRH–pituitary receptor leading to desensitization of the receptor, ultimately resulting in the inhibition of gonadotropin secretion and return of sex steroids to prepubertal levels (9). Several active principles and formulations are available. Depot formulations are generally preferred because of better patient compliance. Drug choice depends on physician experience, patient needs, and government regulations of drug prescription (6, 7). GnRHa is generally safe and well tolerated. Local events such as bruising, pain, injection reactions, and sterile abscesses are the most common side effects, followed by minor menopausal symptoms – that is, hot flushes, headaches, and nausea (7) – while anaphylaxis is extremely rare (10).

In the last decades, the widespread use of GnRHa has increasingly demonstrated its favorable effects on statural growth, although the net height gain (HG) associated with the treatment and predictors of long-term outcomes remains debated (2, 6, 7, 8), as no randomized controlled trials (RCTs) have been performed and growth estimation suffers from important methodological limitations, which will be discussed later. Moreover, concerns have been raised on the potential negative effects of treatment on weight and metabolic profile, bone mineral density (BMD), and reproductive function in adulthood (2, 3, 6). The aim of our review was to analyze long-term effects of GnRHa on height, body weight, reproductive function, and BMD in patients with CPP, as well as potential predictors of outcome.

A literature search was performed using the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed) and entering the string 'precocious puberty AND (treatment OR GnRH analogues) AND (height OR body mass index OR bone OR fertility OR reproduction OR polycystic ovary syndrome)' with no date limits. Only original studies performed in humans, written in English, reporting data at the beginning and after the completion of treatment were considered for BMI and metabolic parameters, reproductive function, and BMD. Studies focusing on height were considered only if baseline values and adult heights were reported and data expressed as mean (absolute values or SDS) ±S.D. or S.E.M. for study comparison and calculation of treatment efficacy (i.e. HG). Additional articles were identified through a hand search of reference lists in the papers retrieved (Fig. 1).

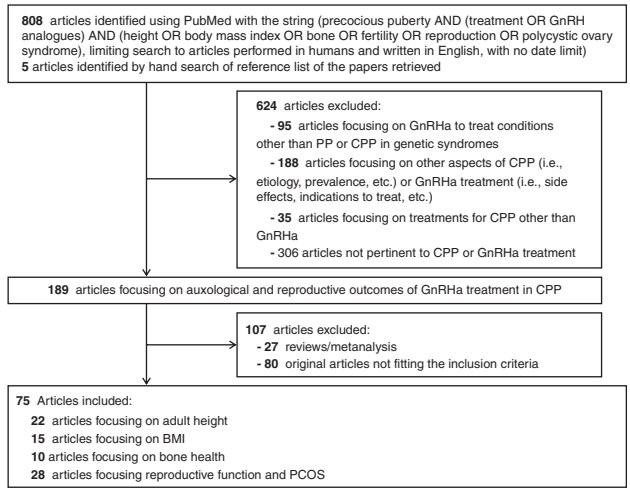


Figure 1

Methodological flow chart summarizing the main steps followed for the identification of articles of interest. CPP, central precocious puberty; GnRHa, gonadotropin-releasing hormone agonists; PCOS, polycystic ovary syndrome; PP, precocious puberty.

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

Outcomes of GnRHa therapy for CPP

Adult height

GnRHa have been extensively used since the 1980s in children with rapidly progressing CPP with the primary aim to restore genetic growth potential otherwise compromised by sex-hormone-driven premature closure of bone growth plates. The great majority of studies indicate some beneficial effect of treatment on statural growth, with limitations related to the absence of RCTs and the fact that the effects of GnRHa therapy have been traditionally analyzed by comparing the achieved adult height with predicted adult height at initiation of treatment or with adult heights of historical, untreated cohorts.

Bone age (BA) assessment is essential in the management of patients with CPP as it allows the identification of rapidly progressing forms of CPP with compromised predicted adult height requiring treatment. It is also important for monitoring treatment efficacy, as deceleration of BA maturation is a desired effect of treatment. Moreover, BA evaluation is valuable in defining the appropriate time for treatment discontinuation, because the best results in terms of adult height are achieved when treatment is discontinued at around 12–12.5 years in girls and 13.5 years in boys (11), although the optimal age for treatment interruption is not clearly defined by international guidelines. It should be pointed out, however, that BA assessment is affected by a great intra-observer variance, and Bayley and Pinneau tables, the reference standards for height prediction, have been validated for height prediction in normal children (11). In patients with CPP, height prediction based on both 'average' and 'advanced' tables is insufficiently reliable, especially when skeletal maturation is markedly advanced, and it is associated with a systematic overestimation of adult height (3.7–5.9 cm in girls, and even greater in boys in historical series) (2, 3).

The comparison of adult heights of treated CPP patients with those of historical cases is of limited value because data are derived from a small number of patients, usually the most severe, and do not take into account the influence of the secular trend on human growth over the decades. Moreover, studies are heterogeneous for patients – that is, chronological and BA at diagnosis and initiation of treatment and idiopathic vs organic forms of CPP – and treatment characteristics (2, 3).

Predictors of treatment outcomes also remain debated. Treatment efficacy appears to depend mainly on the age of CPP onset and treatment initiation with best outcomes reported in girls with onset of CPP before the age of 6 years and treated soon thereafter. BA advancement at the time of initiation of therapy, duration of therapy, mid-parental height, and height at the end of therapy have also been considered predictors of height outcome but with no definite conclusions reached on their appropriateness. The optimal age for treatment discontinuation is also questionable as several auxologic and treatment characteristics involved in post-treatment HG should be taken into account together with the psychological impact of the resumption of pubertal development on the patient and family (7, 8).

To clarify the impact of GnRHa treatment on statural growth and identify the most reliable predictors of height outcome in treated patients with CPP, 20 articles fitting the above-mentioned inclusion criteria were analyzed (Supplementary Table 1, see section on supplementary data given at the end of this article). For each of them, the following parameters, reported by authors or calculated from raw data, were recorded: number of enrolled patients; treatment type; target height (TH); chronological age, BA, and height at the beginning and end of treatment; HG (computed from the difference between adult and predicted height at diagnosis, according to average and/or advanced BA, as per authors' choice); and the difference between adult and predicted height at the end of treatment. Treatment efficacy was estimated from the comparison of adult height with predicted height at the beginning and end of treatment and/or adult height of historical, untreated patients, as well as the pace of bone maturation progression.

Data analysis demonstrated the efficacy of the various GnRHa formulations in halting BA progression, indicated by the statistically significant difference between BA and chronologic age at the end vs the beginning of treatment (Supplementary Table 1). The great majority of patients was female (female (F):male (M) = 947:90) and treated with triptorelin or leuprolide depot formulations administered monthly. Overall, the mean chronologic age at the start of treatment was 7.5 ± 1.2 years in females and 6.7 ± 1.5 years in males, with a mean BA of 10.3 ± 1.4 years in females and 10.6 ± 2.5 years in males. The mean chronological age at the end of treatment was 11.1 ± 0.9 years in females and 12.2 ± 1.8 years in boys, with a mean BA of 12.4 ± 0.7 and 13.6 ± 1.0 years respectively.

Mean adult height was significantly higher in treated patients than in untreated ones reported in an historical series adjusted for age at diagnosis (12, 13) (mean difference in adult height of 8.3 cm in girls and 13.7 cm in boys) (12) and in age- and sex-matched untreated study

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

controls (mean difference in adult height ranging from 3.3 to 8.9 cm) (12, 14, 15, 16).

The great majority of patients reached an adult height consistent with the TH (13, 14, 15, 17, 18, 19, 20, 21, 22, 23, 24, 25), a minority of them did not reach the TH (19, 26), and a very small portion of patients remained shorter than the predicted height before treatment (13, 27). Discordant results were obtained when comparing the efficacy of treatment in females and males. According to a study by Bajpai *et al.* (21), in patients treated with monthly triptorelin depot, mean HG was similar in females and males (mean HG: 6.4 ± 2.4 cm vs 7.6 ± 1.0 cm respectively). In contrast, Galluzzi *et al.* (13) reported a higher HG in boys (7.3 ± 3.8 cm; $n=11$) than in girls (3.3 ± 3.0 cm; $n=22$), with an achieved adult height SDS higher in the former than in the latter (0.13 ± 0.91 vs -0.62 ± 0.88; $P<0.001$). In general, HG was highly variable among studies depending on sample characteristics including the progression of pubertal development. Pubertal development was specified as rapidly progressing in some studies (17, 22, 24, 27, 28, 29), whereas in others pubertal progression was not detailed.

Several factors were postulated to influence the effects of GnRH treatment on statural growth. According to the majority of studies, earlier age at start of puberty (i.e. 5 years (15, 22)) and of treatment (i.e. 6 years (18, 20, 21, 23, 24, 25)) are associated with a taller adult stature. In a study by Klein *et al.* (24) performed in 98 patients (F:M=80:18) treated with histrelin or deslorelin, the average adult height and HG (14.5 ± 9.9 cm vs 6.8 ± 6.9 cm; $P<0.001$) were greater in girls with puberty onset <6 years of age than those with onset of puberty between 6 and 8 years of age. Few studies (12, 26) showed no correlation between HG and age at puberty onset or initiation of treatment, suggesting that girls with late onset CPP benefit from treatment similarly to girls with earlier pubertal onset (12). A longer treatment duration appears to be a positive outcome predictor in the majority (19, 20, 21, 24, 30), although not all (15, 23), of the studies, together with a short interval between pubertal onset and the start of treatment (24, 30), a great growth spurt after the end of treatment (12), low pre-treatment estradiol levels (30), and advanced BA at the start of treatment (14, 18, 19, 20, 21, 25). The impact of advanced BA at the start of treatment on adult height was not documented in the study by Brito *et al.* (30), whereas Carel *et al.* (12) found a negative association between the BA/statural age ratio at the onset of treatment and adult height suggesting that treatment is not capable of restoring a full adult height potential if started after an irreversible advancement of BA. This was also confirmed in a study by Kauli *et al.* (26) showing that therapy is more beneficial if started before BA exceeds 12 years.

Elevated height (or height SDS) before (16, 17, 19, 20, 24, 30) and at the withdrawal of treatment (12, 16, 17, 19, 20, 25, 30), as well as high TH (or TH-SDS) (17, 20, 21, 23, 30), has also been positively associated with adult height, supporting the primary influence of genetic factors in the determination of adult height even in patients treated with GnRHa (20).

Finally, BA at the end of treatment appears to be crucial on adult height, as it determines post-treatment growth potential (7). Indeed, the tallest heights were achieved by patients who stopped treatment at a BA of 12–12.5 years (20) or even <11.5 years (27), whereas continuing treatment after a BA ≥ 13 years negatively impacted on statural growth (20).

The efficacy of the various GnRHa in terms of HG appeared similar (24, 27, 31), except for a study (32) showing a higher adult height SDS in patients treated with leuprolide depot compared to triptorelin depot.

BMI and correlates of metabolic syndrome

Several studies reported an association between overweight and early/precocious puberty (5, 33) suggesting the involvement of various environmental, genetic, and biochemical factors (5, 7, 17, 34, 35) to explain this association. However, what remains to be clarified is whether it is the high BMI that results in precocious pubertal development or is it the latter that promotes the weight gain (33, 35).

Preliminary studies reported weight gain during treatment with GnRHa in patients with CPP, raising concerns for potential permanent obesity in adulthood (33, 35, 36). According to two independent studies (33, 37) analyzing normal-weight and overweight children separately, BMI–SDS during treatment increased in normal-weight children, whereas it remained stable in overweight subjects. The majority of long-term studies showed an increased prevalence of overweight and obesity in patients with CPP at diagnosis (22, 38), but no significant mean or individual BMI–SDS changes were shown at the end of treatment, irrespective of sex, age at puberty onset and at the start and discontinuation of treatment (15, 17, 22, 23, 24, 25, 30, 32, 39), and type of GnRHa (31). Recently, a study by Colmenares *et al.* (39) evaluated the effects of GnRHa in treated ($n=29$) and untreated ($n=8$) CPP patients and in treated ($n=14$) and untreated ($n=20$) rapidly progressing early puberty (EP), during a 3-year follow-up period. Treatment duration was ≥ 2 years.

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

At diagnosis, a higher BMI (*z*-score of 1.1±0.8 vs 0.6±0.7) and a higher prevalence of obesity/overweight (72.9% vs 35.3%) was observed in subjects with CPP when compared to those with EP. BMI *z*-score and obesity/overweight rates did not change significantly in girls with CPP or EP during 3 years of follow-up, regardless of treatment. Weight *z*-scores were higher at 3 years in treated than in untreated girls with CPP, while it was higher in untreated than in GnRHa-treated patients with EP at baseline, 1, 2, and 3 years. Both CPP- and EP-treated patients showed a reduction, although not statistically significant, in BMI *z*-scores and in obesity/overweight rate following treatment discontinuation, supporting the potential, although time limited, detrimental effect of GnRHa on weight. Indexes of glucose and lipid metabolism were in the normal range at diagnosis and remained unchanged during the follow-up period, independent of treatment.

Recently in a case–control study of a historical cohort, Lazar *et al.* (35) assessed the prevalence of obesity, the metabolic outcome (hyperlipidemia, diabetes, and hypertension), and the malignancy rate of former CPP GnRHa-treated and -untreated women between the third and fifth decades of life. The control group comprised women randomly matched for age, year of birth, and community clinic. Weight status of both GnRHa-treated and -untreated former CPP women resembled that of the general population from late adolescence to early-mid adulthood despite their above-average BMI at the onset of puberty. Permanent obesity was detected in women who were already obese in early childhood only. Moreover, weight gain of the treated CPP girls was not aggravated by GnRHa therapy. The incidence of obesity-related complications, such as metabolic dysfunctions and cancer comorbidities, were not increased in former CPP women, reassuring the health status of adult former CPP women.

Results from studies meeting inclusion criteria are summarized in Supplementary Table 2, see section on supplementary data given at the end of this article.

Reproductive function and risk of polycystic ovarian syndrome

The occurrence of menarche, or in some cases resumption of menses, after the discontinuation of either daily or long-acting GnRHa treatment was investigated by follow-up studies of girls in their late teens and women up to 56 years of age (Supplementary Table 3, see section on supplementary data given at the end of this article). The majority of the studies reported a 100% occurrence of menarche, with a few exceptions mostly related to CPP secondary to organic lesions such as hypothalamic hamartoma (40).

Spontaneous menses occurred 0–62 months after the end of treatment (mean 1.1±0.4 years); the mean duration of treatment varied widely among the studies, from 1 to 14 years. It was suggested that the longer time interval to menarche might be related to a longer duration of treatment and/or younger age at the start of therapy (40), but this hypothesis was not confirmed by other authors (41). Age at the discontinuation of treatment, BA, Tanner breast stage, or uterine development at the end of treatment, and the frequency of injections required to suppress the HPG axis function were all proposed as potential predictors of time interval to menarche, without consistency across studies. Interestingly, girls who had experienced menarche prior to GnRHa therapy showed a significantly shorter interval between the last injection and resumption of menses than those who had not experienced menarche before GnRHa treatment (~25 months vs 63 months) (19).

In the last decade, a subcutaneous hydrogel implant releasing histrelin continuously for at least 1 year has become available in the USA. Few reports of follow-up after histrelin implant treatment were published. Gillis *et al.* (31), evaluating a group of CPP patients treated with the monthly GnRHa and one with the histrelin implant showed that the mean time between the removal of the implant or last injection and menarche was shorter in the histrelin implant group. Fisher *et al.* (41) reported the resumption of puberty in 26 of the 30 girls treated with the histrelin implant, with occurrence of menarche 2–36 months after explantation in treatment-naïve and -non-naïve CPP girls, with an older age at explantation correlating with earlier menarche. In a recent study by Silverman *et al.* (43), menarche occurred in two patients, 9 and 2 months after the final explant respectively.

A great variability in the occurrence of regular ovarian cycles was so far reported in CPP-treated patients (44–96%; Supplementary Table 3), probably related to the heterogeneity of the study sample, type and duration of treatment, and follow-up. The highest prevalence of regular cycles (96%) was observed in 87 treated idiopathic-CPP girls during a 7-year follow-up period after the discontinuation of treatment (15). Jay *et al.* (43) described menstrual cycle lengths as becoming increasingly regular, from 41% in the first year post-menarche to 65% at 3 or more years post-menarche (44).

Fertility was reported to be normal in treated CPP girls, in contrast to the untreated ones. Supplementary Table 3 summarizes over 100 pregnancies reported in the

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

literature, with 97 uneventful pregnancies resulting in healthy children, five elective abortions, and 11 early miscarriages. In a recent study by Lazar *et al.* (45) assessing the reproductive outcome of former CPP women between the third and fifth decades of life, the frequency of pregnancy complications, such as early spontaneous abortion or pre-eclampsia, was comparable in the CPP women and controls. In the same study, spontaneous pregnancy was equally achieved by the treated CPP women and their control groups, while the percentage of women requiring ovulation induction and/or IVF was significantly higher in the untreated CPP group (33%) than in either the control (12.6%) or the CPP-treated groups (11.1%) (45). These findings suggest, according to the authors, a protective role for gonadotropin suppressive treatment on the reproductive outcome of CPP women.

PCO morphology detected by ultrasound (US) was reported in 0–37% of treated CPP girls (median 2%) (21, 36, 46, 47, 48, 49, 50, 51), with different lengths of post-treatment follow-up (up to 20 years), as summarized in Supplementary Table 4, see section on supplementary data given at the end of this article. Feuillan *et al.* (40) described the ovarian volume larger than normal at 4–5 years post-treatment, whereas another study including adult CPP-treated women showed the ovarian volume within normal range (52). Ovarian volume >10 ml was observed in 20% of CPP-treated patients (49, 50), a percentage similar to that found in age-matched, healthy controls (48). CPP patients with regular vs irregular menses showed no differences in the ovarian volume (22).

The development of signs and symptoms of polycystic ovarian syndrome (PCOS) in former CPP women is controversial. Data from the literature are limited, and the criteria used for PCOS diagnosis are not uniform among studies. While Heger *et al.* (22) observed a low incidence of PCOS (2%) based on Franks criteria, one study is supportive of the relationship between CPP and PCOS (48). In this cohort, which did not include a control group of untreated CPP girls, the prevalence of PCOS was 32% using the 2003 Rotterdam criteria and 30% using the Androgen Excess Society (AES) criteria. Moreover, the prevalence of hirsutism and biochemical hyperandrogenism was 23 and 48%, respectively, while irregular menses were present in 15% and PCO morphology in 37% of women. High prevalence of PCO morphology by US is also detected in normal young women (up to 33%) (53). Using the 1990 NIH criteria, Magiakou *et al.* (36) found that PCOS prevalence in CPP-treated young women was not different from that in the untreated ones (17.2 and 30.8% respectively), suggesting that GnRHa treatment does not predispose to PCOS development or menstrual irregularities.

Recently, in a large group of treated and untreated former CPP women aged 25–56 years, Lazar *et al.* (45) evaluated clinical signs potentially related to androgen excess, without performing hormonal assessment or imaging procedures. With these limitations, clinical signs of hyperandrogenism (acne/hirsutism with oligomenorrhea) were more frequent in CPP women than in controls with normal puberty matched for age and year of birth but not for BMI. The relative risk for the development of clinical hyperandrogenism with irregular menses was twofold higher in the untreated than the treated group. Moreover, among the treated women a small number had received cyproterone acetate with outcomes similar to those of GnRHa-treated women, suggesting that pubertal suppression itself may reduce the risk of PCOS rather than the kind of medical treatment. Study findings also suggest an association between CPP and ovarian dysfunction later in life, probably related to the underlying neuroendocrine dysfunction, manifesting as CPP and persisting into adult life. The reproductive outcome in early and mid adulthood was normal in the great majority of the patients studied. A high prevalence of fertility problems was present in the untreated CPP group only, suggesting that gonadotropin-suppressive therapy may have a protective effect on the reproductive outcome.

Limited data are available on the reproductive outcome of male patients treated for CPP (Supplementary Table 3). Three small studies showed normal gonadal function in former CPP male adolescents aged 15–18 years (19, 54, 55). Feuillan *et al.* (54) described a progressive increase in testicular volume, similar to controls after 2 years post-therapy, with normal gonadotropins and testosterone levels 1 year after the discontinuation of treatment. Bertelloni *et al.* (55) confirmed normal testicular function in adolescent boys after GnRHa therapy with full pubertal development and, normal testicular volume, gonadotropins, testosterone, and inhibin B levels into normal adult range. Even though paternity rates have not been reported, sperm analysis, performed in six patients, appeared normal for age (55). Following histrelin implant removal, a spontaneous increase in testicular volume was observed within 1 year of histrelin explantation in five boys with CPP (42).

Bone mineral density

Few studies assessed BMD in CPP during GnRHa treatment, showing minor or no changes in BMD parameters

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

(56, 57, 58). Boot *et al*. (56) found normal BMD for chronological age but decreased BMD for BA after 2 years of treatment with GnRHa.

Pasquino *et al*. (15) reported that both mean BMD lumbar spine and spine volumetric BMD at the discontinuation of treatment were significantly lower in treated CPP girls than in untreated controls. However, at the complete resumption of gonadal activity, both increased to levels similar to those detected in controls. In a more recent study, Magiakou *et al*. (36) showed BMD values adjusted for height were not different between GnRHa-treated and -untreated girls, evaluated at least 2 years after cessation of treatment. Alessandri *et al*. (59) evaluated bone mass, body composition, and bone remodeling in two groups of girls with idiopathic CPP, namely, one group assessed at diagnosis and a second group 3 years after GnRH agonist treatment. BMD and body composition were not affected by CPP, and GnRHa treatment did not seem to have a detrimental effect on the acquisition of bone mass. Heger *et al*. (22) described normal BMD for age in women after GnRHa treatment, with a 17% prevalence of osteopenia. In a small group of CPP-treated female adolescents, Bertelloni *et al*. (27) showed patients' BMD was not different from that of their mothers. In male patients, evaluated at adult height, BMD was similar to that found in a group of healthy young Italian men with normal pubertal development (55). The highest prevalence of osteopenia (45%) was observed by Tung *et al*. (60) in a small group of Taiwanese women, but a plausible explanation for the finding was not provided by the authors.

Conclusions

GnRHa therapy is efficacious in restoring the growth potential in the majority of children with CPP under the age of 6 years, although the estimate of HG is variable and difficult to assess because of sample heterogeneity, methodological limitations associated with height prediction, and the absence of randomized trials. Age at puberty onset, BA advancement, age at initiation, and duration of treatment are the most important outcome predictors, although their impact on adult height remains to be established. Above-average BMI is present at diagnosis at a high rate among children with CPP, but long-term GnRHa treatment does not appear to cause or aggravate obesity. Long-term data do not support adverse consequences of GnRHa therapy on BMD. Gonadal function is preserved after treatment cessation with normal reproductive potential. An association between CPP and ovarian dysfunction independent of GnRHa treatment was suggested, with a potential protective role of GnRHa therapy on the reproductive outcome. Data on the long-term risk of PCOS in CPP-treated and -untreated patients are conflicting although the majority of studies are not supportive of an association between GnRHa use and PCOS. Further studies to assess whether CPP has long-term implications on the general health status and the risk for premature ovarian failure and premature menopause in late reproductive years and to evaluate the impact of GnRHa therapy on the fertility, fecundity, and health of offspring are warranted.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-15-0590.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This review did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1 Terasawa E & Fernandez DL. Neurobiological mechanisms of the onset of puberty in primates. *Endocrine Reviews* 2001 **22** 111–151.
2 Carel JC & Leger J. Clinical practice. Precocious puberty. *New England Journal of Medicine* 2008 **358** 2366–2377. (doi:10.1056/NEJMcp0800459)
3 Dixon J & Ahmed S. Precocious puberty. *Paediatrics and Child Health* 2007 **17** 343–348. (doi:10.1016/j.paed.2007.06.009)
4 Bulcao Macedo D, Nahime Brito V & Latronico AC. New causes of central precocious puberty: the role of genetic factors. *Neuroendocrinology* 2014 **100** 1–8. (doi:10.1159/000366282)
5 Biro FM, Greenspan LC, Galvez MP, Pinney SM, Teitelbaum S, Windham GC, Deardorff J, Herrick RL, Succop PA, Hiatt RA *et al*. Onset of breast development in a longitudinal cohort. *Pediatrics* 2013 **132** 1019–1027. (doi:10.1542/peds.2012-3773)
6 Bertelloni S & Mul D. Treatment of central precocious puberty by GnRH analogs: long-term outcome in men. *Asian Journal of Andrology* 2008 **10** 525–534. (doi:10.1111/j.1745-7262.2008.00409.x)
7 Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR, ESPE-LWPES GnRH Analogs Consensus Conference Group, Antoniazzi F, Berenbaum S, Bourguignon JP, Chrousos GP *et al*. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. *Pediatrics* 2009 **123** e752–e762. (doi:10.1542/peds.2008-1783)
8 Carel JC, Lahlou N, Roger M & Chaussain JL. Precocious puberty and statural growth. *Human Reproduction Update* 2004 **10** 135–147. (doi:10.1093/humupd/dmh012)
9 Lahlou N, Carel JC, Chaussain JL & Roger M. Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. *Journal of Pediatric Endocrinology & Metabolism* 2000 **13** (Suppl 1) 723–737.

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

10 Fujisaki A, Kondo Y, Goto K & Morita T. Life-threatening anaphylaxis to leuprorelin acetate depot: case report and review of the literature. *International Journal of Urology* 2012 **19** 81–84. (doi:10.1111/j.1442-2042.2011.02886.x)

11 Lazar L & Phillip M. Pubertal disorders and bone maturation. *Endocrinology and Metabolism Clinics of North America* 2012 **41** 805–825. (doi:10.1016/j.ecl.2012.08.003)

12 Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J & Chaussain JL. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French study group of Decapeptyl in Precocious Puberty. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1973–1978. (doi:10.1210/jcem.84.6.5647)

13 Galluzzi F, Salti R, Bindi G, Pasquini E & La Cauza C. Adult height comparison between boys and girls with precocious puberty after long-term gonadotrophin-releasing hormone analogue therapy. *Acta Paediatrica* 1998 **87** 521–527. (doi:10.1111/j.1651-2227.1998.tb01497.x)

14 Adan L, Chemaitilly W, Trivin C & Brauner R. Factors predicting adult height in girls with idiopathic central precocious puberty: implications for treatment. *Clinical Endocrinology* 2002 **56** 297–302. (doi:10.1046/j.1365-2265.2002.01488.x)

15 Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M & Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 190–195. (doi:10.1210/jc.2007-1216)

16 Poomthavorn P, Suphasit R & Mahachoklertwattana P. Adult height, body mass index and time of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing hormone analogue treatment. *Gynecological Endocrinology* 2011 **27** 524–528. (doi:10.3109/09513590.2010.507289)

17 Lazar L, Padoa A & Phillip M. Growth pattern and final height after cessation of gonadotropin-suppressive therapy in girls with central sexual precocity. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3483–3489. (doi:10.1210/jc.2007-0321)

18 Mul D, Bertelloni S, Carel JC, Saggese G, Chaussain JL & Oostdijk W. Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. *Hormone Research* 2002 **58** 1–7. (doi:10.1159/000063209)

19 Tanaka T, Niimi H, Matsuo N, Fujieda K, Tachibana K, Ohyama K, Satoh M & Kugu K. Results of long-term follow-up after treatment of central precocious puberty with leuprorelin acetate: evaluation of effectiveness of treatment and recovery of gonadal function. The TAP-144-SR Japanese Study Group on Central Precocious Puberty. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 1371–1376. (doi:10.1210/jc.2004-1863)

20 Arrigo T, Cisternino M, Galluzzi F, Bertelloni S, Pasquino AM, Antoniazzi F, Borrelli P, Crisafulli G, Wasniewska M & De Luca F. Analysis of the factors affecting auxological response to GnRH agonist treatment and final height outcome in girls with idiopathic central precocious puberty. *European Journal of Endocrinology* 1999 **141** 140–144. (doi:10.1530/eje.0.1410140)

21 Bajpai A, Sharma J, Kabra M, Gupta AK & Menon PS. Long-acting GnRH analogue triptorelin therapy in central isosexual precocious puberty. *Indian Pediatrics* 2002 **39** 633–639.

22 Heger S, Partsch CJ & Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 4583–4590.

23 Jung MK, Song KC, Kwon AR, Chae HW, Kim DH & Kim HS. Adult height in girls with central precocious puberty treated with gonadotropin-releasing hormone agonist with or without growth hormone. *Annals of Pediatric Endocrinology & Metabolism* 2014 **19** 214–219. (doi:10.6065/apem.2014.19.4.214)

24 Klein KO, Barnes KM, Jones JV, Feuillan PP & Cutler GB Jr. Increased final height in precocious puberty after long-term treatment with LHRH agonists: the National Institutes of Health experience. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4711–4716. (doi:10.1210/jcem.86.10.7915)

25 Liang Y, Wei H, Li J, Hou L, Zhang J, Wu W, Ying Y & Luo X. Effect of GnRHa 3.75 mg subcutaneously every 6 weeks on adult height in girls with idiopathic central precocious puberty. *Journal of Pediatric Endocrinology and Metabolism* 2015 **28** 839–846. (doi:10.1515/jpem-2014-0305)

26 Kauli R, Galatzer A, Kornreich L, Lazar L, Pertzelan A & Laron Z. Final height of girls with central precocious puberty, untreated versus treated with cyproterone acetate or GnRH analogue. A comparative study with re-evaluation of predictions by the Bayley–Pinneau method. *Hormone Research* 1997 **47** 54–61. (doi:10.1159/000185432)

27 Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G & Saggese G. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. *European Journal of Pediatrics* 1998 **157** 363–367. (doi:10.1007/s004310050831)

28 Leger J, Reynaud R & Czernichow P. Do all girls with apparent idiopathic precocious puberty require gonadotropin-releasing hormone agonist treatment? *Journal of Pediatrics* 2000 **137** 819–825. (doi:10.1067/mpd.2000.109201)

29 Nabhan ZM, Feezle LK, Kunselman AR, Johnson NB & Lee PA. Normal adult height among girls treated for central precocious puberty with gonadotropin-releasing hormone analog therapy. *Journal of Pediatric Endocrinology & Metabolism* 2009 **22** 309–316. (doi:10.1515/JPEM.2009.22.4.309)

30 Brito VN, Latronico AC, Cukier P, Teles MG, Silveira LF, Arnhold IJ & Mendonca BB. Factors determining normal adult height in girls with gonadotropin-dependent precocious puberty treated with depot gonadotropin-releasing hormone analogs. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2662–2669. (doi:10.1210/jc.2007-2183)

31 Gillis D, Karavani G, Hirsch HJ & Strich D. Time to menarche and final height after histrelin implant treatment for central precocious puberty. *Journal of Pediatrics* 2013 **163** 532–536. (doi:10.1016/j.jpeds.2013.01.021)

32 Massart F, Federico G, Harrell JC & Saggese G. Growth outcome during GnRH agonist treatments for slowly progressive central precocious puberty. *Neuroendocrinology* 2009 **90** 307–314. (doi:10.1159/000231994)

33 Aguiar AL, Couto-Silva AC, Vicente EJ, Freitas IC, Cruz T & Adan L. Weight evolution in girls treated for idiopathic central precocious puberty with GnRH analogues. *Journal of Pediatric Endocrinology & Metabolism* 2006 **19** 1327–1334. (doi:10.1515/JPEM.2006.19.11.1327)

34 Wagner S IV, abin MA, Pfaffle RW, Hiemisch A, Sergeyev E, Korner A & Kiess W. Effects of obesity on human sexual development. *Nature Reviews. Endocrinology* 2012 **8** 246–254. (doi:10.1038/nrendo.2011.241)

35 Lazar L, Lebenthal Y, Yackobovitch-Gavan M, Shalitin S, de Vries L, Phillip M & Meyerovitch J. Treated and untreated women with idiopathic precocious puberty: BMI evolution, metabolic outcome, and general health between third and fifth decades. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 1445–1451. (doi:10.1210/jc.2014-3748)

36 Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanaka-Gantenbein C, Piaditis G *et al*. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. *Journal of Clinical Endocrinology and Metabolism* 2010 **95** 109–117. (doi:10.1210/jc.2009-0793)

37 Wolters B, Lass N & Reinehr T. Treatment with gonadotropin-releasing hormone analogues: different impact on body weight in normal-weight and overweight children. *Hormone Research in Paediatrics* 2012 **78** 304–311. (doi:10.1159/000346145)

38 van der Sluis IM, Boot AM, Krenning EP, Drop SL & de Muinck Keizer-Schrama SM. Longitudinal follow-up of bone density and body

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

composition in children with precocious or early puberty before, during and after cessation of GnRH agonist therapy. *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 506–512. (doi:10.1210/jcem.87.2.8202)

39 Colmenares A, Gunczler P & Lanes R. Higher prevalence of obesity and overweight without an adverse metabolic profile in girls with central precocious puberty compared to girls with early puberty, regardless of GnRH analogue treatment. *International Journal of Pediatric Endocrinology* 2014 **2014** 5. (doi:10.1186/1687-9856-2014-5)

40 Feuillan PP, Jones JV, Barnes K, Oerter-Klein K & Cutler GB Jr. Reproductive axis after discontinuation of gonadotropin-releasing hormone analog treatment of girls with precocious puberty: long term follow-up comparing girls with hypothalamic hamartoma to those with idiopathic precocious puberty. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 44–49. (doi:10.1210/jcem.84.1.5409)

41 Paterson WF, McNeill E, Young D & Donaldson MD. Auxological outcome and time to menarche following long-acting goserelin therapy in girls with central precocious or early puberty. *Clinical Endocrinology* 2004 **61** 626–634. (doi:10.1111/j.1365-2265.2004.02146.x)

42 Fisher MM, Lemay D & Eugster EA. Resumption of puberty in girls and boys following removal of the histrelin implant. *Journal of Pediatrics* 2014 **164** 912–916 (e911). (doi:10.1016/j.jpeds.2013.12.009)

43 Silverman LA, Neely EK, Kletter GB, Lewis K, Chitra S, Terleckyj O & Eugster EA. Long-term continuous suppression with once-yearly histrelin subcutaneous implants for the treatment of central precocious puberty: a final report of a phase 3 multicenter trial. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 2354–2363. (doi:10.1210/jc.2014-3031)

44 Jay N, Mansfield MJ, Blizzard RM, Crowley WF Jr, Schoenfeld D, Rhubin L & Boepple PA. Ovulation and menstrual function of adolescent girls with central precocious puberty after therapy with gonadotropin-releasing hormone agonists. *Journal of Clinical Endocrinology and Metabolism* 1992 **75** 890–894.

45 Lazar L, Meyerovitch J, de Vries L, Phillip M & Lebenthal Y. Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades. *Clinical Endocrinology* 2014 **80** 570–576. (doi:10.1111/cen.12319)

46 Bridges NA, Cooke A, Healy MJ, Hindmarsh PC & Brook CG. Ovaries in sexual precocity. *Clinical Endocrinology* 1995 **42** 135–140. (doi:10.1111/j.1365-2265.1995.tb01853.x)

47 Jensen AM, Brocks V, Holm K, Laursen EM & Muller J. Central precocious puberty in girls: internal genitalia before, during, and after treatment with long-acting gonadotropin-releasing hormone analogues. *Journal of Pediatrics* 1998 **132** 105–108. (doi:10.1016/S0022-3476(98)70493-7)

48 Franceschi R, Gaudino R, Marcolongo A, Gallo MC, Rossi L, Antoniazzi F & Tato L. Prevalence of polycystic ovary syndrome in young women who had idiopathic central precocious puberty. *Fertility and Sterility* 2010 **93** 1185–1191. (doi:10.1016/j.fertnstert.2008.11.016)

49 Cassio A, Bal MO, Orsini LF, Balsamo A, Sansavini S, Gennari M, De Cristofaro E & Cicognani A. Reproductive outcome in patients treated and not treated for idiopathic early puberty: long-term results of a randomized trial in adults. *Journal of Pediatrics* 2006 **149** 532–536. (doi:10.1016/j.jpeds.2006.05.026)

50 Heger S, Muller M, Ranke M, Schwarz HP, Waldhauser F, Partsch CJ & Sippell WG. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. *Molecular and Cellular Endocrinology* 2006 **254–255** 217–220.

51 Oostdijk W, Rikken B, Schreuder S, Otten B, Odink R, Rouwe C, Jansen M, Gerver WJ, Waelkens J & Drop S. Final height in central precocious puberty after long term treatment with a slow release GnRH agonist. *Archives of Disease in Childhood* 1996 **75** 292–297. (doi:10.1136/adc.75.4.292)

52 Neely EK, Lee PA, Bloch CA, Larsen L, Yang D, Mattia-Goldberg C & Chwalisz K. Leuprolide acetate 1-month depot for central precocious puberty: hormonal suppression and recovery. *International Journal of Pediatric Endocrinology* 2010 **2010** 398639. (doi:10.1186/1687-9856-2010-398639)

53 Michelmore KF, Balen AH, Dunger DB & Vessey MP. Polycystic ovaries and associated clinical and biochemical features in young women. *Clinical Endocrinology* 1999 **51** 779–786. (doi:10.1046/j.1365-2265.1999.00886.x)

54 Feuillan PP, Jones JV, Barnes KM, Oerter-Klein K & Cutler GB Jr. Boys with precocious puberty due to hypothalamic hamartoma: reproductive axis after discontinuation of gonadotropin-releasing hormone analog therapy. *Journal of Clinical Endocrinology and Metabolism* 2000 **85** 4036–4038. (doi:10.1210/jcem.85.11.6951)

55 Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F & Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. *European Journal of Pediatrics* 2000 **159** 369–374. (doi:10.1007/s004310051289)

56 Boot AM, De Muinck Keizer-Schrama S, Pols HA, Krenning EP & Drop SL. Bone mineral density and body composition before and during treatment with gonadotropin-releasing hormone agonist in children with central precocious and early puberty. *Journal of Clinical Endocrinology and Metabolism* 1998 **83** 370–373.

57 Park HK, Lee HS, Ko JH, Hwang IT, Lim JS & Hwang JS. The effect of gonadotrophin-releasing hormone agonist treatment over 3 years on bone mineral density and body composition in girls with central precocious puberty. *Clinical Endocrinology* 2012 **77** 743–748. (doi:10.1111/j.1365-2265.2012.04418.x)

58 Assa A, Weiss M, Aharoni D, Mor A, Rachmiel M & Bistritzer T. Evaluation of bone density in girls with precocious and early puberty during treatment with GnRH agonist. *Journal of Pediatric Endocrinology & Metabolism* 2011 **24** 505–510. (doi:10.1515/jpem.2011.170)

59 Alessandri SB, Pereira Fde A, Villela RA, Antonini SR, Elias PC, Martinelli CE Jr, Castro M, Moreira AC & Paula FJ. Bone mineral density and body composition in girls with idiopathic central precocious puberty before and after treatment with a gonadotropin-releasing hormone agonist. *Clinics* 2012 **67** 591–596. (doi:10.6061/clinics/2012(06)08)

60 Tung YC, Lee JS, Tsai WY & Hsiao PH. The effects of gonadotropin releasing hormone analogue therapy on girls with gonadotropin-dependent precocious puberty. *Journal of the Formosan Medical Association* 2007 **106** 826–831. (doi:10.1016/S0929-6646(08)60047-9)

Received 15 June 2015
Revised version received 4 October 2015
Accepted 14 October 2015

Downloaded from Bioscientifica.com at 04/06/2023 09:20:54PM
via free access

EXHIBIT 12

Hormone Research in Paediatrics

Research Article

Horm Res Paediatr 2020;93:529–538
DOI: 10.1159/000513702

Received: August 14, 2020
Accepted: December 3, 2020
Published online: March 26, 2021

Fertility of Women Treated during Childhood with Triptorelin (Depot Formulation) for Central Precocious Puberty: The PREFER Study

Laetitia Martinerie[a, b] Jacques de Mouzon[c] Joelle Blumberg[d] Luigi di Nicola[e] Pascal Maisonobe[d] Jean-Claude Carel[a, b] on behalf of the PREFER study group

[a]Université de Paris, AP-HP. Nord Université de Paris, Hôpital Universitaire Robert-Debré, Service d'Endocrinologie Diabétologie Pédiatrique et Centre de Référence des Maladies Endocriniennes Rares de la Croissance, Paris, France; [b]NeuroDiderot, INSERM, Université de Paris, Paris, France; [c]INSERM Hôpital Bicêtre, Le Kremlin Bicêtre, France; [d]Ipsen Innovation, Les Ulis, France; [e]Ipsen Pharma, Boulogne-Billancourt, France

Keywords

Fertility · Gonadotropin-releasing hormone analogue · Precocious puberty · Pregnancy · Triptorelin (depot formulation)

Abstract

Background: Gonadotropin-releasing hormone analogues (GnRHa) administered as depot formulations are the standard of care for children with central precocious puberty (CPP). Puberty resumes after treatment discontinuation, but little is known concerning fertility in women who have been treated with GnRHa for CPP during childhood. ***Methods:*** The PREFER (PREcocious puberty, FERtility) study prospectively analysed fertility, via a series of questionnaires, in women treated during childhood with triptorelin (depot formulation) for CPP. Co-primary endpoints were the proportion of women wanting a pregnancy any time before study inclusion and during the follow-up period but not pregnant 6 and 12 months after stopping contraception and the waiting time to pregnancy (WTP). ***Results:*** A total of 574 women were identified, and 194 women were included in the analysis. Although there were not enough data for primary endpoint assessment, few women (1.7%) reported issues with fertility or were unable to become pregnant despite trying to conceive. Most pregnancies (84.4%, 95% CI [67.2–94.7%]) occurred within 1 year of trying to conceive, in line with the WTP for women without previous CPP. ***Conclusion:*** The results, based on a limited sample of patients, suggest that CPP treated with triptorelin does not negatively impact women's fertility in adulthood. These results need to be consolidated with a subsequent study performed when these women will have reached their mid-thirties.

© 2021 The Author(s).
Published by S. Karger AG, Basel

Introduction

Precocious puberty (PP) is generally defined as the appearance of the first signs of puberty (breast development in girls and testis enlargement in boys) before the age of 8 years for girls or 9 years for boys [1, 2]. PP can be sub-

PREFER study group: Anne-Marie Bertrand, Hélène Bony, Michel Bost, Sylvie Cabrol, Hélène Carla, Maryse Cartigny, Michel Colle, Régis Coutant, Marc de Kerdanet, François Despert, Gwenaëlle Diene, Lise Duranteau, Frédéric Huet, Monique Jesuran, Bernard Le Luyer, Claudine Lecointre, Bruno Leheup, Guy André Loeuille, Eric Mallet, Catherine Naud-Saudreau, Marc Petrus, Catherine Pienkowski, Sylvie Soskin, Hélène Thibaud, Kathy Wagner, and Jacques Weill.

karger@karger.com
www.karger.com/hrp

© 2021 The Author(s).
Published by S. Karger AG, Basel

This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission.

Karger
OPEN ACCESS

Jean-Claude Carel
Université Paris Diderot, Sorbonne Paris Cité, Service d'Endocrinologie Diabétologie Pédiatrique, Hôpital Universitaire Robert-Debré
48 boulevard Sérurier, FR–75935 Paris Cedex 19 (France)
jean-claude.carel@inserm.fr

divided into gonadotropin-releasing hormone (GnRH)-dependent and -independent causes. GnRH-dependent PP, also called central precocious puberty (CPP), is due to the early activation of the hypothalamus-pituitary-gonadal axis [3]. Treatment with long-acting GnRH analogues (GnRHa) is the standard of care in children with CPP [4–12]. GnRHa desensitise the pituitary gonadotropic cells to GnRH [13] and decrease FSH and LH secretion and gonadal activation. Their short-term effects on pubertal development are well documented. Long-term effects have been reviewed, but their evaluation is limited by the lack of randomized controlled trials [5, 12].

Discontinuation of GnRHa results in the resumption of puberty [14–16] and in a short post-treatment growth spurt [17–21]. In girls, menarche occurs on average 1 year after treatment discontinuation [17, 22, 23]. There are relatively few data on gonadal function in adolescents and adult women who have been treated for CPP. An increased frequency of signs and symptoms of polycystic ovarian syndrome has been observed in women who had CPP, with potential consequences on fertility, but this remains controversial [5, 12].

The influence of CPP and/or its treatment on reproductive functions is an essential endpoint and is a frequent question asked by parents when GnRHa treatment is discussed. A review of the literature reported that among >100 pregnancies reported in 9 studies in women treated for CPP, there were 97 uneventful pregnancies resulting in healthy children, 5 elective abortions, and 11 early miscarriages [12]. Moreover, the rate of spontaneous pregnancy seems similar between women who have previously been treated with GnRHa for CPP (90.4%; n = 135) and women who did not have CPP during childhood (93.4%; n = 446) [24]. Nevertheless, few large-cohort studies have been published investigating the long-term impact of GnRHa treatment for CPP on fertility in women.

The PREFER (PREcocious puberty, FERtility) study prospectively analysed fertility in a large cohort of women treated during childhood with triptorelin (depot formulation) for CPP. The questionnaire-based study was conducted in France, and the results were compared to those of the general French population.

Methods

The PREFER study was a longitudinal, descriptive, non-comparative, epidemiological study of women treated during childhood with the GnRHa triptorelin (depot formulation; 28-day formulation [3 mg]) for CPP. The study was conducted in 27 centres in France between February 2007 and November 2009. Approval from the French Advisory Committee on the Processing of Information for Medical Research (CCTIRS) was received on June 21, 2006. Approval from the French Data Protection Authority (CNIL) was received on November 3, 2006. The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before enrolment in the study.

Participants

Participants were women aged ≥18 years in 2006 (born in 1988 or earlier) who had been treated during childhood with triptorelin (depot formulation) for idiopathic CPP and had initiated triptorelin therapy between 1984 and 1996. Exclusion criteria were CPP secondary to a peripheral production of androgens or oestrogens (e.g., adrenal hyperplasia or gonadal disorder), CPP of neoplastic origin (except hamartomas), and chromosomal abnormality. Women with CPP associated with adoption were included in the study. Enrolling clinical centres identified potential participants by reviewing archives and checking clinical files against the study inclusion criteria to confirm eligibility.

Study Design

The PREFER study examined fertility in women retrospectively during the 2 years before inclusion and prospectively during a 12-month post-inclusion follow-up period. The primary objective was to analyse the fertility of women treated during childhood with triptorelin (monthly depot formulation) for CPP. Fertility was assessed via a series of questionnaires completed by the women. Secondary objectives were to assess the progress and outcome of any pregnancy, ovarian function and biometrics, concomitant description of fertility with the aetiology of PP and its treatment (duration of GnRHa therapy) or any other medical intervention that might have affected puberty (surgery and other additional treatments), and the socioeconomic consequences of CPP (academic level, relationship status, and occupation).

Assessments

A medical questionnaire was completed by participating centres to gather the following data: chronological age, bone age and Tanner stage at the time of diagnosis and treatment of CPP, GnRH stimulation test results, pelvic ultrasound results, and treatments used (GnRHa therapy and other additional treatments, if applicable). Women were contacted, and their agreement to participate was obtained with a signed informed consent form. Women who agreed to participate completed an inclusion questionnaire on their sociodemographic and fertility status. Follow-up questionnaires were sent to participants 6 months and 12 months after inclusion to assess fertility, pregnancy status, and the outcomes of any pregnancy (see online suppl. Table 1; see www.karger.com/doi/10.1159/000513702 for all online suppl. material).

Endpoints

Co-primary endpoints were the proportion of women desiring pregnancy any time before inclusion and during the follow-up period but not pregnant at 6 and 12 months and the waiting time to pregnancy (WTP: time between attempting to conceive and be-

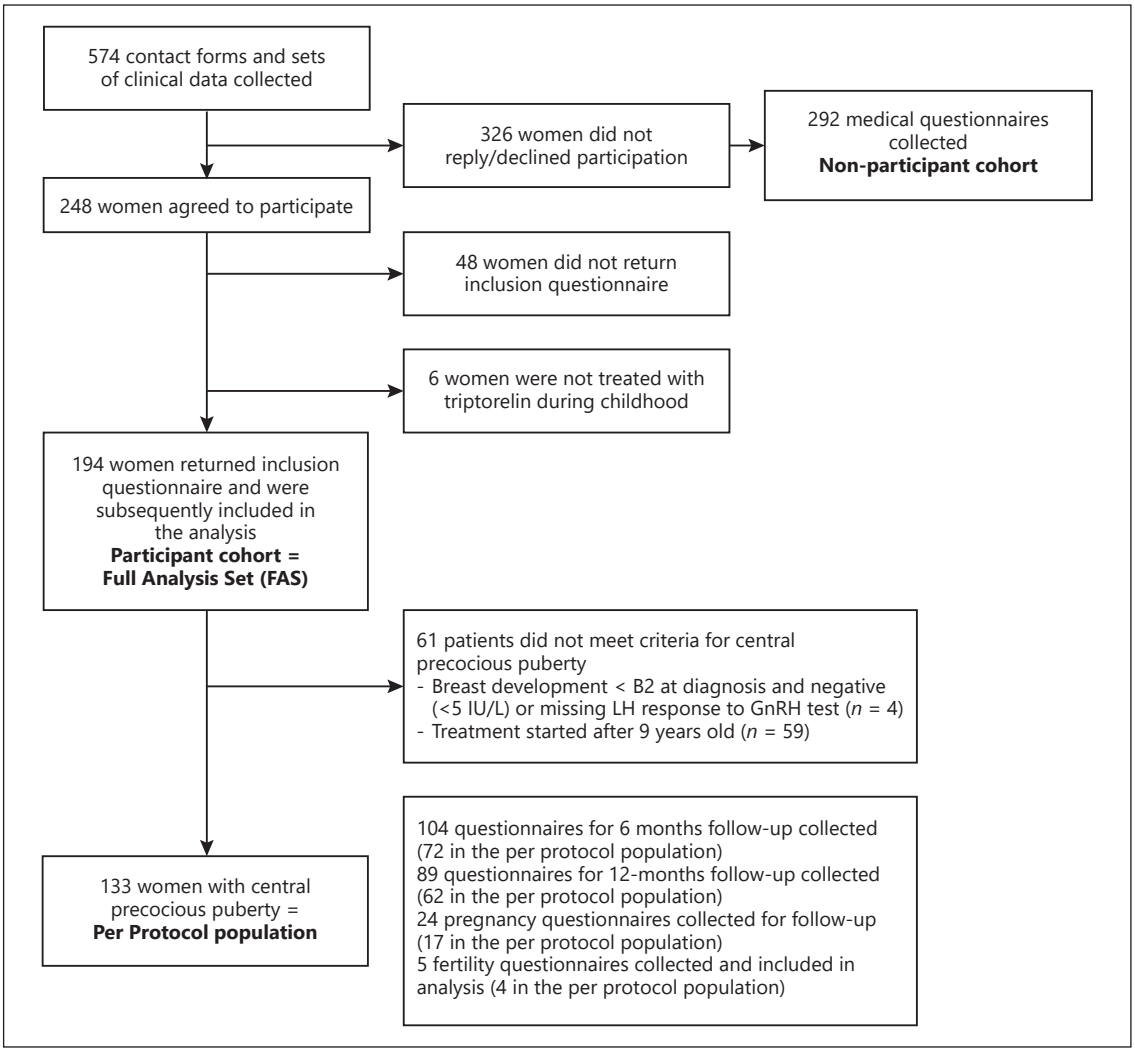


Fig. 1. PREFER study flowchart. FAS, full analysis set; GnRH, gonadotropin-releasing hormone; CPP, central precocious puberty.

coming pregnant) before inclusion. Secondary endpoints (collected at inclusion, 6 months, and 12 months) were the proportion of consultations for infertility or diagnosis of infertility (attempting to conceive for 1 year and no pregnancy or diagnosed during a consultation with a physician) during the 2 years prior to inclusion or during the follow-up period, proportion of unplanned pregnancies prior to the onset of the study, proportion of previous pregnancies and the difficulty in achieving them, proportion of spontaneous abortions and ectopic pregnancies, and the mode of delivery for pregnancies. Only the first pregnancy was considered for all endpoints. Other secondary endpoint data collected at inclusion were age at puberty (defined by onset of menarche), regularity and length of menstrual cycles and menstrual irregularities, current height, weight, and BMI, smoking status, academic level, occupation, and relationship status.

Sample Size and Statistical Analysis

The sample size needed to determine the 1-year pregnancy rate in women was 162. This was based on a 1-year pregnancy rate in the general population of 85% of women attempting pregnancy [25], with a 10% precision rate, an alpha risk of 0.05, and 15% loss of participants to follow-up. Taking into account the age distribution of mothers at the time they give birth [26] and the age distribution of women in France [27], it can be calculated that approximately 27% of women aged 18–30 years will give birth within a 3-year period. Based on these assumptions, a target of 597 patients was set for this study. Assuming that 60% of the patients contacted would be willing to participate (as shown in the feasibility study), 995 women treated for CPP needed to be contacted. Checks for population biases were performed by comparing data (height, weight, chronological age, statural age, bone age, Tanner stage, and proportion of patients with menses) at diagnosis and at the start and end of triptorelin treatment collected from partici-

Table 1. Clinical characteristics of PP in participants and non-participants

Variable	Participants				Non-participants	
	FAS population		per protocol population			
	mean ± SD (range)	*N*	mean ± SD (range)	*N*	mean ± SD*	*N*
Age at diagnosis of CPP, years	8.0±1.5 (1.5–11.3)	186	7.5±1.5 (1.5–9)	129	7.6±1.5	292
Age at initiation of triptorelin therapy, years	8.3±1.4 (1.5–11.3)	178	7.8±1.4 (1.5–9)	122	7.9±1.5	292
Height at initiation of triptorelin therapy, cm	132.7±9.3 (87.5–153.5)	182	130.9±9.8 (87.5–150)	124	132.6±10.7	292
Bone age at initiation of triptorelin therapy, years	10.2±1.5 (3.5–13)	162	9.8±1.6 (3.5–12)	109	10.1±1.6	292
Breast development at initiation of triptorelin (Tanner stage)		165		110		237
B1	2.4%	4	1.8%	2$	0%	0
B2	43%	71	37.3%	41	45.6%	108
B3	47.9%	79	55.5%	61	46.4%	110
B4–5	6.7%	11	5.4%	6	8.0%	19
Pubic hair development at initiation of triptorelin (Tanner stage)		173		118		249
P1	25.4%	44	27.1%	32	19.7%	49
P2	48%	83	49.2%	58	55.4%	138
P3	22%	38	21.2%	25	20.9%	52
P4–5	4.6%	8	2.5%	3	4.0%	10
Age at end of triptorelin therapy, years	10.6±0.9 (3.4–12.8)	177	10.4±1.0 (3.4–12.8)	121	10.3±1.2	292
Duration of triptorelin therapy, years	2.4±1.2 (0.5–8.6)	181	2.7±1.3 (0.5–8.6)	124	na	–
Bone age at the end of triptorelin treatment, years	11.7±1.0 (3.5–13.5)	165	11.7±1.1 (3.5–13.5)	111	11.4±1.1	292
Age at menarche, years	11.8±1.4 (7.0–16.0)	174	11.6±1.4 (7.0–16.0)	119	na	–

PP, precocious puberty; na, not available; CPP, central precocious puberty; FAS, full analysis set. * No range was available for the non-participants' data. $ Two women with Tanner stage B1 were included since they had a peak LH level >5 IU/L.

pants' medical records and also from women who did not reply or declined participation in the study. Data from the questionnaires were entered into an electronic database. However, given the difficulties in retrieving old patient records and chart data, only minimal data monitoring could be performed. Qualitative variables were presented using number of missing data, frequency, and percentage; quantitative variables were presented using frequency of missing and non-missing values, mean, standard deviation, and range (minimum and maximum). Binomial 95% confidence intervals (CI) were computed for proportions. Statistical analysis was performed using SAS® software (v9.4). Inconsistent data were discarded. During the analysis, 2 population of patients were considered, a full analysis set (FAS) population including all participants and a per protocol population excluding patients who did not respect the criteria for CPP, in particular in terms of age at onset (initiating treatment after the age of 9 years, considering a maximum of 1 year between onset and start of treatment), pubertal development (absence of breast development), and GnRH test results (prepubertal) (Fig. 1). A clinical study report was produced in September 2015 and was the basis for an earlier version of this manuscript. However, during the review process, a number of inconsistencies in the analysis were highlighted. Therefore, data analysis was resumed in 2019–2020. The current manuscript and an updated version of the clinical study report are based on this new analysis of the data that had been collected in 2007–2009. The study was approved by the "Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé" on July 21, 2006 (#06.118), and by the "Commission nationale de l'informatique et des libertés" on November 3, 2006 (#906229).

Results

Participants

Overall, 574 women meeting the inclusion criteria were identified at 27 centres in France between February 2007 and November 2009 (Fig. 1; Table 1). There were 3–97 women per centre and 248 accepted to participate (43%, 0–62% for each centre, median 41%), with a final cohort of 194 women included (FAS population) and 133 women in the per protocol population. The clinical characteristics of participants were very similar to those who did not participate (Table 1). The mean age of participants at study inclusion was approximately 24 years, and their self-reported social characteristics and gynaecological history are presented in Table 2. It is noteworthy that the mean height (162 cm) was close to the national average height (163 cm) [28], and that >50% of participants aged ≥25 years had completed full-length higher education programmes (online suppl. Table 2).

Table 2. Characteristics of participants at inclusion (FAS population and per protocol population)

Variable	FAS population		Per protocol population	
	mean ± SD (range)[a]	*N*[b]	mean ± SD (range)[a]	*N*[b]
Age at inclusion, years	24.3±3.0 (18.4–33.3)	187/194	24.3±3.1 (18.4–30.8)	128/133
Proportion with regular menstrual cycles, *n* (%)	126 (68.1)	185/194	86 (67.7)	127/133
Cycle length, days	28.4±1.7 (24–34)	86/126[c]	28.3±1.5 (26–33)	65/86[c]
Age at first sexual intercourse, years	17.5±2.2 (14.0–26.0)	167/173[d]	17.4±2.3 (14.0–26.0)	114/117[d]
Height, cm	161.6±6.1 (145.0–178.0)	188/194	161.9±6.3 (145–178)	128/133
Weight, kg	61.1±13.1 (40.0–147.0)	185/194	61.7±13.6 (43–147)	126/133
BMI, kg/m^2	23.4±4.8 (15.9–50.9)	184/194	23.5±4.8 (15.9–50.9)	125/133
Smoking status, *n* (%)		188/194		128/133
Current smoker	54 (28.7)		37 (28.9)	
Former smoker	23 (12.2)		9 (7.0)	
Non-smoker	111 (59.0)		82 (64.1)	
In a relationship, *n* (%)	123 (68.3)	180/194	81 (66.4)	122/133
Live together	79 (65.3)	121/123[e]	48 (60.8)	79/81[e]
Do not live together	42 (34.7)	121/123[e]	31 (39.2)	79/81[e]
Not in a relationship	57 (31.7)	180/194	41 (33.6)	122/133
Highest academic level, *n* (%)		194		133
None	5 (2.6)		3 (2.3)	
Completed only primary school	1 (0.5)		1 (0.8)	
Completed junior secondary school (up to 15 years)	12 (6.2)		10 (7.6)	
Completed technical college	15 (7.7)		12 (9.0)	
Completed secondary school (baccalaureate)	53 (27.3)		38 (28.6)	
Completed 2-year programme of university studies	28 (14.4)		20 (15.0)	
Achieved full-length university studies	80 (41.2)		49 (36.8)	
Occupation, *n* (%)		192		132
Employed	105 (54.7)		76 (57.6)	
Student or in training	67 (34.9)		44 (33.4)	
Housewife/not working	7 (3.6)		4 (3.0)	
Unemployed	13 (6.8)		8 (6.1)	
Professional category for those employed,[f] *n* (%)		124		87
Employee	78 (62.9)		55 (63.2)	
Senior executive	22 (17.7)		16 (18.4)	
Middle management employee	18 (14.5)		12 (13.8)	
Farmer	2 (1.6)		1 (1.1)	
Self-employed/freelancer	3 (2.4)		2 (2.3)	
Tradeswoman	1 (0.8)		1 (1.1)	

FAS, full analysis set; CPP, central precocious puberty; SD, standard deviation. [a] Unless otherwise stated. [b] Due to the nature of the study, data are not available for all participants for each parameter, and thus the number of participants for which the parameter was available is indicated. [c] Number of women with regular menstrual cycle. [d] Number of women that already had first sexual intercourse at study inclusion. [e] Number of women in a relationship. [f] Excludes participants who responded under professional category that they were students or unemployed.

Pregnancy

At inclusion, 142 women in the FAS population (97 in the per protocol population) had never been pregnant (Table 3). Of these women, 85.2% in the FAS population and 85.6% in the per protocol population declared they did not want to become pregnant, and 2.1 and 3.1%, respectively, declared that they had been unable to become pregnant. At inclusion, 43 women in the FAS population (31 in the per protocol population) declared they had been pregnant and 4/42 (9.5%) reported difficulties to conceive (3/30 [10.0%] in the per protocol population). These 43 women in the FAS population reported 62 past pregnancies (30 [69.8%] 1 pregnancy, 9 [20.9%] 2 pregnancies, and 4 [9.3%] 3 or 4 pregnancies). Similar numbers of pregnancies were observed in the per protocol population. During the study, primigravida pregnancies

Table 3. Participants' desire for pregnancy and pregnancy outcomes before inclusion in the study

Variable	FAS population (*N* = 194) *n* (%)	Per protocol population (*N* = 133) *n* (%)
Did not want to become pregnant	121/142[a] (85.2)	83/133[a] (85.6)
Unable to become pregnant	3/142[a] (2.1)	3/97[a] (3.1)
Women pregnant prior to inclusion, *n*	43/194 (22.2)	31/133 (23.3)
Pregnancies prior to inclusion, *n*	62	46
Wanted	22 (52.4)	16 (53.3)
Unexpected	16 (38.1)	11 (36.7)
Occurred despite using contraception	4 (9.5)	3 (10.0)
Data missing	1	1
Pregnancy outcomes for pregnancies before inclusion or ongoing at time of inclusion	45	32
Delivery	28[b] (62.2)	21[b] (65.6)
Elective abortion	13 (28.9)	8 (25.0)
Abortion for medical reasons[c]	3 (6.7)	2 (6.3)
Miscarriage	1 (2.2)	1 (3.1)

FAS, full analysis set. [a] Denominator is all women never having been pregnant at inclusion in the FAS/per protocol population. [b] Including 1 twin birth. [c] The high number of medical abortions is likely due to a misunderstanding of respondents with elective abortion.

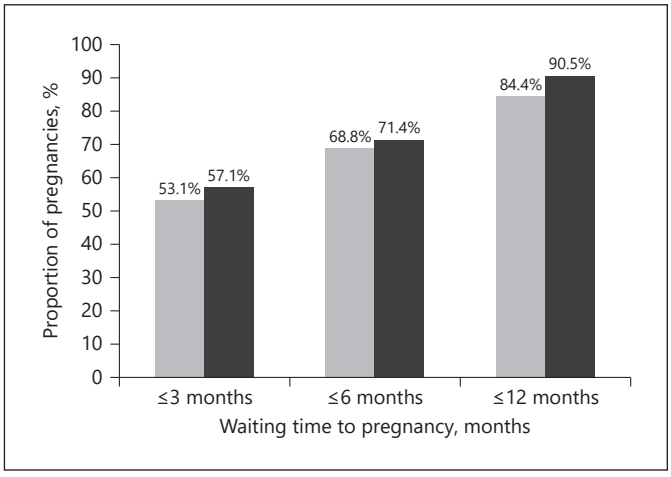


Fig. 2. WTP for pregnancies occurring before inclusion in the PREFER study. The proportion of women with various WTP is represented for the pregnancies with this information available in the FAS population (*n* = 32, black boxes) and in the per protocol population (*n* = 21, grey boxes). WTP, waiting time to pregnancy; FAS, full analysis set.

were reported by 6 women at inclusion, 4 at 6 months, and 2 at 12 months of follow-up in the FAS population. Therefore, at least 55/194 (28.4%) participants (37/133 [27.8%] in the per protocol population) had at least 1 pregnancy before or during study follow-up. WTP was available for 32 pregnancies that occurred prior to inclusion in the study and 21 pregnancies in the per protocol population and showed that a pregnancy was achieved within 12 months for 27/32 (84.4%) women (95% CI [67.2–94.7%]) in the FAS population and 19/21 (90.5%) women in the per protocol population (95% CI [69.6–98.8%]) (Fig. 2).

Fertility

At 6 and 12 months in the study, 78/92 (84.8%) and 66/73 (90.4%), respectively, of participants in the FAS population reported using contraception, therefore limiting the number of patients who were eligible for the infertility and pregnancy questionnaires. At inclusion in the study, among the women in the FAS population with available data, 1/132 (0.8%) reported having a fertility problem, 25/132 (18.9%) reported having no fertility problem, 35/132 (26.5%) did not know whether they had a fertility problem, and 71/132 (53.8%) felt that the question did not apply to them. Results were similar in the per protocol population. Three women had sought advice for infertility before participation in the study, 1 of whom had also reported having a fertility problem.

At 6 months and 12 months in the study, 5/85 (5.9%) and 0/52, respectively, of the participants in the FAS population had consulted a physician during the previous 6 months for difficulties in conceiving. Finally, among the women in the FAS population who had stopped contra-

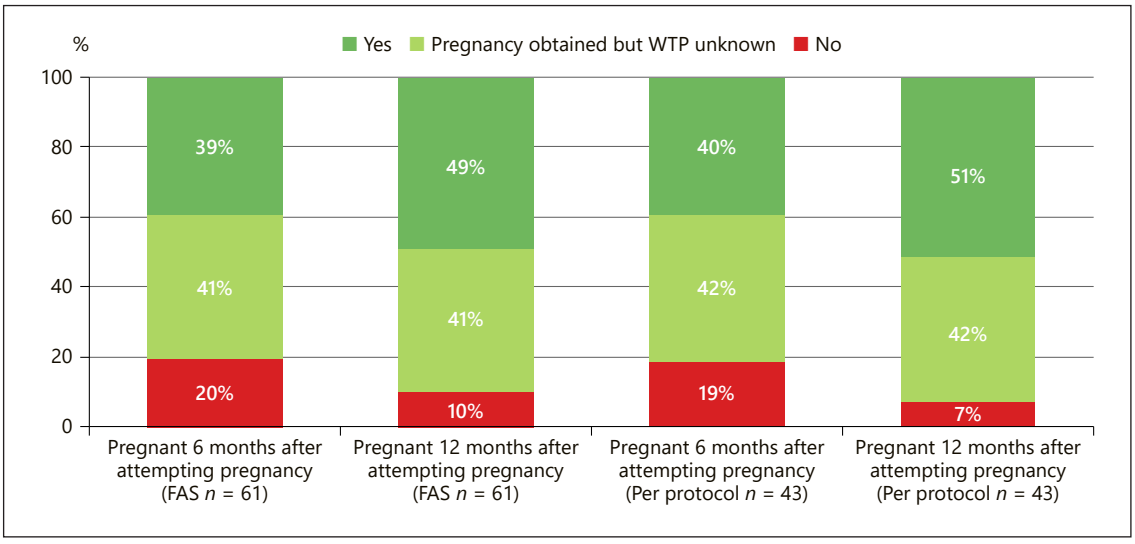


Fig. 3. Proportion of women with pregnancy among those desiring pregnancy 6 and 12 months after having stopped contraception methods. The analysis was performed on women pregnant at least once or trying to get pregnant and having stopped all contraception methods. Modality "unknown" concerns women with unexpected pregnancies or missing dates to calculate WTP. All pregnancies or pregnancy attempts were considered including those before the study, at study inclusion, and at 6-month and 12-month follow-up. WTP, waiting time to pregnancy; FAS, full analysis set.

ception and were trying to conceive during the study, 12/61 (19.7%) and 6/61 (9.8%) were not pregnant after attempting pregnancy for 6 and 12 months, respectively (Fig. 3).

Discussion

In the PREFER study, few (1.7%) women reported problems with fertility or were unable to become pregnant despite trying to conceive. Most pregnancies (84.4%, 95% CI [67.2–94.7%]) in the PREFER study cohort occurred within 1 year of trying to conceive, and the 12-month WTP was similar to that previously published for women without CPP trying to conceive (~85%) [25, 29–31]. Most women who had not been pregnant up to the day of inclusion or during the study declared they did not want a pregnancy. Our results support those from previous studies in patients treated during childhood with GnRHa for CPP [24, 32, 33] and highlight the fact that fertility outcomes are better evaluated in women in their late 20s than mid-20s, given the median age of 28 years at first pregnancy in France 2007 (INED) [34].

The proportion of women who reported a fertility problem in our study (1.7%) was particularly low and needs to be compared with results from other similar studies and from the general population. Lazar et al. [24] reported higher prevalence of fertility problems of 11.1 and 10.9% of women who had received triptorelin treatment for CPP or early puberty, respectively. In the general population, an international review of 25 population surveys sampling 172,413 women reported a median prevalence of infertility of 9% [35]. In a US cross-sectional cohort study of 4,558 women, 623 (13.7%) and 328 (7.2%) reported seeking an infertility evaluation and undergoing subsequent infertility treatment, respectively [36]. The younger age of the population included in the PREFER study (mean 24 years) compared with the Lazar study (mean 33 years) could have contributed to these differences; moreover, fertility mostly declines after the age of 35 years [37].

Interestingly, the PREFER study participants had a higher level of education than expected in the general population, which possibly had an influence on the study results. Over half of the respondents who were 25 years or over had completed full-length higher education programmes, compared with only 18% of 25- to 49-year old women in the general population in France [38]. The proportion of women with an occupation was higher in the PREFER study than in the French general population. There were more senior management executives, employees, and students and less inactive persons in the PREFER study population than in the general population [38]. This may result from selection

Horm Res Paediatr 2020;93:529–538
DOI: 10.1159/000513702

biases, either from increased awareness of CPP in families with a higher level of education or from increased willingness to complete the questionnaire in those with a higher educational/professional status. In contrast, Lazar et al. [24] reported that the educational level of women with CPP (whether treated or untreated) was similar to that of the general population. In addition, early puberty in general (i.e., not associated with CPP per se) has been reported to detrimentally affect academic performance and subsequent academic achievement, including the lesser likelihood of pursuing a college education and the tendency to be employed in lower-paying, less prestigious jobs [39]. Although the design of the PREFER study does not allow us to explain why its patient population has such a high level of education, it is clear that this affects our analysis of fertility in this cohort, given the association between age at first pregnancy and level of education with a mean of 29 years for high versus 26 years for intermediate and 24 years for low educational levels in France [40].

The PREFER study has several limitations. The primary objective was to analyse prospectively the fertility of women treated during childhood with triptorelin (depot formulation) for CPP. However, once all the questionnaires had been collected, there were insufficient data to conclude on the primary endpoint (i.e., the proportion of women desiring a pregnancy but not pregnant 6 and 12 months after having stopped all contraception methods). Therefore, the proportion of women achieving pregnancy after 12 months (84.4%) was calculated on a small sample of 32 pregnancies leading to wide confidence intervals (95% CI [67.2–94.7%]). The design of the questionnaires also meant that certain parameters could not be fully documented (e.g., although data on total number of pregnancies were collected, most detailed information was collected on a maximum of 3 pregnancies per woman, but some women were pregnant >3 times). Consequently, some planned analyses could not be performed, and some aberrant values were discarded. Data that could not be presented were duration of pregnancy, distribution of birth weight and sex ratio, rate of preterm births and macrosomy, rate of stillbirths and birth defects, episodes of amenorrhoea or menstrual irregularities, acne and body hair, hormonal treatments initiated before or since puberty, hormone monitoring and abnormal hormone levels, characterisation of CPP, any episodes of triptorelin treatment suspension, and concomitant treatments.

In addition, a high proportion of patients declined to participate or did not respond to the invitation to participate. We were able to compare height, weight, chronological age, bone age, and Tanner stage at the time of diagnosis of CPP and at the beginning and end of treatment with triptorelin for the 292 non-participants and the 194 women included in the study. No statistically significant difference was found between participants and non-participants. While this suggests that there was no selection bias based on these parameters, the educational status of women differed, however, between the PREFER study cohort and populations in other studies and in the general population. This may have resulted from patient- or centre-selection bias. Nevertheless, the method of data collection in the PREFER study allowed a large cohort to be studied with the use of standardized questionnaires.

Conclusion

The PREFER study showed that the WTP and pregnancy rate for women treated during childhood with triptorelin (depot formulation) for CPP was consistent with that reported for the general population in France, although with a wide confidence interval. Women in the PREFER study cohort had a low prevalence of infertility. These results, based on a limited sample of patients, suggest that CPP treated during childhood with the GnRHa triptorelin does not negatively impact women's fertility in adulthood. Given the age profile of the PREFER cohort, these results need to be consolidated with a subsequent study performed 10 years later to assess, retrospectively, fertility and infertility rates when these women will have reached their mid-thirties.

Acknowledgements

We acknowledge the participation of the PREFER study group and thank Anne-Marie Bertrand, Hélène Bony, Michel Bost, Sylvie Cabrol, Hélène Carla, Maryse Cartigny, Michel Colle, Régis Coutant, Marc de Kerdanet, François Despert, Gwenaëlle Diene, Lise Duranteau, Frédéric Huet, Monique Jesuran, Bernard Le Luyer, Claudine Lecointre, Bruno Leheup, Guy André Loeuille, Eric Mallet, Catherine Naud-Saudreau, Marc Petrus, Catherine Pienkowski, Sylvie Soskin, Hélène Thibaud, Kathy Wagner, and Jacques Weill for their contributions to the study and article. We acknowledge the role of Ceri Medical, Paris 75,017, in the collection and management of data. The authors take full responsibility for the content of this article and thank Martin Gilmour of ESP Bioscience, Crowthorne, UK (supported by Ipsen), for editorial assistance in the preparation of the manuscript. We also acknowledge the contribution of Brigitte Palestro, Medical Director at Ipsen Pharma, and Pascal Colin, Clinical Data Group Leader at Ipsen Innovation.

Statement of Ethics

The study was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant before enrolment in the study. Approval for use of medical records and data was obtained from the French Advisory Committee on the Processing of Information for Medical Research (CCTIRS) and the French Data Protection Authority (CNIL).

Conflict of Interest Statement

Jean-Claude Carel is a co-ordinating investigator for a study sponsored by Ipsen Pharma. Jacques de Mouzon had a contract as a scientific advisor for Ipsen Pharma, performed the statistical analyses, and created a study report for the initial PREFER study. Laetitia Martinerie has received lecture fees from Ipsen Pharma and has been invited by Ipsen Pharma to attend international scientific meetings. Joelle Blumberg, Luigi di Nicola, and Pascal Maisonobe are present or former employees of Ipsen Pharma.

References

1 Carel JC, Léger J. Clinical practice. Precocious puberty. N Engl J Med. 2008;358(22):2366–77.
2 British Society for Paediatric Endocrinology and Diabetes. Shared care guidelines: use of gonadotrophin releasing hormone (GnRH) agonists – triptorelin. British Society for Paediatric Endocrinology and Diabetes; 2012.
3 Eugster EA, Palmert MR. Precocious puberty. J Clin Endocrinol Metab. 2006;91(9):E1.
4 Carel JC, Blumberg J, Seymour C, Adamsbaum C, Lahlou N. Triptorelin 3-month C. P. P. study group. Three-month sustained-release triptorelin (11.25 mg) in the treatment of central precocious puberty. Eur J Endocrinol. 2006;154:119–24.
5 Carel JC, Eugster EA, Rogol A, Ghizzoni L, Palmert MR; Espe-Lwpes GnRH Analogs Consensus Conference Group, et al. Consensus statement on the use of gonadotropin-releasing hormone analogs in children. Pediatrics. 2009;123(4):e752–62.
6 Oostdijk W, Hümmelink R, Odink RJ, Partsch CJ, Drop SL, Lorenzen F, et al. Treatment of children with central precocious puberty by a slow-release gonadotropin-releasing hormone agonist. Eur J Pediatr. 1990;149(5):308–13.
7 Partsch CJ, Hümmelink R, Peter M, Sippell WG, Oostdijk W, Odink RJ, et al. Comparison of complete and incomplete suppression of pituitary-gonadal activity in girls with central precocious puberty: influence on growth and predicted final height. The German-Dutch Precocious Puberty Study Group. Horm Res. 1993;39(3–4):111–7.
8 Carel JC, Lahlou N, Guazzarotti L, Joubert-Collin M, Roger M, Colle M, et al. Treatment of central precocious puberty with depot leuprorelin. French Leuprorelin trial group. Eur J Endocrinol. 1995;132(6):699–704.
9 Chiocca E, Dati E, Baroncelli GI, Cassio A, Wasniewska M, Galluzzi F, et al. Central precocious puberty: treatment with triptorelin 11.25 mg. ScientificWorldJournal. 2012;2012:583751.
10 Martinez-Aguayo A, Hernandez MI, Beas F, Iniguez G, Avila A, Sovino H, et al. Treatment of central precocious puberty with triptorelin 11.25 mg depot formulation. J Pediatr Endocrinol Metab. 2006;19:963–70.
11 Carel JC, Lahlou N, Jaramillo O, Montauban V, Teinturier C, Colle M, et al. Treatment of central precocious puberty by subcutaneous injections of leuprorelin 3-month depot (11.25 mg). J Clin Endocrinol Metab. 2002;87(9):4111–6.
12 Guaraldi F, Beccuti G, Gori D, Ghizzoni L. Management of endocrine disease: long-term outcomes of the treatment of central precocious puberty. Eur J Endocrinol. 2016;174(3):R79–87.
13 Lahlou N, Carel JC, Chaussain JL, Roger M. Pharmacokinetics and pharmacodynamics of GnRH agonists: clinical implications in pediatrics. J Pediatr Endocrinol Metab. 2000;13 Suppl 1(Suppl 1):723–37.
14 Bertelloni S, Baroncelli GI. Current pharmacotherapy of central precocious puberty by GnRH analogs: certainties and uncertainties. Expert Opin Pharmacother. 2013;14(12):1627–39.
15 Jaruratanasirikul S, Thaiwong M. Outcome of gonadotropin-releasing analog treatment for children with central precocious puberty: 15-year experience in southern Thailand. J Pediatr Endocrinol Metab. 2011;24(7–8):519–23.
16 Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, et al. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. J Clin Endocrinol Metab. 1988;67(2):368–72.
17 Kauli R, Kornreich L, Laron Z. Pubertal development, growth and final height in girls with sexual precocity after therapy with the GnRH analogue D-TRP-6-LHRH. A report on 15 girls, followed after cessation of gonadotrophin suppressive therapy. Horm Res. 1990;33(1):11–7.
18 Carel JC, Roger M, Ispas S, Tondu F, Lahlou N, Blumberg J, et al. Final height after long-term treatment with triptorelin slow release for central precocious puberty: importance of statural growth after interruption of treatment. French Study Group of Decapeptyl in Precocious Puberty. J Clin Endocrinol Metab. 1999;84(6):1973–8.
19 Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, et al. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. J Clin Endocrinol Metab. 2010;95(1):109–17.
20 Mul D, Bertelloni S, Carel JC, Saggese G, Chaussain JL, Oostdijk W. Effect of gonadotropin-releasing hormone agonist treatment in boys with central precocious puberty: final height results. Horm Res. 2002;58(1):1–7.
21 Nabhan ZM, Feezle LK, Kunselman AR, Johnson NB, Lee PA. Normal adult height among girls treated for central precocious puberty with gonadotropin-releasing hormone analog therapy. J Pediatr Endocrinol Metab. 2009;22(4):309–16.
22 Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab. 2008;93(1):190–5.
23 Poomthavorn P, Suphasit R, Mahachoklertwattana P. Adult height, body mass index and time of menarche of girls with idiopathic central precocious puberty after gonadotropin-releasing hormone analogue treatment. Gynecol Endocrinol. 2011;27(8):524–8.
24 Lazar L, Meyerovitch J, de Vries L, Phillip M, Lebenthal Y. Treated and untreated women with idiopathic precocious puberty: long-term follow-up and reproductive outcome between the third and fifth decades. Clin Endocrinol. 2014;80(4):570–6.
25 de Mouzon J, Spira A, Schwartz D. A prospective study of the relation between smoking and fertility. Int J Epidemiol. 1988;17(2):378–84.
26 Blondel B, Supernant K, du Mazaubrun C, Breart G. Perinatal National Survey 2003. 2005.
27 Prioux F. Recent demographic developments in France. Population-F. 2004;59:683–724.
28 Sempé M, Pédron G, Roy-Pernot M. Auxologie, Méthode et Séquences. Paris: Théraplix; 1979.
29 Gnoth C, Godehardt D, Godehardt E, Frank-Herrmann P, Freundl G. Time to pregnancy: results of the German prospective study and impact on the management of infertility. Hum Reprod. 2003;18(9):1959–66.

30 Juhl M, Nyboe Andersen AM, Grønbaek M, Olsen J. Moderate alcohol consumption and waiting time to pregnancy. Hum Reprod. 2001;16(12):2705–9.
31 Juul S, Karmaus W, Olsen J. Regional differences in waiting time to pregnancy: pregnancy-based surveys from Denmark, France, Germany, Italy and Sweden. The European Infertility and Subfecundity Study Group. Hum Reprod. 1999;14:1250–4.
32 Heger S, Müller M, Ranke M, Schwarz HP, Waldhauser F, Partsch CJ, et al. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. Mol Cell Endocrinol. 2006; 254–255:217–20.
33 Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab. 1999; 84(12):4583–90.
34 European Commission. EuroStat births and fertility data. 2013.
35 Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. Hum Reprod. 2007;22(6):1506–12.
36 Kessler LM, Craig BM, Plosker SM, Reed DR, Quinn GP. Infertility evaluation and treatment among women in the United States. Fertil Steril. 2013;100(4):1025–32.
37 Kimberly L, Case A, Cheung AP, Sierra S, AlAsiri S, Carranza-Mamane B, et al. Advanced reproductive age and fertility: no. 269, November 2011. Int J Gynaecol Obstet. 2012; 117(1):95–102.
38 Institut national de la statistique et des études économiques. Insee. 2009.
39 Mendle J, Turkheimer E, Emery RE. Detrimental psychological outcomes associated with early pubertal timing in adolescent girls. Dev Rev. 2007;27(2):151–71.
40 Robert-Bobée I, Rendall M, Couet C, Lappegard T, Rønsen M, Smallwood S. Âge au premier enfant et niveau d'études : une analyse comparée entre la France, la Grande-Bretagne et la Norvège. In: Données sociales : La société française Édition 2006. Institut nationational de la statistique et des éstudes économiques; 2006. p. 69–76.

EXHIBIT 13

INTERNATIONAL REVIEW OF PSYCHIATRY, 2016
VOL. 28, NO. 1, 13–20
http://dx.doi.org/10.3109/09540261.2015.1115754

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Gender dysphoria in childhood

Jiska Ristori[a] and Thomas D. Steensma[b,c]

[a]Department of Experimental, Clinical and Biomedical Sciences, Careggi University Hospital, Florence, Italy; [b]Department of Medical Psychology, VU University Medical Centre, Amsterdam, the Netherlands; [c]Centre of Expertise on Gender Dysphoria, VU University Medical Center, Amsterdam, the Netherlands

ABSTRACT

Gender dysphoria (GD) in childhood is a complex phenomenon characterized by clinically significant distress due to the incongruence between assigned gender at birth and experienced gender. The clinical presentation of children who present with gender identity issues can be highly variable; the psychosexual development and future psychosexual outcome can be unclear, and consensus about the best clinical practice is currently under debate.

In this paper a clinical picture is provided of children who are referred to gender identity clinics. The clinical criteria are described including what is known about the prevalence of childhood GD. In addition, an overview is presented of the literature on the psychological functioning of children with GD, the current knowledge on the psychosexual development and factors associated with the persistence of GD, and explanatory models for psychopathology in children with GD together with other co-existing problems that are characteristic for children referred for their gender. In light of this, currently used treatment and counselling approaches are summarized and discussed, including the integration of the literature detailed above.

ARTICLE HISTORY
Received 26 October 2015
Accepted 27 October 2015
Published online 7 January 2016

KEYWORDS
Gender identity; gender dysphoria; childhood; psychosexual development; persistence; treatment

Introduction

Children can vary in the extent to which they show gender role expressions, behaviours, interests, and preferences. For most children these expressions are largely congruent with their experience of being male or female – their gender identity – and in line with the gender assigned at birth. This is in contrast to children who experience gender dysphoria (GD). These children show extreme and enduring forms of gender nonconforming/gender variant behaviours, preferences, and interests because they do not identify with their birth-assigned gender. Because of the incongruence between their assigned gender and experienced gender, these children may experience clinically significant distress and are consequently often in need of clinical attention (American Psychiatric Association, 2013).

Although there has been much opposition against diagnosing GD in prepubescent children, primarily due to the stigmatizing effect of having a mental disorder (e.g. Drescher, 2013), the condition is included in the current edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association, 2013) as well as in the *International Classification of Diseases* (ICD-10; World Health Organization, 1992). The World Health Organization (WHO) is, however, in the process of revising the tenth version of the ICD; but instead of removal of the childhood diagnosis the terminology will most likely be changed from 'gender identity disorder of childhood' into 'gender incongruence of childhood' (Drescher, Cohen-Kettenis, & Winter, 2012).

According to the DSM-5, a diagnosis of GD of childhood can be made if a child experiences a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by six out of eight criteria. One *sine qua non* criterion must be the experience of a strong desire to be of another gender or an insistence to be another gender. In addition to this, there are two criteria focusing on anatomic dysphoria; a dislike of one's sexual anatomy and the desire for primary/secondary sex characteristics of the experienced gender. In addition there are five behavioural criteria. The behavioural criteria concern the preference for cross-dressing; adopting cross-gender roles in fantasy play; a strong preference for toys, games and activities of the other gender; a preference for playmates of the other gender; and a strong aversion or rejection of typically gender congruent roles, interests, preferences and behaviours. Furthermore, the condition is associated with clinically

CONTACT Jiska Ristori jiskaristori@libero.it Department of Experimental, Clinical and Biomedical Sciences, Careggi University Hospital, Viale Pieraccini 6, 50139 Florence, Italy

© 2016 Taylor & Francis

significant distress or impairment in social, school, or other important areas of functioning (American Psychiatric Association, 2013).

Valid information on the prevalence of childhood GD is not available yet due to the absence of formal prevalence studies. An estimate of the prevalence of gender nonconforming/gender variant behaviours can, however, be made on the basis of studies where the Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983) was used. On the CBCL – a parent-report questionnaire on behavioural problems – two items are related to gender variance: Item 5 ('Behaves like opposite sex') and item 110 ('Wishes to be of opposite sex'). Information from the Dutch normative sample of the CBCL shows that in children, both items are more frequently endorsed by parents of girls than of boys; 'Behaves like opposite sex' in 2.6% of the boys and 5.0% of the girls, 'Wishes to be of opposite sex' in 1.4% of the boys and 2.0% of the girls (Verhulst, van der Ende, & Koot, 1996). These findings are in concordance with data from the normative sample of the CBCL in North-America (Achenbach & Edelbrock, 1981; Zucker, Bradley, & Sanikhani, 1997), and are largely replicated in a study of Dutch twins (N = 23,393) at ages 7 and 10 (Van Beijsterveldt, Hudziak, & Boomsma, 2006). Therefore, gender variance/gender nonconformity seems to be present in a small percentage of children and is more prominent in girls than in boys.

Interestingly, from what we know about the referrals to specialized gender identity clinics, the sex ratios for referred prepubescent children have always been in favour of natal men, which may be a direct effect of a difference in increased acceptance of masculinity in girls compared to femininity in boys (e.g. Blakemore, 2003; Cohen-Kettenis et al., 2003; Steensma et al., 2014; Wallien, Veenstra, Kreukels, & Cohen-Kettenis, 2010; Zucker, Wilson-Smith, Kurita, & Stern, 1995). Over the last decades the reported sex ratios have, however, gradually changed. For example, in the period before 2000 the ratio between boys and girls was 5.75:1 in Canada and 2.93:1 in the Netherlands (Cohen-Kettenis et al., 2003). In the period after 2000, the sex ratios decreased in Canada to 3.41:1 (2008–2011) for boys and girls respectively (Wood et al., 2013); and a similar pattern was observed in the Netherlands with a sex ratio of 1.68:1 between 2008 and 2011 (Steensma, 2013). For both countries this change in ratios is caused by fewer referrals of boys. Although empirical evidence is currently not available, the decrease of referrals in boys may indicate an increasing tolerance over time towards gender nonconforming behaviours in both countries.

Psychological functioning, social tolerance, and other co-existing problems

Besides the gender nonconforming presentation, children with GD who are referred to clinical settings have been shown to be more psychologically vulnerable in comparison to non-referred controls (Bates, Bentler, & Thompson, 1973, 1979) and in comparison to the general population (e.g. Cohen-Kettenis et al., 2003; Singh, Bradley, & Zucker, 2011; Steensma et al., 2014). Furthermore, these studies show that these psychological problems are more of an internalized nature (such as depression, social withdrawal, and anxiety), instead of an externalizing nature (such as aggression) (Bates et al., 1973, 1979; Coates & Person, 1985; Rekers & Morey, 1989; Zucker & Bradley, 1995; Cohen-Kettenis et al., 2003; Steensma et al., 2014). However, as Zucker, Wood, and VanderLaan (2014) recently concluded from their summary of studies reporting on the psychological functioning of gender-referred children, there is a considerable variability across the different studies. For example, the percentage of clinical-range cases reported in studies using the total behaviour problem score of the CBCL, ranged from 12.5% up to 84% of the described children over the different studies (for an overview see Zucker et al., 2014).

To understand this association between GD and the variability of psychological functioning within the population of children with GD, the empirical literature indicates the effect is largely mediated through social (in)tolerance towards gender nonconformity/gender variance. Indeed, a wide range of studies in children from the general population showed that gender nonconforming behaviour is often evaluated negatively by other children (e.g. Carter & McCloskey, 1984; Levy, Taylor, & Gelman, 1995; Ruble et al., 2007; Signorella, Bigler, & Liben, 1993; Stoddart & Turiel, 1985). Peer relations in general are therefore poorer for clinically referred children with GD than for non-referred children/youth (e.g. Cohen-Kettenis et al., 2003; Zucker et al., 1997, 2012); and, as we might expect, poor peer relations are associated with a negative well-being and poor psychological functioning in children with GD (e.g. Cohen-Kettenis et al. 2003; Steensma et al., 2014). Consequently the variability in psychological functioning detailed within the literature is likely inversely correlated with the intensity of social intolerance experienced by the children with GD. For example, a cross-national study between children referred for their gender from Canada and from the Netherlands showed a much higher prevalence of emotional and behavioural problems in the Canadian children than in the Dutch children. Interestingly, quality of peer relations rather

than IQ, parental social class, marital status, or ethnicity, turned out to be the strongest predictor in both countries. Furthermore, the quality of peer relations was lower in Canada than in the Netherlands. This indicates that psychological functioning is highly dependent upon how gender nonconformity is accepted within a certain culture or environment (Steensma et al., 2014).

However, this may not be the only factor that results in poorer psychological functioning. Over the years other models postulated in the literature focused, for example, upon generic risk factors for psychopathology and behavioural problems (such as parental psychopathology, social class background) in relation to GD; and considered them as an inherent cause of psychological problems in children with GD. Evidence for these relations is, however, still scarce and both models are under-studied in comparison to other factors such as social (in)tolerance (Zucker et al., 2014).

As far as co-occurring problems in children with GD are concerned, the relationship between Autistic Spectrum Disorders (ASD) and GD is important to mention. Although there are few studies investigating the relationship between the two, one study by de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers (2010) showed that in a sample of 108 gender-referred children ASD was present in 6.4% of the children. This is significantly higher than the prevalence of 0.6–1% of ASD in the general population (Fombonne, 2005). Corresponding with these findings, a study by VanderLaan et al. (2015) of children referred for gender studied obsessional interests – which may be an indication of ASD – and showed that obsessions were more frequently reported by children referred for their gender in comparison with the general population. With regard to how ASD and GD are related, the question arises as to whether GD is an expression of ASD, or whether ASD is a symptom of GD; alternatively, of course, the two may be present without being related to each other (see van der Miessen et al., this issue).

Psychosexual development and related factors for persistence of GD

A central question in the counselling of children with GD is what their psychosexual outcome will be. Will the child grow up and identify as a gay man, lesbian woman, bisexual man or woman, or heterosexual man or woman without experiencing feelings of gender incongruence which require any intervention; or will the child need medical treatment in the future because the gender dysphoric feelings will persist and further intensify?

To date, there are 10 prospective follow-up studies described in the literature, together reporting on 317 gender nonconforming children who were followed-up in adolescence or early adulthood. The follow-up information in Zucker & Bradley (1995) is not included in this summary. In personal correspondence with Dr. Zucker it became clear that the 45 cases described are also included in the samples of Drummond, Bradley, Peterson-Badali, & Zucker (2008) (5 natal girls) and Singh (2012) (40 natal boys).

The conclusion from these studies is that childhood GD is strongly associated with a lesbian, gay, or bisexual outcome and that for the majority of the children (85.2%; 270 out of 317) the gender dysphoric feelings remitted around or after puberty (see Table 1).

However, there may be a number of arguments to nuance this high percentage of desistence. As is shown in Table 1 there is much variation in the reported persistence rates between the studies, ranging from 2% to 39%. Interestingly the studies before the year 2000 reported much lower persistence rates in comparison to the more recent studies after the year 2000. Furthermore, the persistence rates reported in two Canadian studies (Drummond et al., 2008; Singh, 2012) were identical (12%) but clearly lower in comparison to the follow-up study by Wallien & Cohen-Kettenis (2008) from the Netherlands. The explanation for these differences may be threefold:

First, the variation in intensity of GD in the children included differs across studies: 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 the publication of DSM-III in 1980 there was no formal diagnosis of GD for children (Drescher, 2014). 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

Table 1. Follow-up studies in children with GD.

Study	Sample	Age at follow-up (range)	Persistence rate
Bakwin (1968) Lebovitz (1972) Zuger (1984) Money & Russo (1979) Davenport (1986) Kosky (1987)	55 natal boys	(13–36)	9% (5 out of 55)
Green (1987)	44 natal boys	19 (14–24)	2% (1 out of 44)
Drummond et al. (2008)	25 natal girls	23 (15–37)	12% (3 out of 25)
Wallien & Cohen-Kettenis (2008)	40 natal boys 14 natal girls	19 (16–28)	39% (21 out of 54)
Singh (2012)	139 natal boys	21 (13–39)	12% (17 out of 139)

studies consisted of clinically referred samples of children, which was not the case for the earlier studies. For example, in the study by Green (1987) the sample of feminine boys was recruited through advertisement.

Secondly, and in line with the intensity explanation, there are possible cultural differences in referral: As described earlier, the sex ratios of child referrals in Canada are historically in greater favour of boys than girls as compared to the Netherlands. This may indicate that femininity in boys is experienced as more problematic in Canada –resulting in more referrals of boys with less extreme GD than in the Netherlands. As a result, the persistence rates are higher in the Netherlands compared to Canada.

Thirdly, we can consider the time of follow-up: As can be seen in Table 1, the time of follow-up differed across the studies and one could hypothesize that the studies with a later follow-up age (of older adolescents or adults) and those having a longer follow-up time, would report higher persistence rates than the studies where the follow-up took place at a younger age (i.e. shorter follow-up time). This trend is however not observed over the reported studies. To test this hypothesis, Steensma & Cohen-Kettenis (2015) recently published a report on the first 150 childhood cases from Amsterdam, the Netherlands, and checked whether a longer follow-up period would result in higher persistence rates. The children were at the time of first assessment – between 5 to 12 years old and between 19 to 38 years of age at the time of follow-up. Out of the 150 cases, 40 re-entered the clinic during adolescence (12–18 years of age) and turned out to be persisters (26.7%). However, after checking the files of the adult clinic (which sees nearly all adults with gender dysphoria in the Netherlands), it appeared that five individuals applied for treatment after the age of 18, raising the persistence rate to 30% and showing the importance of long-term follow-ups. Based on this information, it seems reasonable to conclude that the persistence of GD may well be higher than 15%. However, desistence of GD still seems to be the case in the majority of children with GD.

Two other clinically relevant questions are (1) whether we know anything with regard to the factors that are associated with the persistence or desistence of childhood GD and (2) how the process of persistence or desistence is experienced.

As to the factors associated with the persistence of GD, knowledge is still limited but fortunately slowly increasing. A central finding from all quantitative studies focusing on the topic is that the persistence of GD is most closely linked to the intensity of the GD in childhood and the amount of reported cross-gendered behaviour; in other words the more intense GD is in childhood, and the more cross-gendered behaviour is reported by parents or through self-report, the higher the chance that the GD persists (Drummond et al., 2008; Singh, 2012; Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013; Wallien & Cohen-Kettenis, 2008). In addition to this, several other factors are linked to persistence of GD: For example, Steensma et al. (2013) and Wallien & Cohen-Kettenis (2008) showed that the persistence rate is generally higher in natal girls than in natal boys; And Steensma et al. (2013) and Singh (2012) found that the assessment age in childhood was higher in children where the GD persisted than for desisters; Further, Singh (2012) reported a higher social class in the parents of desisters compared to the parents of persisters.

In addition, Steensma et al. (2013) found that a social transition in childhood, especially in natal boys, and verbal identification with the desired/experienced gender was predictive for the persistence of GD. Interestingly, the identification finding was reported in an earlier qualitative study by Steensma, Biemond, de Boer & Cohen-Kettenis (2011) who observed differences in reported experiences of GD between persisters and desisters who were interviewed. For example, the persisters explicitly indicated that they felt they *were* the 'other' sex and the desisters indicated that they only *wished* they were the 'other' sex. The primary aim of the Steensma et al. (2011) study was to get a better understanding of the processes that contribute to the persistence and desistence of childhood GD. By interviewing adolescents (14 persisters, 11 desisters) who all fulfilled the DSM-IV or DSM-IV-TR criteria of a gender identity diagnosis in childhood (APA, 1994, 2000), it became clear that the period between 10 and 13 years was considered crucial. Both persisters and desisters stated that the changes in their social environment, the anticipated and actual feminization or masculinization of their bodies, and the first experiences of falling in love and sexual attraction in this period, contributed to an increase (in the persisters) or decrease (in the desisters) of their gender related interests, behaviours, and feelings of gender discomfort.

Treatment and counselling of children with GD

Over the last decade, the care for prepubescent children with GD has been rapidly changing and there is a growing number of specialized gender clinics for young people (Hsieh & Leininger, 2014; Khatchadourian, Ahmed, & Metzger, 2014; Riittakerttu, Sumia, Työläjärvi, & Lindberg, 2015). Best clinical practice in gender referred children is still controversial and raises debates among dedicated professionals. General agreement does, however, exist that the care for children with

GD should be focused on reducing the child's distress related to their GD; on help with other psychological difficulties; and optimizing psychological adjustment and wellbeing (e.g. Byne et al., 2012; Coleman et al., 2011). As for the counselling of the gender dysphoric feelings in children with GD; empirical treatment models do not exist and general consensus between clinicians is not always easy to obtain (Byne et al., 2012). In the current professional literature, three treatment models for the care of gender variant children can be distinguished (e.g. Byne et al., 2012; Drescher, 2013) and it is these to which we now turn.

The first approach focuses on working with the child and caregivers to lessen cross-gender behaviour and identification, to persuade the child that the 'right gender' is the one assigned at birth (Giordano, 2012), to decrease the likelihood that GD will persist into adolescence, and prevent adult transsexualism. Critics of this approach have linked it to 'reparative therapy', a term more commonly used to describe efforts to change same sex attraction to heterosexuality in gay adults or 'pre-homosexual' children (Drescher, 2013). In the past, such behavioural and psychodynamic therapies to lessen the GD have been largely used in children with GD with overall unsatisfactory results (Byne et al., 2012; Möller, Schreier, Li, & Romer, 2009). Instead, children often seem to become distressed if their preferences and/or behaviours are blocked (Richardson, 1999). At present, interventions aimed to lessen GD are referred to as unethical by the World Professional Association for Transgendered Health (WPATH: Coleman et al., 2011) and many other international professional organizations. The American Academy of Child & Adolescent Psychiatry, for example, has explicitly formulated their position against any psychological treatment aimed to change gender nonconforming behaviours (Adelson, 2012).

The second approach is focused on dealing with the potential social risks for the child (Byne et al., 2012). Because its aim is to allow the progress of the GD in the child to unfold in a natural way, it is often referred to as 'watchful waiting' (Drescher, 2013). Counselling based on this approach may include interventions that focus on the co-existing problems of the child and/or the family; helping parents and the child to bear the uncertainty of the child's psychosexual outcome; and providing psychoeducation to help the child and the family to make balanced decisions regarding topics such as the child's coming out, early social transitioning, and/or how to handle peer rejection or social ostracism. In practice, the child and parents are encouraged to find a balance between an accepting and supportive attitude toward GD, while at the same time protecting the child against any negative reactions and remaining realistic about the chance that GD feelings may desist in the future. Parents are encouraged to provide enough space for their child to explore their gender dysphoric feelings, while at the same time keeping all future outcomes open (e.g., de Vries & Cohen-Kettenis, 2012; Di Ceglie, 1998, 2014).

The third approach is focused on affirming the child's (trans)gender identification and helps the child to build a positive self-identity and gender resilience. In particular, the child is supported in transitioning to the desired/experienced gender role. The rationale for supporting social transition before puberty is that children can revert to their originally assigned gender if necessary since the transition is solely at a social level and without medical intervention (e.g. Byne et al., 2012; Drescher, 2013; Hill, Menvielle, Sica, & Johnson, 2010). Critics of this approach believe that supporting gender transition in childhood may indeed be relieving for children with GD but question the effect on future development. The debate thereby focuses on whether a transition may increase the likelihood of persistence because, for example, a child may 'forget' how to live in the original gender role and therefore will no longer be able to feel the desire to change back; or that transitioned children may repress doubts about the transition out of fear that they have to go through the process of making their desire to socially (re)transition public for a second time (Steensma, 2013). The fact that transitioning for a second time can be difficult was indeed shown in the qualitative study by Steensma et al. (2011) where children who transitioned early in childhood reported a struggle with changing back to their original gender role when their feelings desisted, with the fear of being teased or excluded by their peers reported as the main reason for this.

Unfortunately, empirical answers about the best way to counsel children with GD and their caregivers are currently not available. The WPATH have therefore formulated a balanced position in their Standards of Care (Coleman et al., 2011), where clinicians are encouraged to help families by providing information about what is known about the development of children with GD and to help them to make decisions where the potential benefits and challenges of particular choices are weighted.

Conclusion

According to the DSM-5 diagnostic criteria for gender dysphoria, children with GD experience clinically significant distress because of the incongruence between their assigned gender at birth and experienced gender (APA, 2013). The clinical presentation of children who

present with gender identity issues is characterized by gender-nonconformity and a vulnerability to having psychological problems – primarily of an internalized nature (e.g. Cohen-Kettenis et al., 2003; Steensma et al., 2014), and an increased likelihood of ASD symptomatology (de Vries et al., 2010; VanderLaan et al., 2015). The extent and intensity of all three characteristics can be variable.

When considering the development of children with GD; studies show that gender dysphoric feelings eventually desist for the majority of children with GD, and that their psychosexual outcome is strongly associated with a lesbian, gay, or bisexual sexuality which does not require any medical intervention, instead of an outcome where medical intervention is required (e.g. Drummond et al., 2008; Wallien & Cohen-Kettenis, 2008; Singh, 2012). Factors predictive for the persistence of GD have been identified on a group level, with higher intensity of GD in childhood identified as the strongest predictor for a future gender dysphoric outcome (Steensma et al., 2013). The predictive value of the identified factors for persistence are, however, on an individual level less clear cut, and the clinical utility of currently identified factors is low.

Taken together this shows that there can be a great variability with regard to presentation of children with GD and their psychosexual outcome. The counselling of children with GD can therefore be complex and clinically challenging. To date, there is general agreement that the care for children with GD should not be aimed at avoiding adult same sex attraction or transsexualism; that no medical intervention should be provided in childhood (before puberty); that counselling should therefore be focused on reducing the child's distress related to the GD, on help with other psychological difficulties, and on optimizing psychological adjustment and wellbeing (e.g. Byne et al., 2012; Coleman et al., 2011).

However, besides these basic clinical values, there is currently no general consensus about the best approach to dealing with the (uncertain) future development of children with GD, and making decisions that may influence the functioning and/or development of the child – such as a social transition. Different clinical approaches are presented in the literature, and indeed taking the variability in presentation of children with GD into account, it seems important to underline that a 'one size fits all' approach is not best practice for children with GD. Therefore, different kinds of treatment options should be available which respect the unique needs of every child. In particular, the child's clinical psychological profile and gender development, as well as the contextual psychosocial characteristics of the child's family (e.g. belief system, supportive behaviours, access to health care) should always be taken into account in order to make balanced decisions. Currently, the limited empirical evidence in favour of a particular treatment makes treatment of teenagers with GD a controversial issue that raises intense, and often polarized, debate. Therefore, studies comparing different psychological treatment options are needed as well as research which aims to identify the factors involved in the persistence process of GD on an individual level. The primary goal is therefore to determine the safest and most efficacious mental and medical approach for the individual child with GD.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Achenbach, T.M., & Edelbrock, C.S. (1981). Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monographs of the Society for Research in Child Development*, 46(1), Serial No.188.

Achenbach, T.M., & Edelbrock, C.S. (1983). *Manual for the child behavior checklist and revised child behavior profile*. Burlington, VT: University of Vermont, Department of Psychiatry.

Adelson, S.L. (2012). Practice parameter on gay, lesbian, or bisexual sexual orientation, gender nonconformity, and gender discordance in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 51, 957–974.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: American Psychiatric Press.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: American Psychiatric Press.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (fifth edition). Washington, DC: American Psychiatric Press.

Bakwin, H. (1968). Deviant gender-role behavior in children: Relation to homosexuality. *Pediatrics*, 41, 620–629.

Bates, J.E., Bentler, P.M., Thompson, S.P. (1973). Measurement of deviant gender development in boys. *Child Development*, 44, 591–598.

Bates, J.E., Bentler, P.M., Thompson, S.P. (1979). Gender-deviant boys compared with normal and clinical control boys. *Journal of Abnormal Child Psychology*, 7, 243–259.

Blakemore, J. E. O. (2003). Children's beliefs about violating gender norms: Boys shouldn't look like girls, and girls shouldn't act like boys. *Sex Roles*, 48, 411–419.

Byne, W., Bradley, S.J., Coleman, E., Eyler, A.E., Green, R., Menvielle, E.J., . . . Tompkins, D.A. (2012). Report of the American Psychiatric Association Task Force on Treatment

of Gender Identity Disorder. *Archives of Sexual Behavior*, 41, 759–796.

Carter, D.B., & McCloskey, L.A. (1984). Peers and the maintenance of sex-typed behavior: The development of childrens' conceptions of cross-gender behavior in their peers. *Social Cognition*, 2, 294–314.

Coates, S., & Person, E.S. (1985). Extreme boyhood femininity: Isolated behavior or pervasive disorder? *Journal of the American Academy of Child Psychiatry*, 24, 702–709.

Cohen-Kettenis, P.T., Owen, A., Kaijser, V.G., Bradley, S.J., & Zucker, K.J. (2003). Demographic characteristics, social competence, and problem behavior in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. *Journal of Abnormal Child Psychology*, 31, 41–53.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., . . . Zucker, K. (2011). Standards of care for the health of transsexual, transgender and gender non-conforming people, version 7. *International Journal of Transgenderism*, 13, 165–232.

Davenport, C.W. (1986). A follow-up study of 10 feminine boys. *Archives of Sexual Behavior*, 15, 511–517.

de Vries, A. L. C., Noens, I.L., Cohen-Kettenis, P.T., van Berckelaer-Onnes, I.A., & Doreleijers, T. A. H. (2010). Autism spectrum disorders in gender dysphoric children and adolescents. *Journal of Autism and Developmental Disorders*, 40, 930–936.

de Vries, A.L., & Cohen-Kettenis, P.T. (2012). Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *Journal of Homosexuality*, 59, 301–320.

Di Ceglie, D. (1998). Management and therapeutic aims with children and adolescents with gender identity disorders and their families. In: D. Di Ceglie & D. Freedman (Eds.), *A Stranger in my own body: Atypical gender identity development and mental health*. London: Karnac Books, pp. 185–197.

Di Ceglie, D. (2014). Care for Gender-Dysphoric Children. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 151–169.

Drescher, J. (2013). Controversies in Gender Diagnoses. *LGBT Health*, 1, 10–14.

Drescher, J. (2014). Gender identity diagnoses: History and controversies. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 137–150.

Drescher, J., Cohen-Kettenis, P., & Winter, S. (2012). Minding the body: situating gender identity diagnoses in the ICD-11. *International Review of Psychiatry*, 24, 568–577.

Drummond, K.D., Bradley, S.J., Peterson-Badali, M., Zucker, K.J. (2008). A follow-up study of girls with gender identity disorder. *Developmental Psychology*, 44, 34–45.

Fombonne, E. (2005). Epidemiology of autistic disorder and other pervasive developmental disorders. *Journal of Clinical Psychiatry*, 66(Suppl 10), 3–8.

Giordano, S. (2012). *Children with gender identity disorder, a clinical, ethical and legal analysis*. London and New York: Routledge.

Green, R. (1987). *The 'sissy boy syndrome' and the development of homosexuality*. New Haven, CT: Yale University Press.

Hill, D.B., Menvielle, E., Sica, K.M., & Johnson, A. (2010). An affirmative intervention for families with gender variant children: Parental ratings of child mental health and gender. *Journal of Sex and Marital Therapy*, 36, 6–23.

Hsieh, S., & Leininger, J. (2014). Resource list: Clinical care programs for gender-nonconforming children and adolescents. *Pediatric Annals*, 43, 238–244.

Khatchadourian, K., Ahmed, S., & Metzger, D.L. (2014). Clinical management of youth with gender dysphoria in Vancouver. *The Journal of Pediatrics*, 164, 906–911.

Kosky, R.J. (1987). Gender-disordered children: Does inpatient treatment help? *Medical Journal of Australia*, 146, 565–569.

Lebovitz, P.S. (1972). Feminine behavior in boys: Aspects of its outcome. *American Journal of Psychiatry*, 128, 1283–1289.

Levy, G.D., Taylor, M.G., & Gelman, S.A. (1995). Traditional and evaluative aspects of flexibility in gender roles, social conventions, moral rules, and physical laws. *Child Development*, 66, 515–531.

Möller, B., Schreier, H., Li, A., & Romer, G. (2009). Gender Identity Disorder in Children and Adolescents. *Current Problems in Pediatric and Adolescent Health Care*, 39(5), 117–143.

Money, J., & Russo, A.J. (1979). Homosexual outcome of discordant gender identity/role: Longitudinal follow-up. *Journal of Pediatric Psychology*, 4, 29–41.

Rekers, G.A., & Morey, S.M. (1989). Relationship of maternal report of feminine behaviors and extraversion to clinician's rating of gender disturbance. *Perceptual and Motor Skills*, 69, 387–394.

Richardson, J. (1999). Response: finding the disorder in gender identity disorder. *Harvard Review of Psychiatry*, 7, 43–50.

Riittakerttu, K., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child and Adolescent Psychiatry and Mental Health*, 9, 9–9.

Ruble, D.N., Taylor, L., Cyphers, L., Greulich, F.K., Lurye, L.E. & Shrout, P.E. (2007). The role of gender constancy in early gender development. *Child Development*, 78, 1121–1136.

Signorella, M.L., Bigler, R.S., & Liben, L.S. (1993). Developmental differences in children's gender schemata about others: A meta-analytic review. *Developmental Review*, 13, 147–183.

Singh, D. (2012). A follow-up study of boys with gender identity disorder. Unpublished doctoral dissertation, University of Toronto.

Singh, D., Bradley, S.J., & Zucker, K.J. (2011). Commentary on 'An Affirmative Intervention for Families with Gender Variant Children: Parental Ratings of Child Mental Health and Gender' by Hill, Menvielle, Sica, and Johnson (2010). *Journal of Sex and Marital Therapy*, 37, 151–157.

Steensma, T.D. (2013). From gender variance to gender dysphoria: Psychosexual development of gender atypical children and adolescents. Dissertation, VU University, Amsterdam, the Netherlands.

Steensma, T.D., Biemond, R., de Boer, F., & Cohen-Kettenis, P.T. (2011). Desisting and persisting gender dysphoria after childhood: A qualitative follow-up study. *Clinical Child Psychology and Psychiatry*, 16, 499–516.

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*, 54, 147–148.

Steensma, T.D., McGuire, J.K., Kreukels, B.P., 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.

Steensma, T.D., Zucker, K.J., Kreukels, B. P. C., VanderLaan, D.P., Wood, H., Fuentes, A., & Cohen-Kettenis, P.T. (2014). Behavioral and emotional problems on the Teacher's Report Form: A cross-national, cross-clinic comparative analysis of gender dysphoric children and adolescents. *Journal of Abnormal Child Psychology*, 42, 635–647.

Stoddart, T., & Turiel, E. (1985). Childrens'concepts of cross-gender activities. *Child Development*, 56, 1241–1252.

Van Beijsterveldt, C.E., Hudziak, J.J., & Boomsma, D.I. (2006). Genetic and environmental influences on cross-gender behavior and relation to behavior problems: A study of Dutch twins at ages 7 and 10 years. *Archives of Sexual Behavior*, 35, 647–658.

VanderLaan, D.P., Postema, L., Wood, H., Singh, D., Fantus, S., Hyun, J., ... Leef, J., (2015). Do Children With Gender Dysphoria Have Intense/Obsessional Interests? *Journal of Sex Research*, 52, 213–219.

Verhulst, F.C., van der Ende, J., & Koot, H.M. (1996). *Handleiding voor de CBCL/4-18 [Manual for the CBCL/4-18]*. Erasmus University, Department of Child and Adolescent Psychiatry, Sophia Children's Hospital: Rotterdam, Netherlands.

Wallien, M.S., & Cohen-Kettenis, P.T. (2008). Psychosexual outcome of gender-dysphoric children. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47, 1413–1423.

Wallien, M. S. C., Veenstra, R., Kreukels, B. P. C., & Cohen-Kettenis, P.T. (2010). Peer Group status of gender dysphoric children: A sociometric study. *Archives of Sexual Behavior*, 39, 553–560.

Wood, H., Sasaki, S., Bradley, S.J., Singh, D., Fantus S., Owen-Anderson, A., & Singh, D. (2013). Patterns of referral to a gender identity service for children and adolescents (1976–2011): age, sex ratio, and sexual orientation. *Journal of Sex & Marital Therapy*, 39, 1–6.

World Health Organization (1992). *International statistical classification of diseases and related health problems* (10th edition). Geneva: World Health Organization.

Zucker, K.J., & Bradley, S. (1995). *Gender identity disorder and psychosexual problems in children and adolescents*. New York: Guilford Press.

Zucker, K.J., Bradley, S.J., Owen-Anderson, A., Kibblewhite, S.J., Wood, H., Singh, D., & Choi, K. (2012). Demographics, behavior problems, and psychosexual characteristics of adolescents with gender identity disorder or transvestic fetishism. *Journal of Sex and Marital Therapy*, 38, 151–189.

Zucker, K.J., Bradley, S.J., & Sanikhani, M. (1997). Sex differences in referral rates of children with gender identity disorder: Some hypotheses. *Journal of Abnormal Child Psychology*, 25, 217–227.

Zucker, K.J., Wilson-Smith, D.N., Kurita, J.A., & Stern, A. (1995). Children's appraisals of sextyped behavior in their peers. *Sex Roles*, 33, 703–725.

Zucker, K.J., Wood, H., & VanderLaan, D.P. (2014). Models of psychopathology in children and adolescents with gender dysphoria. In: B.P.C. Kreukels, T.D. Steensma, A.L.C. de Vries (Eds.), *Gender dysphoria and disorders of sex development: Progress in Care and Knowledge*. New York: Springer Science + Business Media, pp. 171–192.

Zuger, B. (1984). Early effeminate behavior in boys. Outcome and significance for homosexuality. *Journal of Nervous and Mental Disease*, 172, 90–97.

EXHIBIT 14

Gender Identity 5 Years After Social Transition

Kristina R. Olson, PhD,[a] Lily Durwood, PhD,[b] Rachel Horton, BS,[a] Natalie M. Gallagher, PhD,[a] and Aaron Devor, PhD[c]

abstract

BACKGROUND AND OBJECTIVES: Concerns about early childhood social transitions among transgender youth include that these youth may later change their gender identification (ie, retransition), a process that could be distressing. The current study aimed to provide the first estimate of retransitioning and to report the current gender identities of youth an average of 5 years after their initial social transitions.

METHODS: The current study examined the rate of retransition and current gender identities of 317 initially transgender youth (208 transgender girls, 109 transgender boys; $M = 8.1$ years at start of study) participating in a longitudinal study, the Trans Youth Project. Data were reported by youth and their parents through in-person or online visits or via e-mail or phone correspondence.

RESULTS: We found that an average of 5 years after their initial social transition, 7.3% of youth had retransitioned 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. A total of 2.5% of youth identified as cisgender and 3.5% as nonbinary. Later cisgender identities were more common among youth whose initial social transition occurred before age 6 years; their retransitions often occurred before age 10 years.

CONCLUSIONS: These results suggest that retransitions are infrequent. More commonly, transgender youth who socially transitioned at early ages continued to identify that way. Nonetheless, understanding retransitions is crucial for clinicians and families to help make retransitions as smooth as possible for youth.

Increasing numbers of children are socially transitioning to live in line with their gender identity, rather than the gender assumed by their sex at birth, a process that typically involves changing a child's pronouns, first name, hairstyle, and clothing. Some concerns about childhood social transitions have been raised,[1] including that these children may not continue to identify as transgender, rather they might "retransition" (also called a "detransition" or "desistence"), which some suggest could be distressing for youth.[1–3] Research has suggested that ages 10 to 13 years may be particularly key times for retransition and that identity may be more stable after this period for youth who show early gender nonconformity.[3]

Other clinicians argue that early social transitions can be beneficial for some gender-diverse youth.[4–6] Some clinicians and scholars who support early childhood social transitions encourage families to remain open to later retransitions,[7,8] which are seen by some as part of a youth's exploration of their gender.[9]

Unfortunately, very few data about retransitions exist in the scientific literature. We have been able to find limited data on the number of youth

[a]Department of Psychology, Princeton University, Princeton, New Jersey; [b]Department of Psychology, University of Washington, Seattle, Washington; and [c]Department of Sociology, University of Victoria, Victoria, BC, Canada

Dr Olson conceptualized the current study, supervised data collection, carried out the initial analyses, and drafted the initial manuscript. Dr Durwood and Dr Devor conceptualized the current study and provided extensive revisions on the manuscript. Ms Horton acquired and compiled the data and tables and provided feedback on the manuscript. Dr Gallagher acquired, compiled, and analyzed the data and provided feedback on the manuscript. All authors approved the manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2021-056082

Accepted for publication Apr 22, 2022

Address correspondence to: Kristina Olson, PhD, Department of Psychology, Princeton University, Peretsman Scully Hall, Princeton, NJ 08540. E-mail: krolson@princeton.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2022 by the American Academy of Pediatrics

FUNDING: The collection of data in this report and some of the authors' time (Dr Olson, Ms Horton, and Dr Gallagher) over the course of this project have been supported by National Institutes of Health grant HD092347; National Science Foundation grants BCS-1523632, SMA-1837857, and SMA-2041463; an Arcus Foundation grant (all to Dr Olson); and a National Science Foundation GRFP grant to Dr Durwood. In addition, Dr Olson receives financial support from the MacArthur Foundation. The funders played no role in determining the research questions asked nor have they seen the results before review.

CONFLICT OF INTEREST DISCLOSURES: The authors have indicated that they have no potential conflicts of interest to disclose.

To cite: Olson KR, Durwood L, Horton R, et al. Gender Identity 5 Years After Social Transition. *Pediatrics*. 2022;150(2):e2021056082

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

who socially transition in childhood and then go on to retransition afterward. One paper included 4 youth who socially transitioned; none of them had retransitioned 7 years later.[10] We know of 3 mentions of early-transitioning youth who retransition.[8,9] However, these papers include no mention of how many other youth the same clinical team saw who did not retransition, making it impossible to guess a retransition rate.

In the present paper, we aimed to compute an estimate of retransition among a cohort of more than 300 early-transitioning children. Here, we report the retransition rate an average of 5 years after initial (binary) social transition, as well as how many of these participants are living as binary transgender youth, nonbinary youth, and cisgender youth at the same timepoint.

METHODS

A total of 317 binary socially transitioned transgender children (M_{age} = 8.07; SD = 2.36; 208 initially transgender girls, 109 initially transgender boys; see Table 1 for additional demographics) joined this longitudinal study (The Trans Youth Project) between July 2013 and December 2017. For inclusion in The Trans Youth Project, children had to be between 3 and 12 years of age and had to have made a "complete" binary social transition,[10] including changing their pronouns to the binary gender pronouns that differed from those used at their births.

As part of the larger longitudinal study, parents and youth were regularly asked about whether they had begun using puberty blockers and/or gender-affirming hormones. At most visits, they were not asked about whether puberty had begun, though our available data suggests that because these youth had socially transitioned at such early ages, most participants were followed by an endocrinologist well before puberty began. The endocrinologists helped families identify the onset of Tanner 2 (the first stage of puberty) and prescribed puberty blockers within a few months of this time; therefore, the onset of puberty blockers is used as our proxy for the onset of puberty in youth who received blockers. Of the youth in this sample, 37 (11.7%) had begun puberty blockers before beginning this study.

This study did not assess whether participants met criteria for the Diagnostic and Statistical Manual of Mental Disorders, Fifth edition, diagnosis of gender dysphoria in children. Many parents in this study did not believe that such diagnoses were either ethical or useful, even if they had been diagnosed, and some children did not experience the required distress criterion after transitioning. Based on data collected at their initial visit, these participants showed signs of gender identification and gender-typed preferences commonly associated with their gender, not their sex assigned at birth.[11] Further, parent report using the Gender Identity Questionnaire for Children[12] indicated that youth showed significant "cross-sex" identification and preferences (when scored based on sex at birth).[12]

Final identity classification for these analyses was based on our most recent interaction with the child and/or their parent before January 1, 2021. Because some families have not participated recently, we also separately report (Table 2) the results of the n = 291 youth with whom the research team had an interaction within the 2 years before that deadline. This additional analysis allows us to assess whether those who retransitioned were more likely to have missed their more recent appointments with our team. Importantly, only 1 of the 26 families with whom we did not meet in the past 2 years has formally dropped out of the study; the others often did not complete participation during these 2 years because of personal circumstances at the time we attempted re-recruitment. We anticipate that many in this group will participate again in the future.

TABLE 1 Participant Demographics (N = 317)

Demographics	%
Race	
White, non-Hispanic	69
White, Hispanic	9
Black	2
Asian	3
Native American	<1
Multiracial	17
Annual household income, $	
<25 000	3
25 001–50 000	10
50 001–75 000	21
75 001–125 000	31
>125 000	35
Location	
Northeast	15
Midwest/Upper Plains	21
Southeast	15
Mountain West	13
Pacific Northwest	20
Pacific South	16

Based on pronouns at follow-up, participants were classified as binary transgender (pronouns associated with the other binary assigned sex), nonbinary (they/them pronouns or, n = 3, a mix of they/them and binary pronouns), or cisgender (pronouns associated with their assigned sex). We confirmed this classification by reviewing other information available to the research team (eg, child's self-categorization in an interview or survey, e-mail communications with the parents). Only 1 classification was debatable; this participant was classified by pronouns (and in this paper) as nonbinary but could have been

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

TABLE 2 Participant Information and Current Identity at Last Visit Before January 1, 2021, Overall, for Those With Recent Visits Only, and by Initial Social Transition and Gender

	Total Sample	Recent Sample (With Visits in 2019 or 2020)	Sample Who Initially Socially Transitioned Before Age 6	Sample Who Initially Socially Transitioned at Age 6 or Later	Transgender Girls (At Recruitment)	Transgender Boys (At Recruitment)
Sample size	317	291	124	193	208	109
Assigned male at birth, %	65.6	65.3	73.4	60.6	100	0
Mean age at first transition, y	6.5	6.4	4.3	7.9	6.2	7.1
Mean age at start of study, y	8.1	8.0	5.9	9.5	7.7	8.7
Average time since start of study, y	3.8	4.1	3.8	3.8	3.9	3.7
Average time since first transition, y	5.4	5.7	5.4	5.4	5.5	5.3
Current identity, *n* (%)						
Binary transgender	298 (94.0)	276 (94.8)	112 (90.3)	186 (96.4)	194 (93.3)	104 (95.4)
Cisgender	8 (2.5)	6 (2.1)	7 (5.6)	1 (0.5)	7 (3.40)	1 (0.9)
Nonbinary	11 (3.5)	9 (3.1)	5 (4.0)	6 (3.1)	7 (3.40)	4 (3.7)

classified as binary transgender (and not retransitioned).

This study has been approved by the University of Washington and Princeton University institutional review boards.

RESULTS

The overall rate of retransition was 7.3%. An average of 5.37 years (SD = 1.74 years) after their initial binary social transition, most participants were living as binary transgender youth (94.0%; Table 2). Included in this group were 4 individuals (1.3% of the total sample) who retransitioned twice (to nonbinary then back to binary transgender). Some youth (3.5%) were currently living as nonbinary, including one who had retransitioned first to cisgender then to nonbinary. Finally, 2.5% were using pronouns associated with their sex at birth and could be categorized as cisgender at the time of data collection, including one who first retransitioned to live as nonbinary. Similar percentages were observed when examining the 291 youth who were in touch with the research team in the past 2 years (Table 2), when examining only those 280 youth who had not begun puberty blockers at the start of the study (Table 3), or if we examine only the 200 youth who had gone at least 5 years since their initial transition (Table 3).

We observed 1 potential (post hoc) age effect. Youth who initially socially transitioned before age 6 (n = 124), were more likely to be living as cisgender (n = 7; 5.6%) than youth who transitioned at age 6 or later (n = 1 of 193; 0.5%), Fisher exact test (comparing binary, cisgender, nonbinary; before vs. age 6 years or later), P = .02, although low rates of retransition were seen in both groups. In Table 2, we also report the results separately for children assigned male versus female at birth; this distinction was not significantly associated with later identity, P = .47, Fisher exact test. Finally, for exploratory purposes, in Table 3, we report outcomes separately for several subsets of our participants, including youth who had started puberty blockers, youth who had used puberty blockers and gender-affirming hormones, and youth who are at least 14 years old (the age at which past work[3] has suggested retransitions will be less likely).

DISCUSSION

Five years after an initial binary social transition, 7% of youth had retransitioned at least once. Most youth (94%) were living as binary transgender youth at the time of data analysis, including 1.3% who retransitioned initially to cisgender or nonbinary and then retransitioned back to binary trans identities. A small number of youth were living as cisgender youth (2.5%) or nonbinary youth (3.5%). We observed comparable rates when examining all participants who began the study (n = 317), those who had been in touch with the research team in the last two years (n = 291), those who had gone at least 5 years since initial social transition (n = 200), and

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

TABLE 3 Participant Information and Current Identity at Last Visit Before January 1, 2021, as a Function of Stages of Medical Transition and/or Age

	Total Sample	Sample of Youth Who Had Not Begun Blockers at Start of the Study	Sample of Youth Who Have Begun Blockers (and Not Gender-Affirming Hormones) at the End of the Study	Sample of Youth Who Have Begun Gender-Affirming Hormones at the End of the study	Sample of Youth 5+ y of Age Since Initial Binary Social Transition	Sample of Youth Who Are Currently 14+ y of Age
Sample size	317	280	92	98	200	70
Assigned male at birth, %	65.6	69.6	57.6	58.2	69.0	52.9
Mean age at first transition, y	6.5	6.1	6.6	8.4	6.2	8.9
Mean age at start of study, y	8.1	7.6	8.3	10.2	8.0	10.8
Average time since start of study, y	3.8	3.9	4	4.3	4.5	4.4
Average time since first transition	5.4	5.5	5.8	6.1	6.4	6.3
Current identity						
Binary transgender	n = 298; 94.0%	n = 263; 93.9%	n = 88; 95.7%	n = 97; 99.0%	n = 190; 95.0%	n = 69; 98.6%
Cisgender	n = 8; 2.5%	n = 8; 2.9%	n = 1; 1.1%	n = 0	n = 4; 2.0%	n = 1; 1.4%
Nonbinary	n = 11; 3.5%	n = 9; 3.2%	n = 3; 3.3%	n = 1, 1.0%	n = 6; 3.0%	n = 0

those who started the study before beginning puberty blockers (n = 280). We found no differences as a function of participant sex at birth. We observed slightly higher rates of retransition, and particularly later cisgender identity, among youth who initially socially transitioned before age 6 years. However, even in these youth, retransition rates were very low.

Among those who had begun puberty blockers and/or gender-affirming hormones, only 1 had retransitioned to live as cisgender (and this youth had begun blockers, but not gender-affirming hormones). One likely reason so few retransitions to cisgender occurred among those accessing medical transition is that most retransitioning in this cohort happened at early ages. All but 1 of the 8 cisgender youth had retransitioned by age 9 years (the last retransition was at age 11 years). Some of these youth are still not eligible for blockers because they are still prepubertal; we anticipate that those who identify as cisgender are unlikely to seek blockers or hormones, but that the participants who have not begun puberty and who identify as binary transgender or nonbinary likely will.

Past work has suggested that the ages 10 to 13 years are an especially critical time for retransition.[3] In our sample, many of the youth who retransitioned did so before that time frame, particularly the cisgender youth. In the nonbinary group, however, 6 of 11 retransitioned between ages 10 and 13 years, with the remainder retransitioning before age 10. Importantly, our sample differed from the past work on which this age range was determined in several key ways, including that our participants socially transitioned at earlier ages (perhaps pushing retransitions earlier, too), had undergone complete social transitions including pronouns and names (not just hairstyle and clothing changes as in most cases in previous studies[3]), and are living at a different historic time in a different country. Any, or all, of these may turn out to be key differences related to age of retransition.

Our observed low retransition rate is consistent with a study in which 4 youth who had completely socially transitioned had not retransitioned 7 years later.[10] That finding is in the same ballpark as our study's estimate of ~2.5% if we examine the percentage living as cisgender at the end of the study (ie, those "desisting" from gender-diverse outcomes). Together, these papers suggest this outcome is relatively rare in this group.

Our observation that few youth who have begun medical intervention have retransitioned to live as cisgender is consistent with findings in the literature. Several studies reporting on outcomes among transgender youth receiving blockers and gender-affirming hormones have reported relatively low rates of regret or stopping treatment,[13] which are potential indicators of retransition, though stopping treatment can occur for other reasons as well (eg, side

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

effects), as can regret (eg, experiences of transphobia).

Our key finding, that there was a relatively low rate of retransition about 5 years after initial social transition, may, on the surface, appear contradictory with past clinic-based research on what is sometimes called persistence and desistence[3] of childhood gender dysphoria. Several large studies attempted to recontact adolescents and adults who had previously been evaluated for gender dysphoria in childhood.[14–17] Many of those were formally diagnosed with what was, at the time, called gender identity disorder. Those studies reported that a minority of youth later identified in a way that might indicate a transgender identity by today's definition.

Interpretation of those results, and especially comparison with the present work, is difficult for several reasons. First, in past studies, when asked "are you a boy or a girl?" about 90% of the children supplied answers that aligned with their sex at birth,[18] leading some to question whether the majority of those children were the equivalent of transgender children today or not.[19–21] Second, participants in those studies were children between the 1960s and the 1990s, and many features of society have changed since then, including greater rates of acceptance and acknowledgment of transgender identities. Third, the parents of the youth in the current study support their children's identities, as indicated by their approval of their social transitions, whereas many of the parents of youth in past studies explicitly discouraged gender nonconformity or "cross-gender" identification.[15,22] In addition, it would have been exceedingly rare for youth in those studies to socially transition, especially completely.[1,10] Finally, there were substantial drop-out rates in all of the previous studies,[14,15,17] making the true estimates of persistence or desistence difficult to obtain.[19,21] Because there are so many possible contributors to differences in rates of persistence (in past work) and retransition in the current work, we urge caution about overinterpreting differences, or overconfidence about which contributing factors explain the differences.

There are also some reasons why we might have had such a low retransition rate. First, on average, participants had socially transitioned 1.6 years before joining our study. It is possible that some youth initially try socially transitioning and then change their minds quickly. Such youth would be unlikely to be enrolled in this study because their eligibility period would have been quite short and therefore the odds of finding the study and completing it would have been low. This means the children in our study may have been especially unlikely, compared with all children who transition, to retransition because they had already lived and presumably been fairly content with that initial transition for more than a year. Second, it is possible that families who failed to participate in the past 2 years of our study ($n = 26$) were disproportionately those whose children retransitioned and who were therefore hesitant to participate again. If true, their exclusion could have reduced our retransition rate. We are skeptical of this possibility for a few reasons. First, 4 of these participants did retransition and had told us about that outcome, so it does not appear that hesitancy in telling us was widespread in this group. Second, many of these families continue to be in touch with our research team and only missed participation because of ongoing personal issues (eg, COVID-19, emergency family circumstances). We anticipate that most of these families will be able to participate as we continue to follow these youth. Finally, from the beginning of the study, the research team has been clear in discussing with the families that we are open to any outcome in their youth.

As with past work, the present work has several key limitations. First, this is a volunteer community sample, meaning there could be biases in the kinds of families who sign up to participate. We know, for example, that unlike many samples of transgender youth, this sample of youth have normative levels of depression and only slight elevations in anxiety.[23] The parents of the participants in this study are disproportionately higher income and went to college at higher rates than the general population. We do not know whether these potential biases in the sample reflect biases in the cohort of children who socially transitioned in the mid-2010s in the United States and Canada. Therefore, whether the results generalize to youth without these characteristics is unknown.

Another potential limitation is that we used pronouns as the criterion for retransitions. Not everyone who, for example, uses they/them pronouns identifies as nonbinary and someone might identify as transgender even if they are currently using pronouns associated with their sex at birth. However, examination of other data provided by families suggests that our pronoun-based criteria were largely consistent with classification that would have arisen from other types of information provided to the research team (eg, labels used in an interview). Only 1 of the youth categorized as "retransitioned" might, by some other criteria, not meet that definition. However, because pronouns were the initial

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

inclusion criterion (that is, to be in the study children had to be using pronouns not associated with their sex at birth), they were the most consistent route of classification.

A related potential concern with these analyses is that we classified a change from using, for example, binary transgender to nonbinary as a retransition. Not everyone would categorize this change as a retransition. Many nonbinary people consider themselves to be transgender.[24] If we had used a stricter criterion of retransition, more similar to the common use of terms like detransition or desistence, referring only to youth who are living as cisgender, then our retransition rate would have been lower (2.5%).

One additional limitation in the present work is that the initial sample was disproportionately made up of trans girls. This is counter to recent reports that more peri- and postpubertal transgender youth seeking clinical services recently are transmasculine.[25–27] Historically, and consistent with our data, samples of parent-identified prepubertal gender nonconforming youth have included more assigned males at birth.[15,16,22] Importantly, we did not observe a significant gender effect in terms of rates of retransition, so we do not predict any change in pattern of results if we had a different ratio of participants by sex at birth.

We anticipate continuing to follow this cohort into adolescence and adulthood. This continued follow-up is necessary because it is possible that as more youth move into adolescence and adulthood, their identities could change. As we already saw, some youth will retransition more than once, so the present identities should not be interpreted as final.

As more youth are coming out and being supported in their transitions early in development, it is increasingly critical that clinicians understand the experiences of this cohort and not make assumptions about them as a function of older data from youth who lived under different circumstances. Though we can never predict the exact gender trajectory of any child, these data suggest that many youth who identify as transgender early, and are supported through a social transition, will continue to identify as transgender 5 years after initial social transition. These results also suggest that retransitions to one's gender assumed at birth (cisgender) might be likely to occur before age 10 years among those who socially transition at the earliest ages (before age 6 years), though retransitions are still unlikely in this group. These data suggest that parents and clinicians should be informed that not all youth will continue the same trajectory over time. Further understanding of how to support youth's initial and later transitions is needed.

ACKNOWLEDGMENTS

The authors thank the families for their participation in this research.

REFERENCES

1. Steensma TD, Cohen-Kettenis PT. Gender transitioning before puberty? *Arch Sex Behav.* 2011;40(4):649–650
2. de Vries ALC, Cohen-Kettenis PT. Clinical management of gender dysphoria in children and adolescents: the Dutch approach. *J Homosex.* 2012;59(3):301–320
3. Steensma TD, Biemond R, de Boer F, Cohen-Kettenis PT. Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study. *Clin Child Psychol Psychiatry.* 2011; 16(4):499–516
4. Ashley F. Thinking an ethics of gender exploration: against delaying transition for transgender and gender creative youth. *Clin Child Psychol Psychiatry.* 2019;24(2):223–236
5. Sherer I. Social transition: supporting our youngest transgender children. *Pediatrics.* 2016;137(3):e20154358
6. Temple Newhook J, Pyne J, Winters K, et al. A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *Int J Transgenderism.* 2018; 19(2):212–224
7. Leibowitz S. Social gender transition and the psychological interventions. In: Janssen A, Leibowitz S, eds. *Affirmative Mental Health Care for Transgender and Gender Diverse Youth.* New York: Springer International Publishing; 2018:31–47
8. Edwards-Leeper L, Spack NP. Psychological evaluation and medical treatment of transgender youth in an interdisciplinary "Gender Management Service" (GeMS) in a major pediatric center. *J Homosex.* 2012;59(3):321–336
9. Menvielle E. A comprehensive program for children with gender variant behaviors and gender identity disorders. *J Homosex.* 2012;59(3):357–368
10. Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2013;52(6):582–590
11. Gülgöz S, Glazier JJ, Enright EA, et al. Similarity in transgender and cisgender children's gender development. *Proc Natl Acad Sci USA.* 2019;116(49):24480–24485
12. Johnson LL, Bradley SJ, Birkenfeld-Adams AS, et al. A parent-report gender identity questionnaire for children. *Arch Sex Behav.* 2004;33(2):105–116
13. Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body dissatisfaction and mental health outcomes of youth on gender-affirming hormone therapy. *Pediatrics.* 2020;145(4):e20193006
14. Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. *Dev Psychol.* 2008;44(1):34–45
15. Green R. *The Sissy Boy Syndrome: The Development of Homosexuality.* New Haven, CT: Yale University Press; 1987

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

16. Singh D, Bradley SJ, Zucker KJ. A follow-up study of boys with gender identity disorder. *Front Psychiatry.* 2021;12:632784

17. Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. *J Am Acad Child Adolesc Psychiatry.* 2008; 47(12):1413–1423

18. Zucker KJ, Bradley SJ, Sullivan CB, Kuksis M, Birkenfeld-Adams A, Mitchell JN. A gender identity interview for children. *J Pers Assess.* 1993;61(3):443–456

19. Ashley F. The clinical irrelevance of "desistance" research for transgender and gender creative youth [published online ahead of print 2021]. *Psychol Sex Orientat Gend Divers.* 10.1037/sgd0000504

20. Olson KR. Prepubescent transgender children: what we do and do not know. *J Am Acad Child Adolesc Psychiatry.* 2016;55(3):155–156

21. Temple Newhook J, Pyne J, Winters K, et al. A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *Int J Transgenderism.* 2018;19(2):212–224

22. Zucker K, Bradley S. Gender identity disorder and psychosexual problems. In: *Children and Adolescents.* New York: Guilford Press; 1995

23. Gibson DJ, Glazier JJ, Olson KR. Evaluation of anxiety and depression in a community sample of transgender youth. *JAMA Netw Open.* 2021;4(4):e214739

24. Darwin H. Challenging the cisgender/transgender binary: nonbinary people and the transgender label. *Gend Soc.* 2020;34(3):357–380

25. Aitken M, Steensma T, Blanchard R, et al. Evidence for an altered sex ratio in clinic-referred adolescents with gender dysphoria. *J Sex Med.* 2015;12(3):756–763

26. de Graaf NM, Carmichael P, Steensma TD, Zucker KJ. Evidence for a change in the sex ratio of children referred for gender dysphoria: data from the Gender Identity Development Service in London (2000-2017). *J Sex Med.* 2018;15(10):1381–1383

27. Meyenburg B, Renter-Schmidt K, Schmidt G. Transidentität in Jugend und Adoleszenz: Zur Veränderung der Sexratio und der Prävalenz in den letzten eineinhalb Jahrzehnten [Changes of sex ratio and prevalence in transgender teenagers over the past 15 years]. *Z Kinder Jugendpsychiatr Psychother.* 2021;49(2):93–100

Downloaded from http://publications.aap.org/pediatrics/article-pdf/150/2/e2021056082/1344022/peds_2021056082.pdf
by guest

EXHIBIT 15

ORIGINAL RESEARCH—INTERSEX AND GENDER IDENTITY DISORDERS

Puberty Suppression in Adolescents With Gender Identity Disorder: A Prospective Follow-Up Study

Annelou L.C. de Vries, MD,* Thomas D. Steensma, MSc,† Theo A.H. Doreleijers, MD, PhD,* and Peggy T. Cohen-Kettenis, PhD†

*Department of Child and Adolescent Psychiatry, VU University Medical Center, Amsterdam, the Netherlands; †Department of Medical Psychology, VU University Medical Center, Amsterdam, the Netherlands

DOI: 10.1111/j.1743-6109.2010.01943.x

ABSTRACT

Introduction. Puberty suppression by means of gonadotropin-releasing hormone analogues (GnRHa) is used for young transsexuals between 12 and 16 years of age. The purpose of this intervention is to relieve the suffering caused by the development of secondary sex characteristics and to provide time to make a balanced decision regarding actual gender reassignment.

Aim. To compare psychological functioning and gender dysphoria before and after puberty suppression in gender dysphoric adolescents.

Methods. Of the first 70 eligible candidates who received puberty suppression between 2000 and 2008, psychological functioning and gender dysphoria were assessed twice: at T0, when attending the gender identity clinic, before the start of GnRHa; and at T1, shortly before the start of cross-sex hormone treatment.

Main Outcome Measures. Behavioral and emotional problems (Child Behavior Checklist and the Youth-Self Report), depressive symptoms (Beck Depression Inventory), anxiety and anger (the Spielberger Trait Anxiety and Anger Scales), general functioning (the clinician's rated Children's Global Assessment Scale), gender dysphoria (the Utrecht Gender Dysphoria Scale), and body satisfaction (the Body Image Scale) were assessed.

Results. Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved significantly during puberty suppression. Feelings of anxiety and anger did not change between T0 and T1. While changes over time were equal for both sexes, compared with natal males, natal females were older when they started puberty suppression and showed more problem behavior at both T0 and T1. Gender dysphoria and body satisfaction did not change between T0 and T1. No adolescent withdrew from puberty suppression, and all started cross-sex hormone treatment, the first step of actual gender reassignment.

Conclusion. Puberty suppression may be considered a valuable contribution in the clinical management of gender dysphoria in adolescents. **de Vries ALC, Steensma TD, Doreleijers TAH, and Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. J Sex Med 2011;8:2276–2283.**

Key Words. Gender Identity Disorder; Transsexualism; Puberty Suppression; Gonadotropin-Releasing Hormone Analogues; Adolescents

Introduction

In recent years, the possibility of puberty suppression has generated a new dimension to clinical management of adolescents with a gender identity disorder (GID), the official diagnosis according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [1]. GID is characterized by feelings of gender dysphoria associated with strong

 © 2010 International Society for Sexual Medicine

cross-gender identification as well as a persistent discomfort with one's natal sex. The most extreme form of GID, for which the term *transsexualism* is used in the International Classification of Diseases, Tenth Edition (ICD-10) [2], is accompanied by a strong wish for gender reassignment (GR). Gender dysphoria will remit in most prepubertal children with GID (e.g., references [3–6]), but not in most gender dysphoric adolescents [7,8]. Previous studies on the effectiveness of GR, starting with cross-sex hormone (CSH) treatment between the ages of 16 and 18, showed that the gender dysphoria had dissipated, 1 year or more after GR surgery and that psychological and social functioning of these young transsexuals was favorable [7,8]. Age 16 was chosen because some cognitive and emotional maturation is desirable when starting partially irreversible interventions and Dutch adolescents are legally competent to make a medical decision without parents' consent. However, as secondary sex characteristics develop before the age of 16, waiting for medical interventions is highly upsetting for most younger adolescents.

By prescribing gonadotropin-releasing hormone analogues (GnRHa), we enable gender dysphoric adolescents under the age of 16 to explore their gender dysphoria and the wish for GR without the distress of physical puberty development [9]. If an adolescent continues to pursue GR, arresting the development of secondary sex characteristics results in a lifelong advantage of a convincing physical appearance congruent with the desired gender role. Puberty suppression is fully reversible and can be discontinued should the adolescent decide not to pursue GR [10]. It is meant to prevent the emotional problems many young transsexuals experience when puberty has started [11,12]. While on GnRHa, a gender role change is not required, as no physical cross-gender characteristics develop yet. At the Amsterdam gender identity clinic, adolescents are eligible for puberty suppression when they are diagnosed with GID, have shown persistent gender dysphoria since childhood, live in a supportive environment, and have no serious comorbid psychiatric disorders that may interfere with the diagnostic assessment. For example, it can be complicated to disentangle whether the gender dysphoria evolves from a general feeling of being just "different" or a whether a true "core" cross-gender identity exists in adolescents who suffer from an autistic spectrum disorder [13]. In addition, adolescents should have physical changes of puberty to at least Tanner stage 2–3, confirmed by pubertal hormonal levels, so that they have experienced some of their biological puberty [14–16].

GR commences with the partially irreversible CSH treatment. CSH may be prescribed when adolescents reach the age of 16 and fulfill the same eligibility criteria as for puberty suppression, with the exception of the Tanner stage criterion. The irreversible step of GR surgery is not performed prior to legal adulthood, at the age of 18.

Although some gender identity clinics have adopted this strategy of puberty suppression for adolescents with GID, other professionals working with gender dysphoric youth remain critical (e.g., Viner et al. [17]). They are concerned that GnRHa may be physically hazardous for adolescents and that psychological functioning may be negatively affected by suppressing puberty. Furthermore, they state that one's gender identity is still subject to change during adolescence and that adolescents are therefore unable to make decisions regarding GR.

Aims

Thus far, no studies have been performed that compare psychological functioning and gender dysphoria before and after the start of GnRHa. This prospective follow-up study assessed psychological functioning and gender dysphoria of the first 70 puberty suppressed young transsexuals before and after the start of puberty suppression.

Methods

Participants

Between 2000 and 2008, 140 of 196 consecutively referred adolescents were considered eligible for medical intervention at the Amsterdam gender identity clinic of the VU university medical center (VUmc) (for a description of the protocol, see Delemarre-van de Waal and Cohen-Kettenis [15]). The 29 adolescents who were age 16 years or older were prescribed CSH. The other 111 adolescents were prescribed GnRHa to suppress puberty. Participants of this study were the first 70 adolescents (mean age at assessment 13.6 [standard deviation {*SD*} = 1.8] years, 33 natal males and 37 natal females), who had subsequently started CSH treatment between the years 2003 and 2009.

Mean ages of the participants at first assessment, at the start of GnRHa treatment and at the start of CSH are presented in Table 1. Table 1 further shows participants' intelligence, as measured by either the Wechsler Intelligence Scale for Children, revised or

Table 1 General characteristics

Variable	All participants (N = 70)	Natal males (N = 33)	Natal females (N = 37)	t or χ^2	df	P
Age (in years)						
At assessment						
M (SD)	13.65 (1.85)	13.14 (1.55)	14.10 (1.99)	–2.24	66.82	0.028*
Range	11.1–17.0	11.1–16.8	11.2–17.0			
At start GnRHa†						
M (SD)	14.75 (1.92)	14.25 (1.79)	15.21 (1.95)	–2.14	67.93	0.036*
Range	11.3–18.6	11.6–17.9	11.5–18.6			
At start CSH‡						
M (SD)	16.64 (1.90)	16.24 (1.21)	16.99 (1.07)	–2.73	64.22	0.008*
Range	13.9–19.2	13.9–18.9	15.9–19.3			
Time between start GnRHa and CSH						
M (SD)	1.88 (1.05)	1.99 (0.94)	1.78 (1.16)	0.838	67.41	0.405
Range	0.42–5.06					
Full-Scale IQ						
M (SD)	98.2 (15.0)	97.1 (13.3)	99.2 (15.2)	–0.60	63.81	0.55
Range	70–131	70–123	72–131			
Parents' marital status N, (%)						
Both parents§	44 (62.9)	23 (69.7)	21 (56.8)	1.25	1	0.26
Other	26 (37.1)	10 (30.3)	16 (43.2)			
Parents' educational level¶, N (%)						
High	7 (10.6)	1 (3.3)	6 (16.7)	3.75	2	0.15
Middle	44 (66.7)	23 (76.7)	21 (58.3)			
Low	15 (22.7)	6 (20.0)	9 (25.0)			
Sexually attracted to, N (%)						
Own natal sex**	62 (88.6)	29 (87.9)	33 (89.2)	2.70	3	0.44
Both sexes	6 (8.6)	2 (6.1)	4 (10.8)			
Other††	2 (2.8)	2 (6.0)	0			

*Significant difference in mean age between natal males and natal females, $P < 0.05$.
†Gonadotropin-releasing hormone analogues.
‡Cross sex hormones.
§For marital status, the category "Both parents" included "adopted" (n = 2, 2.9%).
¶Parents' educational level was measured by a 5-point scale where 1 = *university degree* and 5 = *grade 6 or less.* Education level was divided in three groups; 1 = high, 2 and 3 = middle, and 4 and 5 = low.
**Sexual attraction was coded as "attracted to own natal sex" when adolescents responded that they fell in love "only with boys or only with girls" or "mainly with boys or mainly with girls" (according to their natal sex) and as "attracted to both sexes" when their response was "somewhat more with boys or somewhat more girls" or "both with boys and girls."
††The category "Other" consisted of one natal male who responded "only with girls" and one adolescent who responded "don't know yet." [Correction added after online publication 14-Jul-2010: "only with boys" has been changed to "only with girls".]
M = mean; *SD* = standard deviation.

third edition, or the Wechsler Adult Intelligence Scale, third edition, depending on age and year of assessment [18–20], marital status and educational level of the parents. Compared with natal males, the age of natal females was significantly higher at the time of first assessment, at the start of treatment with GnRHa, and at the start of treatment with CSH. Significant differences between natal males and natal females regarding IQ, marital status, and educational level of the parents were not observed.

Participants' sexual orientation at T1 is also presented in Table 1. Understandably, at T0, quite a few could not report on their sexual orientation because they sometimes were not older than 11 or 12 years. At T1, adolescents answered to the question, "Do you know if you fall in love with girls or boys?" Response categories were "only with boys, mainly with boys, somewhat more with boys, both with boys and girls, somewhat more with girls, mainly with girls, only with girls, or don't know yet". Participants were coded as "attracted to own natal sex" when their answer was "only with boys or only with girls" or "mainly with boys or mainly with girls" (according to their natal sex) and as "attracted to both sexes" when their answer was "somewhat more with boys or girls" or "both with boys and girls." One natal male responded to the question with "only with boys" and one adolescent with "don't know yet." Separate results for both sexes are presented in Table 1.

When attending the clinic for the first time, the participants were not yet consistently and officially living in the cross-gender role (e.g., using a new first name). However, many were already seen and treated by their families and friends as a member of the other gender. During the diagnostic phase, which usually takes between half a year and a year, all but one made a more official transition. They adopted a new first name and asked their social environment (family, friends, school) to use the appropriate personal pronouns. A legal gender change could, of course, only be made after surgery at age 18.

Procedure

Participants were assessed twice: first, shortly after their attendance at the gender identity clinic (T0); and second, shortly before starting CSH treatment (T1). Both assessments were part of the diagnostic procedure during which eligibility is assessed for puberty suppression and CSH treatment.

The VUmc medical ethics committee approved the study, and all participants and their parents gave informed consent.

Main Outcome Measures

Psychological Functioning

Behavioral and emotional problems were measured by the Child Behavior Checklist (CBCL) and the Youth Self-Report (YSR) administered to the parents and the adolescents, respectively [21,22]. These are widely used questionnaires, assessing a broad range of behavioral and emotional problems, with good psychometric properties. In this study, *T*-scores and percentages in the clinical range were used for total problem behavior, internalizing and externalizing behavior. A *T*-score above 63 is considered to be in the clinical range. Of the Dutch adolescent norm group, the percentage scoring in the clinical range on the total problem score is 8–9% on both the CBCL and YSR [21,22]. Because the CBCL and YSR were intended to measure general behavior disturbance and not gender dysphoria (which was measured by other means), items referring to gender atypical behavior were scored as 0 for all the analyses in this study to avoid any artificial inflation (for a full description of the items that may refer to gender dysphoric behavior, see Cohen-Kettenis et al. [23]).

In addition, the adolescents completed the Beck Depression Inventory (BDI). This is a 21-item inventory in multiple-choice format measuring presence and degree of depression in adolescents and adults, with good psychometric properties [24]. The BDI-II has been developed to assess a depression. A score between 14 and 19 is suggestive of a mild depression, a score between 20 and 28 of a moderate depression, and a score of more than 29 of a severe depression. Furthermore, the Trait Anger and Anxiety (TPI and STAI, respectively) Scales of the State-Trait Personality Inventory were administered [25,26]. Only the "trait" versions were used, assessing the tendency to respond with anxiety or anger to a threatening or annoying situation, respectively. They each contain 20 statements concerning the frequency with which the emotions of anger and anxiety are experienced. Each response can range from 1 (*almost* never) to 4 (*almost* always). Total scores are often used to assess and evaluate feelings of anxiety and anger over time. Finally, the attending clinician rated the Children's Global Assessment Scale (CGAS), one of the most widely used measures of the overall severity of disturbance in children [27].

An official Dutch version of each of these instruments was available and used in this study.

Gender Dysphoria

The Utrecht Gender Dysphoria Scale (UGS) was used to measure adolescents' gender dysphoria. This is a 12 item questionnaire on which the subject rates his or her agreement on a 5-point scale. An example of an item is "I feel a continuous desire to be treated as a man/woman." The higher the score, the more gender dysphoria is indicated (for psychometric data, see Cohen-Kettenis and van Goozen [7]). In addition, the Body Image Scale (BIS) was administered to measure body satisfaction [28]. The scale consists of 30 body features, which the subject is asked to rate on a 5-point scale. Each of the 30 items falls into one of three basic groups based on its relative importance as a gender-defining body feature: primary sex characteristics, secondary sex characteristics, and neutral body characteristics. A higher score indicates more dissatisfaction. For this study, an adaptation for the Dutch population was used [29].

Statistical Analyses

Independent *t*-tests and Chi-square tests were used to ascertain differences between natal males and females.

Repeated-measures analysis of variance (ANOVA) was used to ascertain within-subject differences between baseline functioning (T0, before the start of GnRHa) and the start of CSH (T1), with sex entered as a between-subject variable.

Not all 70 adolescents completed both assessments, for example, because some lists were added to the test battery after the first eligible adolescents had started GnRHa. Only data of adolescents who administered questionnaires on both assessments could be used (CBCL, YSR: 54; BDI, TPI, STAI, CGAS, and UGS: 41; BIS: 57). Independent *t*-tests between mean scores on the CBCL, YSR, BDI, TPI, STAI, CGAS, UGS, and BIS of adolescents who completed both assess-

ments and mean scores of adolescents who completed only one of the assessments revealed no significant differences on all used measures, neither at T0 nor at T1.

Results

Psychological Functioning

Adolescents showed a significant decrease in behavioral and emotional problems over time on mean *T*-scores of the total problem scale, the internalizing and externalizing scale of both CBCL and YSR (see Table 2). In addition, the percentage of adolescents scoring in the clinical range significantly decreased between T0 and T1, on the CBCL total problem scale (44.4% vs. 22.2%, $\chi^2[1] = 6.00$, $P = 0.001$), and the internalizing scale (29.6% vs. 11.1%, $\chi^2[1] = 5.71$, $P = 0.017$) of the YSR. Depressive symptom scores on the BDI-II significantly decreased and global functioning ratings on the CGAS significantly increased between T0 and T1 (see Table 2). No significant change was observed in mean TPI or STAI scores over time, representing feelings of anger and anxiety, respectively (see Table 2).

With regard to sex differences, natal females showed significantly more problem behavior at T0 and T1 than natal males in mean externalizing *T*-scores of the CBCL and the YSR (see Table 2). In addition, compared with natal males, natal females reported significantly more feelings of anger and anxiety and had a significantly lower score on the global assessment of functioning scale at T0 and T1 (see Table 2).

There was no significant interaction effect between natal sex and time for any of the used measures.

Gender Dysphoria

No significant changes in gender dysphoria or body image scores between T0 and T1 emerged (see Table 3). Compared with natal males, natal females reported significantly more gender dysphoria and were more dissatisfied with their primary and secondary sex characteristics both at T0 and T1 (see Table 3). There was a significant interaction effect between natal sex and the changes of gender dysphoria between T0 and T1; natal females became more dissatisfied with their secondary ($F[1,55] = 14.59$, $P < 0.001$) and neutral ($F[1,55] = 15.26$, $P < 0.001$) sex characteristics compared with natal males.

Table 2 Psychological functioning of adolescents with gender dysphoria before (T0) and while on puberty suppression (T1)

	T0			T1			T0-T1 significance		Between-sex significance	
	All *M (SD)*	Natal males *M (SD)*	Natal females *M (SD)*	All *M (SD)*	Natal males *M (SD)*	Natal females *M (SD)*	*F (df, errdf,)*	*P*	*F (df. erdf)*	*P*
CBCL (N = 54)										
Total *T* score	60.70 (12.76)	59.42 (11.78)	61.73 (13.60)	54.46 (11.23)	50.38 (10.57)	57.73 (10.82)	26.17 (1,52)	<0.001	2.64 (1,52)	0.110
Internalizing *T*-score	61.00 (12.21)	60.00 (9.51)	61.80 (14.12)	54.46 (10.22)	52.17 (9.81)	56.30 (10.33)	22.93 (1,52)	<0.001	1.16 (1,52)	0.286
Externalizing *T*-score	58.04 (12.99)	54.71 (12.91)	60.70 (12.64)	53.81 (11.86)	48.75 (10.22)	57.87 (11.66)	12.04 (1,52)	0.001	6.29 (1,52)	0.015
YSR (N = 54)										
Total *T*-score	55.46 (11.56)	53.56 (12.26)	57.10 (10.87)	50.00 (10.56)	47.84 (10.86)	51.86 (10.11)	16.24 (1,52)	<0.001	1.99 (1,52)	0.164
Internalizing *T*-score	56.04 (12.49)	55.88 (11.81)	56.17 (13.25)	49.78 (11.63)	49.24 (12.24)	50.24 (11.28)	15.05 (1,52)	<0.001	0.049 (1,52)	0.825
Externalizing *T*-score	53.30 (11.87)	48.72 (11.83)	57.24 (10.59)	49.98 (9.35)	46.52 (9.23)	52.97 (8.51)	7.26 (1,52)	0.009	9.14 (1,52)	0.004
Depression (BDI) (N = 41)	8.31 (7.12)	5.71 (4.31)	10.34 (8.24)	4.95 (6.72)	3.50 (4.58)	6.09 (7.93)	9.28 (1,39)	0.004	3.85 (1,39)	0.057
Trait anger (TPI) (N = 41)	18.29 (5.54)	5.22 (2.76)	6.43 (2.78)	17.88 (5.24)	5.00 (3.07)	6.39 (2.59)	0.46 (1,39)	0.503	5.70 (1,39)	0.022
Trait anxiety (STAI) (N = 41)	39.43 (10.07)	4.33 (2.68)	7.00 (2.36)	37.95 (9.38)	4.39 (2.64)	6.17 (2.62)	1.21 (1,39)	0.276	16.07 (1,39)	<0.001
Global functioning (CGAS) (N = 41)	70.24 (10.12)	73.10 (8.44)	67.25 (11.06)	73.90 (9.63)	77.33 (8.69)	70.30 (9.44)	8.76 (1,39)	0.005	5.77 (1,39)	0.021

M = mean; *SD* = standard deviation; CBCL = Child Behavior Checklist; YSR = Youth Self Report; BDI = Beck Depression Inventory; TPI = Spielberger's Trait Anger Scale; STAI = Spielberger's Trait Anxiety Scale; CGAS = Children's Global Assessment Scale; df = degrees of freedom.

Table 3 Gender dysphoria of adolescents with gender dysphoria before (T0) and while on puberty suppression (T1)

	T0			T1			T0-T1 significance		Between-sex significance	
	All *M (SD)*	Natal males *M (SD)*	Natal females *M (SD)*	All *M (SD)*	Natal males *M (SD)*	Natal females *M (SD)*	*F (df, erdf)*	*p*	*F (df, erdf)*	*P*
Gender dysphoria scale (UGDS) (N = 41)	53.20 (7.91)	47.95 (9.70)	56.57 (3.89)	53.9 (17.42)	49.67 (9.47)	56.62 (4.00)	0.959 (1,39)	0.333	15.98 (1,39)	<0.001
Body image (BIS) (N = 57)										
Primary sex characteristics	4.10 (0.56)	4.02 (0.61)	4.16 (0.52)	3.98 (0.71)	3.74 (0.78)	4.17 (0.58)	2.18 (1,55)	0.145	4.11 (1,55)	0.047
Secondary sex characteristics	2.74 (0.65)	2.66 (0.50)	2.81 (0.76)	2.82 (0.68)	2.39 (0.69)	3.18 (0.42)	0.327 (1,55)	0.569	11.57 (1,55)	0.001
Neutral characteristics	2.41 (0.63)	2.60 (0.58)	2.24 (0.62)	2.47 (0.56)	2.32 (0.59)	2.61 (0.50)	0.248 (1,55)	0.620	0.081 (1,55)	0.777

M = mean; *SD* = standard deviation; UGDS = Utrecht Gender Dysphoria Scale; BIS: Body Image Scale; df = degrees of freedom.

Discussion

This is the first prospective study showing that psychological functioning of adolescents diagnosed with GID had improved in many respects after an average of nearly 2 years of GnRHa use. Adolescents showed fewer behavioral and emotional problems, reported fewer depressive symptoms, feelings of anxiety and anger remained stable, and their general functioning improved.

There may be various explanations for these results. Foremost, suppression of the development of secondary sex characteristics resulted in a physical appearance allowing for a smooth transition into the desired gender role. In adult transsexuals, postoperative psychopathology is associated with difficulties in passing in their new gender [30]. Furthermore, by receiving puberty suppression, gender dysphoric adolescents may trust that GR will be offered if needed. In addition, stigmatization and discrimination (e.g., references [11,31].) may have been limited because the adolescents in this study received extensive family or other social support. Finally, the adolescents were all regularly seen by one of the clinic's psychologists or psychiatrists. Psychological or social problems could thus be timely addressed. All these factors may have contributed to the psychological well-being of these gender dysphoric adolescents.

As expected, puberty suppression did not result in an amelioration of gender dysphoria. Previous studies have shown that only GR consisting of CSH treatment and surgery may end the actual gender dysphoria [7,8,32]. None of the gender dysphoric adolescents in this study renounced their wish for GR during puberty suppression. This finding supports earlier studies showing that young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood [7,8].

Although both adolescent natal boys and girls had profited from GnRHa treatment, there were some sex differences. At baseline, gender dysphoric natal males were younger and showed less problem behavior than natal females. With a mean age of 14, most natal females had developed breasts and had their menarche. Why natal female gender dysphoric adolescents do not come to the gender identity clinic at an earlier age should be investigated further. One hypothesis is that parents of gender dysphoric natal female adolescents may consider some puberty development (e.g., menstruation) not as dramatic as beard growth or breaking of the voice in gender dyspho-

ric boys because it is less visible for the environment. The higher problem scores of natal females in this study may indicate that this assumption would be erroneous. Another explanation is that, in the period that this very first cohort received GnRHa treatment, the public as well as referring clinicians may not have been aware yet that girls might also profit from puberty suppression. In further studies, this explanation could be tested. Finally, a reason for a later referral of natal females may be that the threshold for seeking clinical help in girls is higher than in boys. Indeed, prepubertal girls with GID seen at two large gender identity clinics appeared to show more extreme gender dysphoria than boys and came to the clinics at a later age [23].

Some limitations of this study warrant comment. This study of psychological functioning and gender dysphoria did not focus on social and sexual relationships. Although it is not likely that the gender dysphoric adolescents would report favorable psychological functioning in the absence of satisfactory relationships with their peers and family, the topic deserves more attention. This is also applicable to sexuality, which is a complicated issue for young people having primary sex characteristics that do not match their gender identity.

Furthermore, this study only focused on the functioning of gender dysphoric adolescents before the actual GR. It showed that their situation improved, as compared with the pre-GnRHa phase. Long-term follow-up studies, however, should be performed to examine whether these adolescents will be able to maintain their relatively good functioning into their adult years after GR. In addition, effects of GnRHa on physical parameters are needed before broad conclusions can be drawn regarding the safety of puberty suppression [15].

Finally, this study was a longitudinal observational descriptive cohort study. Ideally, a blinded randomized controlled trial design should have been performed. However, it is highly unlikely that adolescents would be motivated to participate. Also, disallowing puberty suppression, resulting in irreversible development of secondary sex characteristics, may be considered unethical [33].

Conclusions

Gender dysphoria did not resolve as a result of puberty suppression. Psychological functioning, however, improved in various respects. We cautiously conclude that puberty suppression may be a valuable element in clinical management of adolescent gender dysphoria. It relieves the acute distress accompanying gender dysphoria. Hence, by offering youths the possibility of healthy psychological development, puberty suppression helps in the exploration of suitable treatment options and making a balanced decision regarding GR.

Acknowledgements

This study was supported by a personal grant awarded to the first author by the Netherlands Organization for Health Research and Development. The authors thank all members of the Amsterdam child and adolescent gender identity clinic for collecting these data as well as the adolescents and their parents who participated in this study.

Corresponding Author: Annelou L.C. de Vries, MD, Child and Adolescent Psychiatrist, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands. Tel: (+31) 204440861; Fax: (+31) 204440851; E-mail: alc.devries@vumc.nl

Conflict of Interest: None.

Statement of Authorship

Category 1

(a) **Conception and Design**
Annelou L.C. de Vries; Thomas D. Steensma; Theo A.H. Doreleijers; Peggy T. Cohen-Kettenis

(b) **Acquisition of Data**
Annelou L.C. de Vries; Thomas D. Steensma; Peggy T. Cohen-Kettenis

(c) **Analysis and Interpretation of Data**
Annelou L.C. de Vries; Thomas D. Steensma; Theo A.H. Doreleijers; Peggy T. Cohen-Kettenis

Category 2

(a) **Drafting the Article**
Annelou L.C. de Vries; Thomas D. Steensma; Theo A.H. Doreleijers; Peggy T. Cohen-Kettenis

(b) **Revising It for Intellectual Content**
Annelou L.C. de Vries; Thomas D. Steensma; Theo A.H. Doreleijers; Peggy T. Cohen-Kettenis

Category 3

(a) **Final Approval of the Completed Article**
Annelou L.C. de Vries; Thomas D. Steensma; Theo A.H. Doreleijers; Peggy T. Cohen-Kettenis

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-IV-TR, 4th edition, text revision. Washington, DC: American Psychiatric Association; 2000.

2 World Health Organization. International statistical classification of diseases and related health problems. 10th edition. Geneva: World Health Organization; 1993.
3 Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. J Am Acad Child Adolesc Psychiatry 2008;47:1413–23.
4 Zucker KJ, Bradley S. Gender identity disorder and psychosexual problems in children and adolescents. New York, NY: Guilford; 1995.
5 Cohen-Kettenis PT. Gender identity disorder in DSM? [letter]. J Am Acad Child Adolesc Psychiatry 2001;40:391.
6 Drummond KD, Bradley SJ, Peterson-Badali M, Zucker KJ. A follow-up study of girls with gender identity disorder. Dev Psychol 2008;44:34–45.
7 Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: A follow-up study. J Am Acad Child Adolesc Psychiatry 1997;36:263–71.
8 Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: A prospective follow-up study. J Am Acad Child Adolesc Psychiatry 2001;40:472–81.
9 Cohen-Kettenis PT, van Goozen SH. Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. Eur Child Adolesc Psychiatry 1998;7:246–8.
10 Shalev JE, Leung PC. Gonadotropin-releasing hormone and reproductive medicine. Obstet Gynaecol Can 2003;25:98–113.
11 Wren B. "I can accept my child is transsexual but if I ever see him in a dress I'll hit him": Dilemmas in parenting a transgendered adolescent. Clin Child Psychol Psychiatry Special Issue: Sexual identity and gender identity. 2002;7:377–97.
12 Grossman AH, D'Augelli AR. Transgender youth and life-threatening behaviors. Suicide Life Threat Behav 2007;37:527–37.
13 de Vries AL, Noens IL, Cohen-Kettenis PT, van Berckelaer-Onnes IA, Doreleijers TA. Autism spectrum disorders in gender dysphoric children and adolescents. J Autism Dev Disord 2010 Jan 22 [Epub ahead of print] doi: 10.1007/s10803-010-0935-9.
14 Cohen-Kettenis PT, Delemarre-van de Waal HA, Gooren LJ. The treatment of adolescent transsexuals: Changing insights. J Sex Med 2008;5:1892–7.
15 Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspects. Eur J Endocrinol 2006;155(suppl 1):S131–7.
16 Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ, 3rd, Spack NP, Tangpricha V, Montori VM . Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:3132–54.
17 Viner RM, Brain C, Carmichael P, Di Ceglie D. Sex on the brain: Dilemmas in the endocrine management of children and adolescents with gender identity disorder. Arch Dis Child 2005;90(suppl II):A78.
18 WISC-R Project group. Wechsler Intelligence Scale for Children-Revised (WISC-R), Dutch version. Lisse: Swets and Zeitlinger; 1986.
19 Wechsler D, Kort W, Compaan EL, Bleichrodt N, Resing WCM, Schittkatte M. Wechsler Intelligence Scale for Children—Third Edition (WISC-III). 3rd edition. Lisse: Swets and Zettlinger; 2002.
20 Wechsler D. Wechsler Adult Intelligence Scale—Third edition (WAIS-III), Dutch version. 3rd edition. Lisse: Swets and Zetlinger; 1997.
21 Verhulst FC, van der Ende J, Koot HM. Handleiding voor de Youth Self Report (Manual for the Youth Self Report). Rotterdam: Department of Child and Adolescent Psychiatry, Erasmus University; 1997.
22 Verhulst FC, van der Ende J, Koot HM. Handleiding voor de CBCL 4–18 (Manual for the Child Behavior Checklist and Revised Child Behavior Profile). Rotterdam: Department of Child and Adolescent Psychiatry, Erasmus University; 1996.
23 Cohen-Kettenis PT, Owen A, Kaijser VG, Bradley SJ, Zucker KJ. Demographic characteristics, social competence, and behavior problems in children with gender identity disorder: A cross-national, cross-clinic comparative analysis. J Abnorm Child Psychol 2003;31:41–53.
24 van der Does AJW. BDI-II-NL. Manual for the Dutch version of the Beck Depression Inventory. 2nd edition. Lisse: Harcourt Test Publishers; 2002.
25 van der Ploeg HM. Handleiding bij de Zelf Beoordelings Vragenlijst (Manual of the Dutch version of the Spielberger Trait Anxiety Inventory, STAI-DY). 2nd edition. Lisse: Swets Test Publishers; 2000.
26 Van der Ploeg HM, Defares PB, Spielberger CD. Dutch version of the Spielberger State-Trait Anger Scale. Lisse: Swets and Zeitlinger; 1982.
27 Shaffer D, Fisher P, Lucas CP, Dulcan MK, Schwab-Stone ME. A children's global assessment scale (CGAS). Arch Gen Psychiatry 1983;40:1228–31.
28 Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. Arch Sex Behav 1975;4:639–56.
29 Kuiper AJ. Transsexualiteit: Evaluatie van de Geslachtsaanpassende Behandeling. Amsterdam: Free University Press; 1991.
30 Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: A follow-up of fourteen male-to-female patients. Arch Sex Behav 1989;18:145–53.
31 Savin-Williams RC, Ream GL. Suicide attempts among sexual-minority male youth. J Clin Child Adolesc Psychol 2003;32:509–22.
32 Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf) 2009.
33 Giordano S. Lives in a chiaroscuro. Should we suspend the puberty of children with gender identity disorder? J Med Ethics 2008;34:580–4.

EXHIBIT 16

Understanding the Well-Being of LGBTQI+ Populations

Committee on Understanding the Well-Being of Sexual and Gender Diverse Populations

Charlotte J. Patterson, Martín-José Sepúlveda, and Jordyn White, *Editors*

Committee on Population

Division of Behavioral and Social Sciences and Education

A Consensus Study Report of

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

THE NATIONAL ACADEMIES PRESS
Washington, DC
www.nap.edu

Copyright National Academy of Sciences. All rights reserved.

THE NATIONAL ACADEMIES PRESS 500 Fifth Street, NW Washington, DC 20001

This activity was supported by contracts between the National Academy of Sciences and Gilead Sciences (award no. 05352), the Sexual and Gender Minority Research Office of the National Institutes of Health (award no. 75N98019F00850), the Robert Wood Johnson Foundation (award no. 75874), the TAWANI Foundation (unnumbered), and the Tegan and Sara Foundation (unnumbered). Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.

International Standard Book Number-13: 978-0-309-68081-3
International Standard Book Number-10: 0-309-68081-6
Digital Object Identifier: https://doi.org/10.17226/25877
Library of Congress Control Number: 2020949996

Additional copies of this publication are available from the National Academies Press, 500 Fifth Street, NW, Keck 360, Washington, DC 20001; (800) 624-6242 or (202) 334-3313; http://www.nap.edu.

Copyright 2020 by the National Academy of Sciences. All rights reserved.

Printed in the United States of America

Suggested citation: National Academies of Sciences, Engineering, and Medicine. (2020). *Understanding the Well-Being of LGBTQI+ Populations*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25877.

Copyright National Academy of Sciences. All rights reserved.

The National Academies of

SCIENCES · ENGINEERING · MEDICINE

The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Marcia McNutt is president.

The **National Academy of Engineering** was established in 1964 under the charter of the National Academy of Sciences to bring the practices of engineering to advising the nation. Members are elected by their peers for extraordinary contributions to engineering. Dr. John L. Anderson is president.

The **National Academy of Medicine** (formerly the Institute of Medicine) was established in 1970 under the charter of the National Academy of Sciences to advise the nation on medical and health issues. Members are elected by their peers for distinguished contributions to medicine and health. Dr. Victor J. Dzau is president.

The three Academies work together as the **National Academies of Sciences, Engineering, and Medicine** to provide independent, objective analysis and advice to the nation and conduct other activities to solve complex problems and inform public policy decisions. The National Academies also encourage education and research, recognize outstanding contributions to knowledge, and increase public understanding in matters of science, engineering, and medicine.

Learn more about the **National Academies of Sciences, Engineering, and Medicine** at **www.nationalacademies.org**.

Copyright National Academy of Sciences. All rights reserved.

The National Academies of
SCIENCES · ENGINEERING · MEDICINE

Consensus Study Reports published by the National Academies of Sciences, Engineering, and Medicine document the evidence-based consensus on the study's statement of task by an authoring committee of experts. Reports typically include findings, conclusions, and recommendations based on information gathered by the committee and the committee's deliberations. Each report has been subjected to a rigorous and independent peer-review process and it represents the position of the National Academies on the statement of task.

Proceedings published by the National Academies of Sciences, Engineering, and Medicine chronicle the presentations and discussions at a workshop, symposium, or other event convened by the National Academies. The statements and opinions contained in proceedings are those of the participants and are not endorsed by other participants, the planning committee, or the National Academies.

For information about other products and activities of the National Academies, please visit www.nationalacademies.org/about/whatwedo.

Copyright National Academy of Sciences. All rights reserved.

COMMITTEE ON UNDERSTANDING THE STATUS AND WELL-BEING OF SEXUAL AND GENDER DIVERSE POPULATIONS

CHARLOTTE J. PATTERSON (*Cochair*), Department of Psychology, University of Virginia
MARTÍN-JOSÉ SEPÚLVEDA (*Cochair*), Health Systems and Policy Research, IBM Corporation (*retired*); CLARALUZ Consulting LLC
M.V. LEE BADGETT, Department of Economics, University of Massachusetts Amherst
MARLON M. BAILEY, Department of Women and Gender Studies, School of Social Transformation, Arizona State University
KATHARINE B. DALKE, Department of Psychiatry and Behavioral Health and Humanities, Pennsylvania State University College of Medicine
ANDREW R. FLORES, Department of Government, School of Public Affairs, American University
GARY J. GATES, *retired*
ANGELIQUE C. HARRIS, Department of Medicine, Boston University Medical Campus, Boston University
MARK L. HATZENBUEHLER, Department of Psychology, Harvard University
NAN D. HUNTER, Georgetown University Law Center
TONIA C. POTEAT, Department of Social Medicine, University of North Carolina Chapel Hill
SARI L. REISNER, Brigham and Women's Hospital, Harvard Medical School, Harvard T.H. Chan School of Public Health, and Fenway Health
STEPHEN T. RUSSELL, Department of Human Development and Family Sciences, University of Texas at Austin
DEBRA J. UMBERSON, Population Research Center, University of Texas at Austin

JORDYN WHITE, *Study Director*
KELLAN BAKER, *Consultant*, *Bloomberg School of Public Health, Johns Hopkins University*
KENNE DIBNER, *Senior Program Officer*
TARA BECKER, *Program Officer*
MARY GHITELMAN, *Senior Program Assistant*
MALAY K. MAJMUNDAR, *Director, Committee on Population*

Copyright National Academy of Sciences. All rights reserved.

COMMITTEE ON POPULATION

KATHLEEN MULLAN HARRIS (*Chair*), Department of Sociology, Carolina Population Center, and National Longitudinal Study of Adolescent to Adult Health, University of North Carolina at Chapel Hill
DEBORAH BALK, Marxe School of Public and International Affairs, and CUNY Institute for Demographic Research, Baruch College of the City University of New York
NANCY BIRDSALL, Center for Global Development, Washington, DC
ANN K. BLANC, Population Council, New York, NY
COURTNEY C. COILE, Department of Economics, Wellesley College
VICKI A. FREEDMAN, Institute for Social Research, University of Michigan
DANA A. GLEI, Georgetown University
ROBERT A. HUMMER, Department of Sociology, and Carolina Population Center, University of North Carolina at Chapel Hill
HEDWIG (HEDY) LEE, Department of Sociology, Washington University in St. Louis
JENNIFER J. MANLY, Taub Institute for Research on Alzheimer's Disease and the Aging Brain, Department of Neurology, Columbia University
EMILIO A. PARRADO, Department of Sociology and Population Studies Center, University of Pennsylvania
ANNE R. PEBLEY, Department of Community Health Sciences, Department of Sociology, California Center for Population Research, Bixby Center on Population and Reproductive Health, University of California, Los Angeles
ISABEL V. SAWHILL, The Brookings Institution, Washington, DC
REBECA WONG, University of Texas Medical Branch at Galveston

MALAY K. MAJMUNDAR, *Director*

Copyright National Academy of Sciences. All rights reserved.

PAGE BREAK

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 9 of 54

12

Coverage, Access, and Utilization of Evidence-Based Health Care

Research indicates that access to adequate insurance coverage, culturally responsive providers, and high-quality, evidence-based health care services has the potential to significantly reduce the effects of health disparities on sexual and gender diverse (SGD) populations. This chapter first reviews the literature on access to care, insurance coverage, and health services utilization in SGD populations. It then discusses in detail three topics that are particularly critical to ensure that clinical and policy approaches to health care for SGD populations are evidence based: gender-affirming care for transgender people, conversion therapy targeting sexual orientation or gender identity, and early genital surgeries for infants with intersex traits.

The importance of grounding clinical protocols and health-related policies on a firm evidence base is a central component of providing high-quality care to SGD people and developing effective strategies to improve SGD population health. Evidence indicates that gender-affirming medical care can significantly improve the health and well-being of transgender people. Conversely, virtually all major medical authorities agree that both "conversion therapy" to change the sexual orientation or gender identity of LGBTQ people and procedures to "normalize" the sex characteristics of children with intersex traits who are too young to participate in consent lack evidence of benefit and show evidence of physical and mental health harms.

Over the past decade, the evidence regarding the importance of gender-affirming care for transgender people has grown exponentially, with increasingly robust data on improvements in mental health outcomes and overall

Copyright National Academy of Sciences. All rights reserved.

well-being in particular. With regard to conversion therapy and early genital surgeries on infants with intersex traits, however, the evidence base has evolved in the opposite direction, indicating that these procedures have harmful consequences for the health of SGD people.

COVERAGE, ACCESS, AND UTILIZATION

SGD people often encounter barriers to health care services. These barriers include individual factors, such as health literacy; interpersonal factors, such as individual experiences of discrimination by health care providers and insurers; and broader structural factors, such as lower rates of health insurance coverage and higher rates of poverty among lesbian, gay, bisexual, and transgender (LGBT) communities and households headed by same-sex couples, which puts health care financially out of reach for many. Another common barrier is a widespread lack of training for providers in SGD population health, which means that many individuals, particularly transgender and people with intersex traits, struggle to find culturally and clinically competent health care providers.

This section discusses insurance coverage, access to care, and utilization of health care services by SGD people. It focuses first on discrimination in access to health care and health insurance, which is an important influence on the well-being of SGD populations. It then discusses other insurance coverage issues for SGD people, followed by what is known about health services utilization in SGD populations, including considerations of care quality and health professions training.

Discrimination in Health Care and Health Insurance Coverage

Despite cultural and legal shifts such as the nationwide expansion of marriage equality for same-sex couples, discrimination against LGBT people in health care and coverage remains pervasive in the United States. A 2017 survey conducted by National Public Radio (NPR), the Harvard School of Public Health, and the Robert Wood Johnson Foundation found that 16 percent of LGBT people reported encountering discrimination on the basis of their sexual orientation or gender identity when seeking medical care (NPR, Robert Wood Johnson Foundation, and Harvard T.H. Chan School of Public Health, 2017). Transgender people are particularly likely to encounter discrimination in health care settings. According to the 2015 U.S. Transgender Survey (USTS), 33 percent of transgender people who had seen a health care provider in the previous year had at least one negative experience related to being transgender, such as being verbally harassed, physically assaulted, or refused treatment (James et al., 2016). A 2019 review found that, across eight studies, 27 percent (range: 19–40%)

Copyright National Academy of Sciences. All rights reserved.

of transgender people reported having been denied health care outright (Kcomt, 2019).

In health insurance, discrimination against SGD people has historically taken many forms. Some types of insurance discrimination prevent people from being able to obtain or afford a health insurance plan at all. These include denials of family coverage to same-sex couples, including legally married spouses (CCIIO, 2014), and preexisting condition exclusions targeting conditions such as cancer and HIV (CCIIO, n.d.). Those who do obtain a plan may then encounter barriers to using their coverage. For SGD people living with HIV, these barriers include adverse tiering (when insurers place certain drugs, such as HIV antiretrovirals, in high cost-sharing levels) and coverage exclusions for pre- and post-exposure prophylaxis (Jacobs and Sommers, 2015; Underhill, 2012). For other SGD people, frequent coverage barriers include difficulty accessing preventive screenings (Agénor et al., 2014; CMS, 2015; Tabaac et al., 2018) and exclusion of coverage for such services as mental and behavioral health care, infertility treatments for same-sex couples, and gender-affirming care for transgender people (American Society for Reproductive Medicine, 2013; Baker, 2017; Coursolle, 2019). Among USTS respondents with insurance, 25 percent reported insurance discrimination on the basis of their gender identity (James et al., 2016). Their experiences included being denied coverage for what are often construed as "gender-specific" services, such as mammograms, cervical cancer screenings, and prostate exams (13%); being denied coverage for care not related to gender affirmation (7%); and being denied coverage for gender-affirming surgery (55%) or hormone therapy (25%). Gender-affirming medical care for transgender people is discussed in detail below.

As described in Chapter 11, discrimination has direct negative consequences for health and well-being and exacerbates the significant health disparities that affect LGBT, intersex, and other SGD populations. Encounters with discrimination in health care settings also jeopardize health by engendering avoidance. In the NPR et al. study, 18 percent of LGBT people reported not seeking health care when they needed it for fear of discrimination; in the 2015 USTS, 23 percent of transgender respondents had not sought care they needed in the last year for fear of mistreatment (James et al., 2016; NPR, Robert Wood Johnson Foundation, and Harvard T.H. Chan School of Public Health, 2017). Similarly, people with intersex traits may avoid routine health care due to previous negative experiences with medical providers (Lambda Legal, 2018).

Given the health consequences of discrimination, laws and policies that prohibit discrimination are a critical intervention for protecting and improving the health and well-being of LGBT, intersex, and other SGD people. Both public and private entities have increasingly established

Copyright National Academy of Sciences. All rights reserved.

nondiscrimination protections that include these populations. Beginning in 2006, the U.S. Department of Health and Human Services (HHS) promulgated a number of regulations that sought to ensure that discrimination on the basis of sexual orientation or gender identity did not hinder beneficiaries' access to a wide range of programs, including Medicare's Program of All-Inclusive Care for the Elderly,[1] HHS grants and services,[2] HealthCare.gov and the state-based health insurance marketplaces,[3] Medicaid managed care plans,[4] plans covering the essential health benefits outlined in the Affordable Care Act (ACA),[5] qualified health plans,[6] and ACA-regulated health insurance plans more broadly.[7] In 2011, the Joint Commission, which accredits approximately 80 percent of U.S. hospitals, began requiring accredited entities to establish nondiscrimination policies inclusive of sexual orientation and gender identity (Joint Commission, 2011).

In 2016, HHS released a regulation outlining its enforcement of Section 1557 of the ACA.[8] This ACA provision, sometimes known as the Health Care Rights Law, prohibits discrimination on the basis of race, color, national origin, age, disability (including HIV status), or sex in any federally supported health program or activity.[9] The 2016 regulation clarified that the sex nondiscrimination protections in Section 1557 include gender identity and intersex status (as well as pregnancy status) (Baker, 2016). The department also invited complaints of sexual orientation discrimination as a form of sex stereotyping prohibited under Section 1557. In addition to requiring equal access to health care services and health insurance coverage, the regulation clarified that such actions as refusing to use a transgender person's correct name and pronoun, assigning a transgender person to a hospital room or other facility on the basis of their sex assigned at birth, or excluding coverage for all care related to gender affirmation constitute discrimination (insurance coverage for gender-affirming care is covered in more detail below). Evidence indicates that this regulation was effective in addressing numerous forms of discrimination against LGBT people in health care settings (Gruberg and Bewkes, 2018).

As this report goes to press, the Section 1557 regulation is being contested through lawsuits in federal court regarding the scope of its protec-

[1] 42 C.F.R. § 460.98(b)(3) and § 460.112(a).
[2] 45 C.F.R. § 75.300.
[3] 45 C.F.R. § 155.120(c)(ii) and § 155.220(j)(2).
[4] 42 C.F.R. § 438.3(d)(4), § 438.206(c)(2), and § 440.262.
[5] 45 C.F.R. § 156.125(a) and (b).
[6] 45 C.F.R. § 156.200(e) and § 156.1230(b)(3).
[7] 45 C.F.R. § 147.104(e).
[8] 45 C.F.R. Part 92.
[9] 42 U.S.C. 18116.

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 13 of 54

tions for sex nondiscrimination. It is expected, however, that the Supreme Court's decision in the case of *Bostock v. Clayton County*, in which the Court ruled that the sex nondiscrimination protections in Title VII of the Civil Rights Act include gender identity and sexual orientation (see Chapter 5), will supersede contradicting interpretations of the ACA's sex nondiscrimination provision and lead to SGD populations being protected under Section 1557 (Keith, 2020). Still unresolved, however, are such issues as access to abortion and other health care services that are increasingly targeted by laws allowing health care providers to opt out of nondiscrimination requirements that they claim conflict with their religious beliefs (Keith, 2019). The impact of religious refusal laws on the health and well-being of SGD populations is a critical and understudied issue.

Health Insurance Coverage

Several factors have changed the landscape of health insurance coverage for LGBT people over the past decade. In addition to the nondiscrimination protections described above, these factors include marriage equality for same-sex couples and the implementation of coverage expansions under the ACA.

Legal relationship recognition expands the availability of health insurance coverage for same-sex couples. Prior to the 2015 Supreme Court decision legalizing marriage equality nationwide, state recognition of same-sex domestic partnerships, civil unions, or marriage was associated with narrower coverage gaps for same-sex couples and their children relative to families headed by different-sex couples (Gonzales, 2015; Gonzales and Blewett, 2013, 2014). The effects of the Supreme Court decision itself are difficult to discern given their overlap with the major expansion of coverage driven by the ACA. The ACA, which was enacted in 2010 and went into full effect in 2014, expanded the availability of coverage in two main ways. First, the law created sliding-scale tax credits intended to facilitate the purchase of health insurance coverage through new health insurance marketplaces, such as HealthCare.gov. Second, under the Supreme Court's 2012 interpretation of the ACA, states were given the choice to expand the eligible income ranges for their Medicaid programs.

Both of these mechanisms are important pathways to coverage for LGBT people, who tend to have lower incomes and higher rates of uninsurance than non-LGBT people. In the first half of 2013, prior to the full implementation of the ACA, 34 percent of a nationally representative sample of LGBT people making less than $45,000 per year (the income range eligible for health insurance marketplace subsidies) were uninsured (Baker, Durso, and Cray, 2014). Following the opening of the marketplaces in fall 2013, uninsurance among LGBT people in this income bracket dropped to

Copyright National Academy of Sciences. All rights reserved.

26 percent in 2014 and to 22 percent in 2017 (Baker and Durso, 2017). Data from the Urban Institute's Health Reform Monitoring Survey similarly indicate that the share of LGB adults without health insurance across all income ranges decreased from 21.7 percent in 2013 to 11.1 percent in 2015 (Karpman, Skopec, and Long, 2015). In 2015, uninsurance among transgender USTS respondents stood at 14 percent (James et al., 2016). A 2017 study based on Gallup data, however, found that the adult LGBT population as a whole remained more likely to be uninsured than the non-LGBT population—15 percent and 12 percent, respectively—though this analysis did not account for a greater proportion of young people in the LGBT group.[10]

One risk factor for uninsurance among LGB adults in the post-ACA era is being just older than 26, when coverage for young people through their parents' plans often ends (Gonzales, Driscoll, and Quinones, 2019). Living in the South or Midwest is also a risk factor for uninsurance. These regions comprise the bulk of the states that have not expanded their Medicaid programs and are home to substantial numbers of LGBT people living in poverty. Williams Institute estimates that 24 and 23 percent of LGBT people living in the South and the Midwest, respectively, have incomes below the federal poverty level (Choi, Badgett, and Wilson, 2019). An analysis of data from the 2014 Behavioral Risk Factor Surveillance System (BRFSS) indicated that a lack of Medicaid expansion is associated with higher prevalence of uninsurance among lower-income LGB adults: LGB adults with annual household incomes under $25,000 in states that did not expand Medicaid in 2014 had higher rates of uninsurance than LGB adults in states that did expand Medicaid—37.5 and 23.3 percent, respectively—though this analysis could not confirm that all of the uninsured would have been eligible for expanded Medicaid (Gonzales and Henning-Smith, 2017a).

Beyond providing coverage to low-income people, Medicaid is also particularly important for LGBT people with specific health care needs, such as people with disabilities and people living with HIV. Both population-based and purposive sampling studies indicate that the prevalence of disability is higher among LGBT people than in the general population. An analysis of Washington state BRFSS data, for instance, found that 35.5 percent of lesbians and 36.2 percent of bisexual women had a disability, compared with 25.9 percent of heterosexual women; 26.2 percent of gay men and 40.1 percent of bisexual men had a disability, compared with 22.5 percent of heterosexual men (Fredriksen-Goldsen, Kim, and Barkan, 2012). Among transgender people, 39 percent of 2015 USTS respondents reported having a disability, compared with 15 percent of the general population (James et

[10] See: https://williamsinstitute.law.ucla.edu/visualization/lgbt-stats/?topic=LGBT#economic.

Copyright National Academy of Sciences. All rights reserved.

al., 2016). In comparison with binary-identified transgender people, nonbinary transgender adults in a pooled BRFSS sample from 30 states and Guam between 2014 and 2016 were more likely to report activity limitations due to physical, mental, or emotional problems (adjusted odds ratio [aOR]: 2.44; 95% confidence interval [CI]: 1.36, 4.34) (Streed, McCarthy, and Haas, 2018).

Though precise statistics are not available, disability for some LGBT people is related to living with HIV. To qualify for Medicaid coverage under pre-ACA eligibility rules, people living with HIV had to have both low incomes and a disability (or otherwise be categorically eligible by, for example, being a parent) (Kaiser Family Foundation, 2019). This led to situations in which people living with HIV could not afford treatment and had to allow their health to deteriorate to a disabling AIDS diagnosis before being able to access Medicaid coverage that could have kept them healthy (IOM, 2011a). The ACA resolved this problem in states that expanded their Medicaid programs. Access to care for people living with HIV is one of the many reasons that Medicaid expansion or broader health system reform, such as "Medicare for All" or another form of universal coverage, is a critical health issue for SGD populations.

Medicaid is also an important source of health insurance coverage for transgender people for both income and medical reasons. In the 2015 USTS, 29 percent of transgender respondents were living below 124 percent of the federal poverty line, which is nearly twice the rate of poverty among the general population (14%). Rates of poverty were higher among transgender respondents who were living with HIV (51%), had a disability (45%), or belonged to communities of color (43, 41, 40, and 38% among Latinx, Native American, multiracial, and Black respondents, respectively). The proportion of USTS respondents insured by Medicaid, however, was slightly smaller (13%) than the general population (15%). Barriers to Medicaid coverage for transgender people include restrictive income eligibility requirements in states that have not expanded Medicaid and the checkered history of Medicaid coverage for gender-affirming services, which is discussed in more detail in a later section of this chapter.

Health Services Utilization

Factors that can encourage or discourage care seeking include insurance coverage and benefit design; income and education; health status, including chronic conditions and acute care needs; health literacy; clinical and cultural competency among medical providers; geographic availability and physical accessibility of providers; and previous positive or negative experiences in health care settings (Committee on Health Care Utilization and Adults with Disabilities, 2018). Given the complexity of this constel-

Copyright National Academy of Sciences. All rights reserved.

lation of factors, it is difficult to characterize or predict broad trends in care utilization among SGD populations. For instance, the establishment of new legal protections may improve SGD population health and thus lead to fewer care visits; at the same time, however, the existence of new protections may encourage SGD people to seek care instead of avoiding it for fear of discrimination, which might lead to more care visits.

Some evidence suggests that sexual minority populations have high baseline care utilization. An analysis of data from the 2003–2011 nationwide Medical Expenditure Panel Survey, adjusted for sociodemographic factors, health risk behaviors, and health conditions, found that both men and women in same-sex partnerships had 67 percent (aOR: 1.67; 95% CI: 1.04, 2.67) increased odds of past-year emergency department visits and 51 percent (aOR: 1.51; 95% CI: 1.11, 2.07) increased odds of more than three physician visits in the previous year in comparison with people in different-sex partnerships (Blosnich et al., 2016). This finding is in keeping with the minority stress model, which suggests that sexual and gender minorities have worse health related to their lower social status and thus may require more medical care than their heterosexual and cisgender peers. Also in keeping with this model, Hatzenbuehler and colleagues (2012) observed a decline in medical care visits and mental health care visits among both partnered and single sexual minority men in the 12 months following the establishment of marriage equality for same-sex couples in Massachusetts.

Among transgender people, an analysis of data from the California Health Interview Survey found that transgender respondents had lower utilization rates of both primary and specialty care than non-transgender respondents (Ehrenfeld, Zimmerman, and Gonzales, 2018). Similarly, a study of transgender Medicare beneficiaries found a decreasing trend in mental health care use between 2009 and 2014 (Progovac et al., 2019). Use of gender-affirming health care services, however, has been rising since 2000 (Canner et al., 2018). This trend is likely related to a combination of a growing transgender population in the United States, improved coding practices that make it easier to identify transgender people and gender-affirming medical services in data sources such as insurance claims, and removal of barriers to insurance coverage for these services.

Further complicating assessments of care utilization is evidence that barriers to care can persist even after coverage becomes more available. Using data from the 2013–2015 National Health Interview Survey, for instance, Hsieh and Ruther (2017) documented numerous issues facing sexual minority people seeking health care, including ongoing use of emergency departments for primary care; delayed or unmet care needs due to cost; and delayed or unmet care needs for nonfinancial reasons, such as

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 17 of 54

not being able to get an appointment with a medical provider or lacking transportation to a provider's office. Gonzales and Henning-Smith (2017b) similarly found that gender-nonconforming people in a 2014–2015 BRFSS sample from 27 states and Guam were almost twice as likely as a reference group of cisgender women to have unmet care needs due to financial issues (aOR: 1.93; 95% CI: 1.02, 3.67), and they were more than twice as likely not to have received a routine check-up in the previous year (aOR: 2.41; 95% CI: 1.41, 4.12). There is a lack of data on utilization among people with intersex traits.

Quality of Care and Health Professions Training

Common frameworks for quality improvement in health care include the six aims of safety, timeliness, effectiveness, efficiency, patient-centeredness, and equity set forth by the Institute of Medicine (2001) and the "triple aim" of improved patient experiences of care, improved population health outcomes, and reduced costs developed by the Institute for Healthcare Improvement (Berwick, Nolan, and Whittington, 2008). Scant research has explored quality of care issues, including definitions, priority outcomes, and measurement, among SGD populations. Another aspect of care quality is attention to the social determinants of health at the population level and to the social needs of individuals in health care contexts. Major negative social influences on the health of SGD populations include but are not limited to discrimination and a lack of access to culturally responsive providers; family and peer rejection and bullying; unemployment and poverty; and a dearth of feelings of community cohesion, safety, and participation (IOM, 2011b). These generate social needs such as trauma, housing insecurity, financial strain, and social isolation, particularly among groups such as SGD youth and older adults. It is important for researchers, care providers, and policy makers to develop and evaluate targeted efforts to address social determinants of health and meet social needs for SGD people. The experiences of SGD patients have also not been fully explored in the context of new care delivery models intended to improve quality, coordinate care, and restrain costs, such as accountable care organizations and patient-centered medical homes (National LGBT Health Education Center, 2016).

Regardless of how care delivery is organized, providing cultural and clinical competency training about SGD populations for the entire health workforce is critical to ensuring that SGD people can access high-quality care. Training in providing culturally responsive and clinically appropriate care for SGD people needs to begin early for medical students and other health professions trainees, including but not limited to nurses, physician assistants, and nurse practitioners (AMA, 2019; Obedin-Maliver et al., 2011; Streed et al., 2019b). The American Association of Medical Colleges

Copyright National Academy of Sciences. All rights reserved.

has published curriculum resources to support early clinician training in SGD health topics (Hollenbach, Eckstrand, and Dreger, 2014).[11]

Another strategy for promoting cultural responsiveness to SGD concerns in health care settings is encouraging the career development of SGD-identified health professionals. Sexual and gender diversity, alongside other forms of representation such as racial diversity, strengthens the health care workforce by bringing in new perspectives to inform the delivery of care and helping patients build trust with providers whose backgrounds mirror theirs (Tanner, 2020). Unfortunately, research indicates that SGD people remain significantly underrepresented in the scientific workforce, and many workforce diversity initiatives—such as those supported by the National Institutes of Health (NIH)—do not include SGD populations despite the designation of sexual and gender minorities as an NIH health disparity population in 2016 (Freeman, 2018).

In terms of SGD cultural responsiveness among practicing providers, a 2016 systematic review by the Agency for Healthcare Research and Quality called for clearer definitions of cultural competency for LGBT populations, clarification on the relationship between cultural competence and patient-centered care, and greater availability and assessment of training curricula (Butler et al., 2016). In 2020, the Human Rights Campaign's Healthcare Equality Index, which provides training and assesses LGBT cultural competency at hospitals and other health care organizations across the country, reported that the 765 health care facilities evaluated nationwide in the previous year had accumulated more than 150,000 hours of LGBT-specific cultural competency training (Human Rights Campaign Foundation, 2020).

Another resource related to cultural responsiveness in working with SGD patients are the federal Culturally and Linguistically Appropriate Services Standards, which include sexual orientation and gender identity among aspects of patient identity that require attention and respect from care providers (Office of Minority Health, 2013). The federal Substance Abuse and Mental Health Services Administration (SAMHSA) also promotes cultural competency training around sexual and gender diversity (SAMHSA, 2020), and the Health Resources and Services Administration (HRSA), which oversees the community health centers program and the Ryan White program, funds the National LGBT Health Education Center at Fenway Health, a federally qualified community health center located in Boston that specializes in serving LGBTQ people and people living with HIV.[12] The National LGBT Health Education Center provides a variety of downloadable resources and continuing medical education modules on

[11] See https://www.aamc.org/what-we-do/mission-areas/diversity-inclusion/lgbt-health-resources.
[12] See https://www.lgbthealtheducation.org.

Copyright National Academy of Sciences. All rights reserved.

culturally responsive and clinically appropriate care for LGBTQ people and people with intersex traits.

In addition to the National LGBT Health Education Center, HRSA supports the Center of Excellence for Transgender Health at the University of California at San Francisco, which conducts research and publishes care guidelines and other resources about various aspects of transgender health, particularly in relation to HIV.[13] Between 2012 and 2017, HRSA partnered with the Center of Excellence and several other community-based organizations on a Special Project of National Significance that investigated strategies for engaging and retaining HIV-positive transgender women of color in high-quality care. Important factors identified in this project included providing transgender-specific cultural and clinical competency training for the health care workforce; addressing social determinants of health, such as housing, as part of the provision of health care services; and recognizing the central role that gender-affirming services and personal empowerment can play in improving care and outcomes for transgender people living with HIV, particularly transgender women of color (Health Resources and Services Administration, n.d.; Rebchook et al., 2017). Resources on serving other specific SGD populations have also been created by both public and private entities: in 2010, the federal Administration on Aging (now the Administration for Community Living) funded the creation of the National Resource Center on LGBT Aging to provide information and resources for health care personnel working with LGBT elders,[14] and organizations such as Lambda Legal have published guidelines for hospitals on establishing affirming policies for transgender people (Lambda Legal, 2016) and people with intersex traits (Lambda Legal, 2018).

Alongside cultural and clinical competency training and a diverse health professions workforce, data collection about sexual orientation, gender identity, and intersex status in health care and public health activities is a critical component of understanding and effectively addressing health disparities among SGD populations. Both *Healthy People 2020*, released in 2010, and *Healthy People 2030*, released in 2020, call for an increase in the number of population health surveys that include sexual orientation and gender identity measures,[15] and federal regulations governing incentive programs for electronic medical records require that certified systems have the capacity to collect, store, and retrieve structured data on sexual orientation and gender identity (Cahill et al., 2016). The NIH Sexual and Gender Minority Research Office also promotes research into the health of

[13] See https://prevention.ucsf.edu/transhealth.
[14] See https://www.lgbtagingcenter.org.
[15] See https://www.healthypeople.gov.

Copyright National Academy of Sciences. All rights reserved.

SGD populations[16] (see Chapter 4 for a more detailed discussion of data collection).

GENDER-AFFIRMING CARE FOR TRANSGENDER PEOPLE

The first U.S. clinics providing gender-affirming care to transgender individuals opened in the 1960s and 1970s. Practice and research in the field of transgender health, however, was stymied in the 1980s and 1990s by the spread of public and private insurance exclusions for gender-affirming care. As these exclusions have begun to be removed, there has been exponential growth in evidence regarding the medical necessity of this care, and gender affirmation has emerged as a core intervention to improve the health and well-being of transgender people. This section reviews the components of and clinical and population evidence concerning gender affirmation.

Components of Gender Affirmation

Broadly speaking, gender affirmation is a process by which people who identify as transgender, non-binary, or gender diverse take steps to fully express their true gender. (An older but still common term for the process of gender affirmation is gender transition.) Gender affirmation may have social, legal, and medical components. Socially, people may use a name or pronoun different from those they were assigned at birth, or they may change aspects of their gender expression, such as hairstyle and clothing. Legal affirmation may include name or gender marker changes on identification documents—such as passports, driver's licenses, and birth certificates—which are affected by state and federal laws and policies. Gender-affirming clinical care may include psychosocial support, hormone therapy, and surgeries.

Psychosocial support for gender affirmation typically focuses on reducing emotional distress and supporting decision making regarding social, legal, and medical steps. Some young transgender people and their families opt for medication to delay the onset of puberty. Adults and some adolescents may take feminizing or masculinizing hormones to achieve gender-congruent secondary sex traits, often in conjunction with medications that suppress menses or block androgens. Many transgender adults and older adolescents undergo surgery to align the appearance of their face, chest or breasts, body shape, and genitals with their gender, and some may also pursue speech therapy or hair removal. Gender affirmation is different for every person: some people may take only social or legal steps, while others may need gender-affirming prescriptions or medical procedures. Regardless

[16] See https://dpcpsi.nih.gov/sgmro.

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 21 of 54

of an individual's path in relation to gender affirmation, social support and integrated, multidisciplinary care are essential for all transgender people, especially youth, and are consistently associated with improved mental health, social involvement, and self-esteem (Rafferty, Committee on Psychosocial Aspects of Child and Family Health, and Committee on Adolescence, 2018).

Guidelines and Policies Related to Gender Affirmation

Clinicians who provide gender-affirming psychosocial and medical services in the United States are informed by expert evidence-based guidelines. In 2012, the World Professional Association for Transgender Health (WPATH) published version 7 of the *Standards of Care for the Health of Transgender, Transsexual, and Gender-Nonconforming People*, which have been continuously maintained since 1979, and revisions for version 8 are currently under way (Coleman et al., 2012). Two newer guidelines have also been published by the Endocrine Society (Hembree et al., 2017) and the Center of Excellence for Transgender Health (UCSF Transgender Care, 2016). Each set of guidelines is informed by the best available data and is intended to be flexible and holistic in application to individual people. All of the guidelines recommend psychosocial support in tandem with physical interventions and suggest timing interventions to optimize an individual's ability to give informed consent. Mental and physical health problems need not be resolved before a person can begin a process of medical gender affirmation, but they should be managed sufficiently such that they do not interfere with treatment.

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 (World Professional Association for Transgender Health, 2016). 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 (American Academy of Family Physicians, 2012; American Academy of Pediatrics, 2018; American College of Nurse Midwives, 2012; American College of Obstetricians and Gynecologists, 2011; AMA, 2008; American Psychiatric Association, 2018; American Psychological Association (APA), 2008, 2015; Endocrine Society, 2017). Accordingly, public and private insurers have expanded access to gender-affirming care; some have done so proactively, while others have been required by state and federal nondiscrimination laws to remove coverage exclusions (Baker, 2017).

Coverage requirements for gender-affirming care typically rely on an overarching principle of parity between medically necessary services for transgender and cisgender people. Treatments that are gender affirming for transgender patients are covered by public and private insurers for

Copyright National Academy of Sciences. All rights reserved.

intersex and cisgender people for a variety of conditions, including genital difference, endocrine disorders, cancer prevention or treatment, and reconstructive surgeries following an injury. Examples of these services include testosterone or estrogen replacement therapy after surgery or menopause, vaginoplasty after pelvic surgery or for women with vaginal agenesis in the context of an intersex condition, and phalloplasty for cisgender male service members injured in war (Baker et al., 2012; Balzano and Hudak, 2018; Spade et al., 2009).

As this report goes to press, 24 states and the District of Columbia have enacted laws or made administrative changes prohibiting transgender-specific insurance exclusions in private coverage (Movement Advancement Project, 2020a). However, Medicaid programs in 10 states continue to explicitly exclude gender-affirming care for transgender individuals, and many states do not address the issue of this coverage in Medicaid (Mallory and Tentindo, 2019). At the federal level, the Medicare program removed its exclusion for "transsexual surgery" in 2014 (HHS, 2014), though coverage decisions related to gender-affirming surgeries are still made on a case-by-case basis (CMS, 2016). As discussed above, Section 1557 of the Affordable Care Act also has substantial ramifications for coverage of gender-affirming care: the 2016 HHS regulation embraced the principle of parity and prohibited categorical exclusions of gender-affirming care under the rubric of sex nondiscrimination. This aspect of the regulation remains contested in court, but it is expected that the original regulation's specific protections for transgender people will be found to be well within the scope of federal law and the agency's authority (Keith, 2020).

In order to justify coverage for gender-affirming care, insurance providers in the United States and most other countries require a supporting diagnosis. In 2013, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), 5th edition (American Psychiatric Association, 2013) replaced the diagnosis of gender identity disorder with gender dysphoria. Whereas gender identity disorder was perceived as pathologizing a person's gender identity, gender dysphoria emphasizes the clinically significant distress and impairment that can accompany incongruence between assigned sex and gender identity (Robles et al., 2016). A person who experiences no distress or impairment due to this incongruence will not meet diagnostic criteria for gender dysphoria. More recently, the *International Classification of Diseases*, 11th revision (WHO, n.d.) has replaced transsexualism and gender identity disorder with gender incongruence and moved the diagnosis out of the mental and behavioral disorders chapter and into a new chapter on sexual health.

Many insurers and some health care providers require documentation that an individual meets guideline requirements, including diagnostic criteria for gender dysphoria, as a prerequisite for hormonal or surgical

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 23 of 54

treatment. Because of the power differential inherent in this construct, this practice has been described as "gatekeeping" and can function as a significant barrier to accessing care. In a survey of transgender adolescents, for instance, participants described distress at having to prove to a mental health provider that they were "trans enough," having to wait for approval for treatment, and perceiving that their therapist feared legal liability should a person later regret the treatment (Gridley et al., 2016). Even transgender people with insurance coverage and access to providers report difficulty in navigating diagnosis-based requirements imposed by providers and insurers (James et al., 2016). Over the past 10 years, some U.S. medical professional organizations have increasingly moved to reduce psychiatric gatekeeping by shifting toward an informed consent and shared decision-making model, especially for adults (Schulz, 2018). Some countries have further underscored that transgender identity is not a pathology by recognizing gender affirmation as fundamental to the human right to self-definition and removing requirements that transgender people seeking gender-affirming medical care present with a diagnosis such as gender dysphoria (Arístegui et al., 2017).

Outcomes of Gender-Affirming Interventions

The evidence base for gender affirmation across age groups has grown rapidly over the last decade. For transgender youth who have not yet reached puberty, social affirmation and support are primary interventions. Using data from electronic records from the Kaiser Permanente system, recent work has suggested that prepubescent transgender children experience increased rates of mental health problems, especially anxiety, depression, and attention deficit disorders, relative to cisgender children (Becerra-Culqui et al., 2018). However, research also shows that, when transgender children in this age group are socially affirmed and supported by their families, their rates of depression are much nearer to those of cisgender children (Durwood, McLaughlin, and Olson, 2017). In one study, transgender youth who were socially affirmed had elevated rates of anxiety relative to their cisgender peers, but this difference was not clinically significant and may have reflected ongoing social stigma and minority stress (Olson et al., 2016). Another study found that using transgender youths' chosen names in home and at school was associated with reduced depression, suicidal ideation, and suicidal behavior (Russell et al., 2018).

Puberty blockers, typically gonadotropin-releasing hormone analogs, have been used since at least the late 1990s to prevent development of irreversible secondary sex traits and to give youth more time to explore their gender identity (Cohen-Kettenis and Van Goozen, 1998). In 2014, a landmark paper provided longitudinal data from a cohort of youth in the Netherlands: among this group, puberty suppression, followed several years

Copyright National Academy of Sciences. All rights reserved.

later by gender-affirming hormones and surgery, was effective in reducing gender dysphoria and restoring well-being equal to or better than same-age cisgender young adults (de Vries et al., 2014). Though most data on puberty suppression are limited and drawn from convenience samples in European clinics, this fully reversible gender-affirming intervention appears to confer improved psychological functioning and may reduce gender dysphoria (Mahfouda et al., 2017).

There is inconsistent and limited evidence regarding risks of irreversible low bone density and infertility (Chew et al., 2018; Mahfouda et al., 2017; Rafferty, Committee on Psychosocial Aspects of Child and Family Health, and Committee on Adolescence, 2018). In recognition of these risks, guidelines recommend monitoring bone density and counseling on fertility preservation prior to treatment (Hembree et al., 2017). Of note, while evidence indicates that social affirmation and puberty suppression are low risk and effective interventions for young transgender youth, there may be a significant delay between recognition and disclosure of gender incongruence: in one cohort, participants reported identification of gender incongruence on average at age 8 and disclosure to caregivers on average at age 17 (Olson et al., 2015). Support from parents and affirmation of gender diversity are critical to creating safe opportunities for young people to access the psychosocial and medical care that they need in a timely manner.

Hormone therapy with testosterone or estrogen is a common gender-affirming treatment for transgender adults and older adolescents. Though limited by heterogeneity of methodology, regimen, and outcomes measures, systematic reviews and meta-analyses consistently find that gender-affirming hormone treatment is associated with significant reductions in gender dysphoria, psychological symptoms, and psychiatric diagnoses and with improved markers of well-being, including quality of life, interpersonal functioning, psychological adjustment, sexual function, body satisfaction, and self-esteem (Costa and Colizzi, 2016; Dhejne et al., 2016; Keo-Meier et al., 2015; Murad et al., 2010; Nguyen et al., 2018; Rowniak, Bolt, and Sharifi, 2019; White Hughto and Reisner, 2016).

Both the WPATH and Endocrine Society guidelines identify age 16 as a general starting point for gender-affirming hormones, with the recognition that some adolescents benefit from earlier treatment (Coleman et al., 2012; Hembree et al., 2017). Evidence for hormone therapy in adolescents comes largely from outside of the United States and inconsistently tracks outcomes (Chew et al., 2018; Olson-Kennedy et al., 2016). The data available suggest that hormone therapy in adolescents likely yields reductions in dysphoria and distress and improvements in well-being similar to those in adults (Mahfouda et al., 2019). Gender-affirming hormone therapy can be managed for most patients by primary care providers,

Copyright National Academy of Sciences. All rights reserved.

as it typically involves long-term maintenance on doses similar to those used for cisgender patients with conditions such as hypogonadism (Wylie et al., 2016).

Surgeries involving the genitals or secondary sex characteristics can also improve health and well-being among transgender people and are an important and medically necessary aspect of gender-affirming care (Bailey, Ellis, and McNeil, 2014; Castellano et al., 2015; Murad et al., 2010; Passos et al., 2020; Wernick et al., 2019). Many factors affect an individual's need for and access to gender-affirming surgeries. In the 2015 USTS, only 25 percent of respondents had undergone some form of gender-affirming surgery, such as genital reconstruction or chest reconstruction, and having surgery was correlated with higher incomes (James et al., 2016). Respondents also reported varying degrees of experience with or need for specific procedures: 97 percent of transgender men had or needed chest reconstruction surgery, and 22 percent of transgender men had or needed phalloplasty. Similarly, 95 percent of transgender women had or needed hair removal procedures, and 76 percent had or needed vaginoplasty. Non-binary individuals generally had and needed fewer surgeries than their binary-identified counterparts: 48 percent of non-binary individuals assigned female at birth had or needed chest surgery, and 12 percent of non-binary individuals assigned male at birth had or needed vaginoplasty.

Surgeries for transgender men and other trans-masculine people may include bilateral chest reconstruction, salpingo-oophrectomy (removal of the ovaries and fallopian tubes), hysterectomy, genital reconstruction (metoidioplasty or phalloplasty with or without prosthesis), and, rarely, vocal surgery. Chest reconstruction, which involves removal of breast tissue and nipple preservation, is associated with significant improvements in mental health and well-being among trans-masculine adolescents and adults (Agarwal et al., 2018; Mahfouda et al., 2019; Van Boerum et al., 2019). A systematic review of studies of genital surgeries that included metoidioplasty indicated that 93 percent of patients were satisfied with the outcome, including preserved erogenous sensitivity, despite significant rates of postoperative complications (Morrison et al., 2016). A systematic review of penile prosthetic outcomes for 792 transgender men over a mean follow-up period of three years found inconsistent reporting of sensory, urinary, satisfaction, and sexual outcomes after surgery, with 36 percent reporting prosthesis complications (Rooker et al., 2019).

Surgeries for transgender women and other trans-feminine people may include breast augmentation, facial feminization, vocal surgery, orchiectomy, and vaginoplasty. Some studies have shown improvements in quality of life and high patient satisfaction following facial feminization procedures for trans-feminine individuals, including reshaping the contours of the face and larynx (Ainsworth and Spiegel, 2010; Van Boerum et al., 2019). A

Copyright National Academy of Sciences. All rights reserved.

systematic review of vaginoplasty for transfeminine individuals identified 26 studies with a total of 1,563 patients; although measures used to track outcomes varied between studies, and complications were frequent, with neovaginal stenosis the most common, patients tended to report high ratings in both sexual function and satisfaction after surgery (Horbach et al., 2015).

The research regarding outcomes for surgery in youth under 18 is sparse, in part because it is generally not clinically recommended for legal minors, though there is only a small amount of low-quality evidence that supports this limitation (Hembree et al., 2017). Chest masculinization is sometimes appropriate for youth 16 or older (Coleman et al., 2012), and some surgeons perform vaginoplasty on minors under specific circumstances (Milrod and Karasic, 2017). Several studies provide positive evidence regarding the benefits of chest reconstruction in minors, with reduced depressive and anxious symptoms and improved chest dysphoria; the most common complications were changes in sensation and scar cosmesis (Mahfouda et al., 2019). There are very few data regarding genitoplasty for minors.

As noted above, available evidence generally indicates that gender-affirming medical interventions, including surgeries, are associated with improvements in gender dysphoria, mental health, and quality of life for transgender people. Evidence also suggests, however, that mental health conditions can persist after treatment: for instance, a 2011 Swedish registry study of 324 patients who had undergone gender-affirming surgeries between 1973 and 2003 found increased rates of suicide attempts and psychiatric hospitalizations relative to population controls (Dhejne et al., 2011). The study notes that surgeries did alleviate gender dysphoria, and the study was unable to determine how patients might have fared without surgery. When a more recent Swedish registry study tracked mental health treatment utilization among people with a gender incongruence diagnosis relative to people without gender incongruence between 2005 and 2015 (N = 2,679), time since gender-affirming surgery was associated with reduced need for mental health services (aOR: 0.92; 95% CI: 0.87, 0.98) (Bränström and Pachankis, 2019). A reanalysis of these data compared individuals with gender incongruence who had gender-affirming surgery with those who did not and found comparable rates of reduced need for treatment for mood disorders between the groups, but higher rates of treatment for anxiety disorders among the group who did have surgery (aOR: 1.40; 95% CI: 1.00, 1.97) (Bränström and Pachankis, 2020). The authors note that the comparator nonsurgical group is heterogeneous, including a mixture of patients who both did and did not want surgery. Furthermore, as was discussed in detail in Chapter 11, transgender people have significantly elevated rates of mental health problems due not just to the experience of

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 27 of 54

gender dysphoria but also because of minority stress and stigma. While social and medical affirmation reduce gender dysphoria and can mitigate the impact of social factors, such as discrimination and family rejection, medical affirmation may not fully resolve or protect from experiences of stigma and stress. Future studies examining outcomes of gender affirmation should assess and control for these factors. Related research needs include exploration of factors that can promote resilience in different family and community settings and across the life course (Bockting et al., 2016).

Another major limitation in research on postsurgical outcomes is the absence of patient-reported outcome measures that have been validated in transgender and non-binary post-operative patient populations (Andréasson et al., 2018; Barone et al., 2017; Dy et al., 2019). Recent data overall suggest that satisfaction after gender-affirming surgeries is high and risk of regret is very low. For example, the Center of Expertise on Gender Dysphoria at the Free University Medical Center in Amsterdam published results from 43 years of clinical care in which regret was reported in only 14 patients (0.5%) of the more than 5,300 patients who underwent gonadectomy as part of gender affirmation (Wiepjes et al., 2018). A smaller study found that only 1 of 68 patients who received chest masculinization surgery experienced regret "sometimes" (Olson-Kennedy et al., 2018), consistent with findings from older research (Gijs and Brewaeys, 2007). Similarly, a 2018 systematic review and meta-analysis of 46 articles with 3,716 cases of vaginoplasty for transgender women reported a cumulative rate of regret of 1 percent, compared with an overall satisfaction rate of 92 percent across different surgical techniques (Manrique et al., 2018). While many studies do not qualitatively assess degree and reasons for regret, in one study patients who reported regret with surgeries reported mild regret and attributed this to cosmetic or functional outcomes rather than the decision to have surgery (van de Grift et al., 2017).

Substantial progress has been made over the past decade in research on outcomes of gender-affirming interventions, and there are ample opportunities for improvement. To address the scarcity of data and difficulties extrapolating findings from relatively homogeneous European samples, a United States-based comprehensive registry that tracks patient-centered outcomes for both youth and adults could lead to valuable insights on the benefits of medically supervised gender affirmation (Kimberly et al., 2018). Much remains to be learned regarding optimal timing and risk profiles for surgeries and other medical interventions, aided by standardized and validated tools for body satisfaction, gender-related quality of life, gender dysphoria, and mental health (Olson et al., 2016). Standardized assessment and reporting of outcomes are particularly essential for helping clinicians and patients understand surgical options. In this area, too, more attention is needed to populations that tend to be invisible or underrepresented in

Copyright National Academy of Sciences. All rights reserved.

clinical research, especially transgender people of color and non-binary individuals. Very little is known about the experiences and options for treatment for transgender individuals with intersex traits, especially those who had irreversible treatments as children. Overall, however, the evidence indicates that gender-affirming interventions, including social affirmation, hormonal treatment, and surgeries, are medically necessary for reducing distress and improving the health and well-being of transgender people.

CONVERSION THERAPY

Efforts to change sexual orientation or gender identity, which initially gained traction in the 1960s and which are often referred to as conversion or reparative therapies, assume that non-cisgender and non-heterosexual identities are abnormal. In 2009 the APA produced a landmark report that systematically reviewed the evidence of efficacy for sexual orientation change efforts (APA, 2009). Most of this research was conducted prior to 1981, and very few studies were experimental in design. The task force found that some people sought sexual orientation change efforts due to distress over their sexual orientation but that the treatments were unable to reduce same-sex attractions or increase other-sex attractions. Furthermore, there was evidence that individuals experienced harm from these treatments, including sexual dysfunction, depression, anxiety, and suicidality. With regard to gender identity, while interest in the so-called "desistence" of transgender identity has been informed by studies suggesting that as high as 80 percent of prepubertal youth presenting to pediatric gender clinics ultimately do not identify as transgender, many of the youth included in these studies did not meet full DSM criteria for a gender incongruence diagnosis (Olson, 2009). Recent evidence supports that early social affirmation of transgender identity is associated with good outcomes (Olson et al., 2016; Durwood, McLaughlin, and Olson, 2017) and that lack of social affirmation correlates with depression, anxiety, and suicidality (de Vries et al., 2016; James et al., 2016).

Consequently, sexual orientation and gender identity conversion efforts have fallen out of favor in mainstream psychological and psychiatric practice. By the time of the 2011 Institute of Medicine report, many medical organizations had issued statements condemning sexual orientation change efforts based on the lack of efficacy and evidence of harm. Many of these organizations have since updated their positions to decry conversion therapy for both sexual orientation and gender identity (AMA and GLMA: Medical Professionals Advancing LGBTQ Equality, 2018; American Academy of Child and Adolescent Psychiatry, 2018; Rafferty, Committee on Psychosocial Aspects of Child and Family Health, and Committee on Adolescence, 2018; SAMHSA, 2015; Streed et al., 2019a).

Copyright National Academy of Sciences. All rights reserved.

However, there is recent evidence that LGBTQ youth and adults continue to be exposed to conversion therapy. A 2019 report from Williams Institute estimated that 698,000 adults between ages 18 and 59 have undergone conversion therapy from a licensed professional or religious advisor, of whom 350,000 were adolescents when treated (Mallory, Brown, and Conron, 2019). The same study estimated that an additional 57,000 youth will receive conversion therapy from a health care or religious provider before 18 years of age. Among 25,000 LGBTQ youth respondents to a 2019 national survey, 67 percent reported that someone attempted to convince them to change their gender identity or sexual orientation (Trevor Project, 2019). A survey of 762 marriage and family therapists and members of the American Academy of Marriage and Family Therapists, which has a position statement against conversion therapy, found that 19.4 percent of respondents believed it was ethical to practice sexual orientation change therapy, and 3.5 percent of respondents had done so. This belief was associated with higher levels of negative beliefs about LGB clients than those of other therapists (McGeorge, Carlson, and Toomey, 2015).

A recent survey was among the first to evaluate the link between sexual orientation change therapy and the health of young people: among 245 white and Latinx LGBT individuals between the ages of 21 and 25, exposure to conversion efforts within or outside of their families during adolescence was associated with higher family religiosity, lower family socioeconomic status, and higher individual gender nonconformity (Ryan et al., 2018). In addition, exposure to conversion efforts during adolescence was significantly associated with increased suicidal ideation, suicide attempts, and depression, as well as diminished life satisfaction, self-esteem, social support, educational attainment, and lower income in young adulthood.

A systematic narrative review of gender identity conversion efforts found few data and a notable absence of research about their effects on both adolescents and adults (Wright, Candy, and King, 2018). However, a recent study using data from the 2015 USTS found that 14 percent of respondents had been exposed to gender identity conversion therapy during their lifetimes; exposure was associated with significantly higher rates of past-month severe psychological distress and lifetime suicide attempts compared with respondents who had not been exposed to such therapy (Turban et al., 2019). Exposure to gender identity conversion therapy before age 10 was associated with nearly twice the rate of lifetime suicide attempts.

The available evidence suggests that sexual orientation and gender identity conversion efforts are ineffective and dangerously detrimental to the health of SGD populations, especially for minors who are unable to give informed consent. As of early 2020, 20 states, the District of Columbia, Puerto Rico, and a number of municipalities had outlawed sexual orientation and gender identity conversion therapy for minors (Move-

Copyright National Academy of Sciences. All rights reserved.

ment Advancement Project, 2020b). As growing numbers of professional organizations and governments call for or legislate an end to conversion therapy, particularly for minors, it is important for clinicians working with SGD populations to understand the effects that these experiences can have on individuals, even many years later. Research on strategies for helping individuals who have experienced conversion therapy to heal and recover is essential. In order to end the practice of conversion therapy, it is not sufficient for professional organizations to recommend against conversion therapy; rather, professionals may require dedicated and specific training on the inefficacy and danger of conversion treatments, and insurance providers should consider limiting coverage for these non-evidence-based practices.

INTERSEX GENITAL SURGERY

The most expansive estimations of the prevalence of intersex traits, including any variation in any marker of sex (chromosomes, internal reproductive anatomy, external genital shape, and secondary sex traits), concludes that up to 1.7 percent of the population has an intersex trait (Fausto-Sterling, 2000). Estimates based on the number of people with clinically identifiable sexual or reproductive anatomic variations are closer to 0.5 percent (Nordenvall et al., 2014). Estimates for prevalence of infants born with obvious genital diversity, sometimes known as ambiguous genitalia, range from 0.03 percent to 0.1 percent (Blackless et al., 2000; Hughes et al., 2007; Thyen et al., 2006). Such variations can include differences in the length of the genital tubercule or glans (as in a shorter penis or longer clitoris), a narrow or absent vaginal opening, or presence of partially fused labia or a partially separated scrotum. This section focuses primarily on early genital surgery for children born with obvious genital diversity, which remains the most contentious area of clinical care—and increasingly, health law and policy—for persons with intersex traits (Dalke et al., 2020).

Genital Diversity and Early Genital Surgeries

Although some infants with genital diversity require urgent surgery to address urinary obstruction or exposed pelvic organs (Woo, Thomas, and Brock, 2010), many have no immediate medical concerns and do not require urgent medical treatment (Romao and Pippi Salle, 2017). Because the appearance of the external genitals is typically the primary datum for the sex assigned to infants at birth, genital diversity can lead to uncertainty about which sex a child with intersex traits should be assigned. Similarly, eventual gender identity cannot be readily predicted for many people with intersex traits based on the appearance of their genitals at birth (see more

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 31 of 54

detailed discussion below). Currently, clinicians and advocates alike typically recommend a binary but flexible sex assignment, informed by the balance of sex markers and the specific intersex condition the child has, which will contribute to the person's gender identity later in life.

Early genital surgeries primarily seek to align genitalia with assigned sex. Feminizing surgeries reduce the size of a clitoris, shape a vulva, or create or lengthen the vagina of a child assigned female. Masculinizing surgeries may reposition a urethra that is not located at the tip of the penis or create a phallus for a child assigned male. Early removal of gonadal tissue may also be recommended to reduce risk of malignancy or the pubertal production of hormones (and therefore secondary sex traits) that are discordant with the child's assigned sex. In the United States, many of these surgeries are performed in infancy.

In 2016, an international consensus group offered an update on genital surgery for children with obvious genital difference and identified a broad set of benefits for surgeries (Mouriquand et al., 2016). Physically, surgeries seek to promote "functional genital anatomy to allow future penetrative intercourse (as a male or a female)" (p. 141), as well as fertility, urinary function, menstruation, and the avoidance of malignancy and secondary sex traits that are discordant with assigned sex. Psychosocially, surgeries also purportedly "foster development of 'individual' and 'social identities'," reduce genital-related stigma, and support "the parents' desire to bring up a child in the best possible conditions" (p. 142). Since the early 1990s, however, intersex advocates have called attention to the physical and emotional harms of surgery, especially when performed before a child is old enough to participate in the decision. Indeed, in the absence of cloacal exstrophy (exposure of pelvic organs), urinary obstruction, or current malignancy, there is no medical urgency for such surgeries; they can be safely deferred until a child is older. At the core of the debate is a question as to what to do and when: what, if any, surgeries should be performed on very young children? This question ultimately calls for the weighing of relative physical and emotional risks, benefits, and alternatives to such surgeries.

Synthesis of the evidence base is complicated by significant heterogeneity of anatomic and medical considerations, surgical procedures, and dynamic psychosocial aspects over the life course. The available research on outcomes also has significant methodological limitations, with many outcomes reported from single surgeons or programs and inconsistency in measurement instruments, study designs, sample sizes, reported outcomes, and follow-up periods. Studies often have insufficient postsurgical follow-up to evaluate outcomes of childhood interventions on adult physical, sexual, and psychological well-being. Many studies also lack an effective comparator group, as there are no standard nonsurgical pathways for children with genital difference.

Copyright National Academy of Sciences. All rights reserved.

A review of these surgeries follows, along with an assessment of what is known about the outcomes of these interventions. The risks and benefits of each group of surgeries are discussed together, as these tend to be specific to the physical intervention itself. Some psychosocial outcomes, however, are discussed in aggregate, to reflect more limited data and overlaps in psychosocial experiences among intersex variations.

Gonadectomy

Removal of the gonads yields two potential benefits in the form of risk reduction: avoiding gonadal malignancy and undesired secondary sex traits. The risk of malignancy tends to be higher for intra-abdominal testes or atypically developed gonads, but it has to be balanced against the potential benefits of hormone-producing tissue (Pyle and Nathanson, 2017). Individuals with complete androgen insensitivity syndrome (AIS) have very low risk of testicular malignancy in childhood or adolescence, do not develop masculine secondary sex traits in puberty, and derive a high bone health benefit from endogenous hormone production; in these cases, it is generally recommended to defer gonadectomy until after puberty. Individuals with gonadal dysgenesis (in which gonads do not fully develop into ovarian or testicular tissue) have a higher risk of malignancy with little hormone production, and childhood gonadectomy is consistently recommended (Mouriquand et al., 2016). Some assigned girls with a 46,XY karyotype, testicular tissue, and full or partial androgen response, as in partial AIS or 5-alpha reductase deficiency, have moderate or low risk of malignancy and less predictable responses to hormone production at puberty. Gonadectomy is sometimes considered for these children to reduce distress and uncertainty around a "mixed" puberty (Mouriquand et al., 2016).

There are significant risks from gonadectomy. Some people with typically developed intra-abdominal testes, as in complete AIS and 5-alpha reductase deficiency, may be capable of producing mature sperm with assisted reproductive technology (Finlayson et al., 2017; Kang et al., 2014). For such people, gonadectomy can amount to sterilization. Removal of sex hormone-producing gonadal tissue can lead to low bone mass, genital changes, sexual dysfunction, and mood changes, for which individuals may require a lifetime of hormone replacement therapy. If the surgery is performed prior to puberty, people may be prescribed hormones congruent with their assigned sex rather than identified gender. Importantly, recent evidence suggests that puberty blockers may be a viable nonsurgical alternative to support gender identity exploration and allow time for informed consent, and in most cases, surgery need not be done in early childhood (Canalichio et al., 2020).

Copyright National Academy of Sciences. All rights reserved.

Feminizing Surgeries

Feminizing surgeries include clitoral and vaginoplasty surgeries. Clitoral surgery is most often recommended for 46,XX children with congenital adrenal hyperplasia (CAH) who are assigned female, with concerns primarily about genital "ambiguity" (Mouriquand et al., 2016). In recognition of inadequacies of earlier techniques, like clitoral amputation and recession, microsurgical approaches aim to preserve clitoral nerve and vascular supply, and in some cases they "bury" rather than remove parts of the clitoris should an individual wish to reverse the surgery in the future (Mouriquand et al., 2016). Vaginoplasty may also be recommended for assigned girls whose vaginas do not connect to the perineum, thereby limiting penetrative sex and impairing fertility and outflow of menstrual blood (Mouriquand et al., 2016). For assigned girls with shorter or absent vaginas and without uteruses (as in AIS, gonadal dysgenesis, or Mullerian agenesis), vaginoplasty carries the sole benefit of allowing penetrative intercourse.

There is some evidence that 46,XX women with CAH were satisfied with feminizing genital surgeries (Mouriquand et al., 2016). Reviewers have concluded from surveys of women who had undergone feminizing genitoplasty as children that women prefer earlier timing of surgery (de Jesus, 2018). Indeed, in one survey of adult women with CAH or AIS who had genital surgeries at an average of 3.8 years, 17 out of 24 reported that surgery had been done at the proper age (Fagerholm et al., 2011). However, these surveys are small and limited. Importantly, a large systematic review and meta-analysis found that only two studies surveyed 46,XX female CAH patients' satisfaction with surgery, of which the majority were satisfied (Almasri et al., 2018).

Long-term data regarding the reversibility of and sensory and sexual outcomes from these procedures are lacking, especially for more novel microsurgical approaches. Data regarding preserved sexual function after clitoral surgery is challenged by studies revealing significant rates of long-term sexual dysfunction and anorgasmia (de Jesus, 2018). Because studies of sexual quality of life may be confounded by psychosocial issues, attempts have been made to study postsurgical sensitivity objectively with a device capable of analyzing thermal and vibratory sensation. Many patients, however, have refused to participate in such studies, which may reflect discomfort or even trauma associated with previous experiences of medical care (de Jesus, 2018). Limited data suggest unfavorable patient satisfaction with cosmesis after vaginoplasty, as well as a high incidence of postsurgical vaginal stenosis. If this occurs, patients may experience pain with intercourse and require self-dilation or repeat surgery. While there has been some evidence supporting benefit of surgery for women with CAH, multiple studies of adult women with CAH find less frequent sexual activ-

Copyright National Academy of Sciences. All rights reserved.

ity and lower frequency of orgasm, including among the small reported number of people with CAH who did not undergo surgery (de Jesus, 2018). Notably, there are no objective scales validated to assess sexual function in women with intersex traits. There are few data evaluating long-term urological complications after feminizing genitoplasty.

Masculinizing Surgeries

Masculinizing surgeries aim to facilitate standing urination, penetrative intercourse, and a "cosmetically pleasing appearance" (Winship, Rushton, and Pohl, 2017). These procedures include hypospadias repair and phalloplasty. Hypospadias is characterized along a spectrum from distal (urethra opening near, but not at, the tip of the penis) to proximal (urethra opening at the base of the penis). Most individuals with distal hypospadias do not have differences of sex development (DSD), so this variation is not reviewed here.

Proximal hypospadias is often associated with diversity of penile and scrotal appearance, and at least one of three children born with proximal hypospadias and an undescended gonad will have other features of a DSD, such as non-XY karyotype (Romao and Pippi Salle, 2017). Phalloplasty may be recommended for 46,XY assigned boys born with a smaller than usual, or absent, penis. Although many of these children were historically assigned female, longitudinal data have revealed higher rates of gender dysphoria for those assigned girls than those assigned boys (Meyer-Bahlburg, 2005), and there is some evidence that urologists increasingly favor male sex assignment (Diamond et al., 2011).

The primary cited benefit of proximal hypospadias repair is avoidance of distress due to difference and stigma (Bush and Snodgrass, 2017), which is accomplished through achieving decreased spraying with urination and capacity for penetrative intercourse. Although long-term outcome studies for proximal hypospadias do not consistently track lower urinary tract symptoms, some studies have reported rates of lower urinary tract symptoms as high as 100 percent after proximal hypospadias surgeries (Gong and Cheng, 2017). Multiple studies have found persistent penile curvature and dissatisfaction with cosmesis after masculinizing surgeries (Tourchi and Hoebeke, 2013), and there is no commonly used objective measure of penile appearance after surgery (Gong and Cheng, 2017). Very few outcome studies for masculinizing surgeries have evaluated erectile dysfunction, and "most pediatric urologists do not follow patients into adulthood and have little experience in sexual medicine" (Winship, Rushton, and Pohl, 2017, p. 287). One study found that more than two-thirds of adult men with proximal hypospadias reported some sexual dysfunction and decreased sexual quality of life after surgery (Chertin et

Copyright National Academy of Sciences. All rights reserved.

al., 2013). Reoperations and complications may contribute to urinary and sexual dysfunction, with complication rates ranging from 4 to 68 percent, and reoperation rates ranging from 23 to 52 percent (Gong and Cheng, 2017). Higher rates of reoperations and complications are associated with longer durations of follow-up, suggesting that long follow-up periods may be important elements of studies examining adverse postoperative outcomes (Gong and Cheng, 2017).

Psychosocial Outcomes after Genital Surgery

Patient Considerations

The absence of holistic and validated tools for assessment of sexual well-being and gender identity, patient satisfaction, and patient-centered surgical outcome measures present significant challenges in identifying robust conclusions regarding the psychosocial risks and benefits of early surgery. There are, however, some data regarding the outcomes of psychosocial distress and gender identity in the context of surgery.

Avoidance of distress due to social stigma and bodily difference has been offered as an indication for feminizing surgeries (de Jesus, 2018), masculinizing surgeries (Bush and Snodgrass, 2017), and gonadectomy for patients who may develop discordant secondary sex traits at puberty (Mouriquand et al., 2016). Of note, as discussed in Chapter 11, evidence indicates greater rates of psychological distress for individuals with intersex traits than the general population, but there is very little research exploring why. Rather, much of the research and clinical discourse reveals an implicit bias that genital or sexual difference is *de facto* abnormal and distressing and that "normalizing" surgery is a solution to this problem (Dalke, Baratz, and Greenberg, 2020). One series of qualitative studies suggested that 46,XX assigned and identified females with CAH experience stigma in medical, social, and sexual settings related to their genitalia and secondary sex traits; however, these studies included both women who did and did not have surgery, suggesting that surgery did not fully protect women from experiencing stigma (Meyer-Bahlburg et al., 2017a, 2017b, 2018). Of note, there are very few robust data exploring the benefits of surgery for patients with intersex traits, especially those who do not have CAH. Because standard practice has been to perform surgery early, however, there are few studies evaluating rates of psychosocial distress or satisfaction among individuals who did not undergo surgery, nor is there clear evidence that genital surgery itself reduces psychosocial stress (Roen, 2019). In a series of interviews, parents of children who did not undergo genital surgery reported that their children had attended school, had friends, and had not experienced bullying or harassment (Human Rights Watch, 2017).

Copyright National Academy of Sciences. All rights reserved.

There is some evidence that early genital surgery may unintentionally compound psychosocial distress. Multiple studies report that genital examinations in childhood can be experienced as intrusive, aversive, stigmatizing, and objectifying, particularly when children are not engaged in dialog with their providers (Roen, 2019). Qualitative research suggests that shame and a sense of "differentness" are correlated with both feminizing and masculinizing interventions: "going through surgery as a child might highlight bodily difference as stigmatising rather than facilitating the management of shame" (Roen, 2019, p. 517). This finding is consistent with information from intersex people themselves, who report experiences of anger, guilt, and trauma related to early surgery that was carried out without their consent, especially when they did not receive adequate information about their bodies or the procedures that were performed on them (Human Rights Watch, 2017).

Of particular interest in genital surgery is gender outcomes, particularly given the risk of developing a gender identity discordant with a sex that was assigned at birth and then surgically reinforced. Some intersex traits, such as complete AIS, complete gonadal dysgenesis, and proximal hypospadias without DSD, are associated with very low likelihood of gender dysphoria (Meyer-Bahlburg et al., 2016). Other intersex traits are associated with much higher rates, such as 46,XY individuals with cloacal exstrophy who are assigned female (Meyer-Bahlburg, 2005). A systematic review and meta-analysis found that 8 to 13 percent of 46,XX assigned female individuals with CAH did not identify as female (Almasri et al., 2018), which is much higher than the estimated 0.6 percent population prevalence of transgender identity among the general population (Flores et al., 2016). One very small, non-U.S. study found 46,XX assigned males with CAH can also experience gender dysphoria (de Jesus, Costa, and Dekermacher, 2019). Few data have been published on gender identity among individuals with partial AIS, 5-alpha reductase deficiency, or 17-beta hydroxysteroid dehydrogenase deficiency. Most studies evaluating gender identity among individuals with intersex traits have taken a binary view of gender, which could underreport rates of non-cisgender identities. Sex assignment at birth has become increasingly nuanced and focused on patient-specific recommendations (Kolesinska et al., 2014). Early and irreversible interventions may limit opportunities for gender affirmation later in life, which supports deferral of surgeries until the person's gender identity and ability to participate in the decision are established.

Parental Considerations

As is discussed in Chapter 11, much of the psychosocial research on intersex issues focuses on the mental health of parents. This work suggests that parents of children with genital difference experience stress similar to parents of children with chronic illness and, in some cases, also have de-

Copyright National Academy of Sciences. All rights reserved.

pression, anxiety, and decreased mental health quality of life (Wisniewski, 2017). Parents report fearing that their children will be teased, excluded, or stigmatized because of their genital differences (Wisniewski, 2017), and reduction of parental distress is often cited as a benefit of early genital surgery. However, there have been no studies examining experiences of bullying among children with intersex traits, and thus no evidence is available to indicate that surgery reduces the risk of bullying. Surgeons may be more likely to find a child's preoperative genital appearance unsatisfactory than parents (Nokoff et al., 2017), and this possibility raises the question of whether parents' perceptions of their child's genitals are influenced by the medical team's implicit bias. Overall, there is no evidence that genitoplasty directly targets parental distress, nor is there evidence that parental distress is intolerable or cannot be addressed in other ways (Roen, 2019).

An important consideration around parents is the process by which they make decisions about their child's health care. One ethical concern involved in this process is informed consent. Ethicists generally assume that parents can give informed consent for their child's health care as actors in the child's best interests (AMA, 2018). However, some scholars have suggested that, because the uniqueness of intersex surgery might affect a child's fundamental human rights, a court order might be required for the parent to give informed consent (Dalke et al., 2020). Evidence has also challenged the integrity of informed consent at a micro-ethics level. One study of self-identified DSD clinics found gaps in informed consent processes: more than two-thirds of the clinics did not document discussion of risks of surgery, including additional procedures, sexual dysfunction, psychosocial distress, gender uncertainty, and that interventions could be deferred until a later time (Rolston et al., 2017). Even with sufficient information, the informed consent process may not be adequate when carried out with parents of a minor child, given the distress that parents experience (Tamar-Mattis et al., 2013). Many families lack access to psychological services to assist in information processing despite multiple consensus recommendations for such services (Rolston et al., 2017). There are emerging data suggesting that the way information is framed can bias families' decision making. For instance, adopting a position of equipoise and patient-centeredness can unintentionally move families toward the surgeon's recommended course of action (Timmermans et al., 2018), and several studies have suggested that families feel as though their options are "surgery or nothing" (Roen, 2019).

Alternatives to Genital Surgery

There is very little research regarding alternatives to surgical intervention. Some doctors have suggested that gonadotropin-releasing hormone analogs can be used in place of gonadectomy for pubertal suppression in

Copyright National Academy of Sciences. All rights reserved.

children whose gender identity or pubertal development is uncertain and that hormonal management of CAH can reduce the size of a clitoris as an alternative to surgery (Mouriquand et al., 2016). Vaginal dilation may be an option in place of vaginoplasty for some. The contours of psychosocial support, including limiting genital exams and engaging patients and families over time to involve them in decision making, are beginning to emerge but as yet have minimal supporting data (Roen, 2019). This approach offers the possibility of helping families and young people learn to cope with and reduce the distress that surgery seeks to, but may not, avert.

In an appraisal of the literature and expert opinion, the Endocrine Society has recommended that parents be counseled on the risks and benefits of surgery and be permitted to make what they feel is the best decision for their child (Speiser et al., 2018). Timmermans and colleagues (2018) found that this approach biases families toward surgery. A growing number of consensus groups and professional medical organizations, including the American Academy of Family Physicians[17] and Physicians for Human Rights,[18] have interpreted the risk-benefit ratio as unfavorable for early genital surgery in instances where the individual is too young to participate in the consent process (Elders, Sacher, and Armona, 2017; Krege et al., 2019; Toler and GLMA Policy and Government Affairs Committee, 2016). These organizations advise the provision of psychosocial support for both parents and children and deferral of early genital surgeries until the child can participate in the decision.

Several international human rights groups have identified early surgery in the absence of informed consent as a violation of the child's human rights to autonomy and an open future, and even as a kind of medical torture (Amnesty International, 2017; Human Rights Watch, 2017; United Nations General Assembly Human Rights Council, 2013; WHO, 2014). In July 2020, Lurie Children's Hospital in Chicago, Illinois, became the first hospital in the nation to publicly acknowledge the harms of early genital surgeries and to adopt a policy that "irreversible genital procedures should not be performed until patients can participate meaningfully in making the decision for themselves, unless medically necessary" (Shanley et al., 2020). Of note, while the statement committed to pausing all genital surgeries that were not medically necessary, it did indicate that there may be a difference in approach for individuals with intersex traits who have CAH relative to people who do not.

Overall, there is mixed evidence that surgery achieves its physical goals and scant evidence that it confers psychosocial benefit. The existing research does provide strong evidence of the risk of irreversible harm from

[17] See https://www.aafp.org/about/policies/all/genital-surgeries.html.
[18] See https://phr.org/news/unnecessary-surgery-on-intersex-children-must-stop/.

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 39 of 54

early genital surgery, including immediate postoperative complications and later revisions, as well as the potentially catastrophic risk of incorrect, surgically reinforced gender assignment. The absence of data on alternative affirming pathways means that there is very little evidence of benefit from deferring surgery. It also means, however, that there is very little evidence of harm from deferring surgery. Factoring in the human rights of children and evidence that individuals with diverse sexualities, bodies, and genders can and do thrive with affirmation and support from parents, peers, and communities, there is insufficient evidence of benefit to justify early genital surgery. Therefore, the deferral of surgery until a child can participate in the decision, except in scenarios with urgent medical need, such as urinary obstruction or immediate cancer risk, may optimize the benefits of informed consent, autonomy, and patients' physical, social, and emotional well-being.

SUMMARY AND CONCLUSIONS

Access to comprehensive, affirming, and high-quality health care services is a human right for all people. Ensuring access to care for SGD populations includes building supportive and protective structures at all levels, from the broad societal level to the level of individual provider practices. At the societal level, laws that guarantee access to health care services, health insurance coverage, and public health programs for all, regardless of sexual orientation, gender identity, and intersex status, are critical to the health and well-being of SGD people. Laws and policies that provide affordable, comprehensive health insurance coverage, such as Medicaid expansion by all states or some form of universal coverage, could combat health risks such as uninsurance and poverty among SGD populations.

CONCLUSION 12-1: Sexual and gender diverse populations need access to a full range of preventive, chronic, and acute health care services delivered in settings that are welcoming, affirming, and both clinically appropriate and culturally responsive.

Health services and procedures that are particularly important for the health and well-being of SGD populations include but are not limited to pre- and post-exposure prophylaxis for HIV; HIV treatment and care; abortion, fertility, and other reproductive health services; affirming mental and behavioral health care services; and gender-affirming care for transgender people. Transgender people, as well as lesbians and bisexual women, also need access to timely and anatomically appropriate preventive screenings.

Important aspects of providing culturally responsive and clinically appropriate care for SGD populations include but are not limited to creating affirming health care environments; using forms that are inclusive of diverse

Copyright National Academy of Sciences. All rights reserved.

identities and family structures; seeking to address social determinants of health and social needs; and requiring routine, high-quality cultural and clinical training on working with SGD populations for the health care and public health workforce. Efforts to promote quality of care and care coordination may have differential effects on populations experiencing disparities, making it important to assess the effects of these efforts on groups such as LGBT people, people with intersex traits, and intersectional groups such as LGBT people of color and people living with HIV. Entities that provide resources and guidance on affirming health care policies and environments for SGD populations include the Academy of Physician Assistants, GLMA: Health Professionals Advancing LGBTQ Equality, Association of American Medical Colleges, American Psychological Association, American Academy of Pediatrics, American Medical Association, National LGBT Health Education Center, and The Joint Commission.

CONCLUSION 12-2: Gender-affirming care, including puberty delay medications, mental health services, hormone therapy, and surgeries, is associated with improved mental and physical health for transgender people.

Gender-affirming care for transgender people, including non-binary and other gender diverse people, is an essential and medically necessary intervention to improve health and well-being. Provision of this care needs to be individualized and conducted in partnership between patients and their providers. Insurance coverage of gender-affirming services and procedures by public and private payers, according to the most updated expert standards in the field and without inappropriate age or other restrictions, is necessary to facilitate access to these services and to avoid discrimination on the basis of sex and gender identity.

CONCLUSION 12-3: Conversion therapy to change sexual orientation or gender identity and elective genital surgeries on children with intersex traits who are too young to participate in consent are dangerous to the health and well-being of sexual and gender diverse people.

Conversion therapy to change sexual orientation or gender identity can cause significant and life-long trauma. Elective genital surgeries on children with intersex traits who cannot participate in consent are similarly detrimental to health and well-being. The American Medical Association, American Academy of Family Physicians, American Academy of Pediatrics, American Psychiatric Association, American Psychological Association, GLMA: Health Professionals Advancing LGBTQ Equality, Physicians for Human Rights, the U.S. Department of Health and Human Services, and

Copyright National Academy of Sciences. All rights reserved.

the World Health Organization recommend that these procedures not be promoted or performed.

REFERENCES

Agarwal, C.A., Scheefer, M.F., Wright, L.N., Walzer, N.K., and Rivera, A. (2018). Quality of life improvement after chest wall masculinization in female-to-male transgender patients: A prospective study using the BREAST-Q and Body Uneasiness Test. *Journal of Plastic, Reconstructive and Aesthetic Surgery*, *71*(5), 651–657. doi: 10.1016/j.bjps.2018.01.003.

Agénor, M., Krieger, N., Austin, S.B., Haneuse, S., and Gottlieb, B.R. (2014). At the intersection of sexual orientation, race/ethnicity, and cervical cancer screening: Assessing Pap test use disparities by sex of sexual partners among Black, Latina, and white U.S. women. *Social Science and Medicine*, *116*, 110–118. doi: 10.1016/j.socscimed.2014.06.039.

Ainsworth, T.A., and Spiegel, J.H. (2010). Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Quality of Life Research*, *19*(7), 1019–1024. doi: 10.1007/s11136-010-9668-7.

Almasri, J., Zaiem, F., Rodriguez-Gutierrez, R., Tamhane, S.U., Iqbal, A.M., Prokop, L.J., Speiser, P., Baskin, L., Bancos, I., and Murad, M.H. (2018). Genital reconstructive surgery in females with congenital adrenal hyperplasia: A systematic review and meta-analysis. *Journal of Clinical Endorinology and Metabolism*, *103*(11), 4089–4096. doi: 10.1210/jc.2018-01863.

American Academy of Child and Adolescent Psychiatry Committee on Sexual Orientation and Gender Identity Issues. (2018). *Conversion Therapy*. Available: https://www.aacap.org/AACAP/Policy_Statements/2018/Conversion_Therapy.aspx.

American Academy of Family Physicians. (2012). *Resolution No. 1004: Transgender Care*. Available: https://www.aafp.org/dam/AAFP/documents/about_us/special_constituencies/2012RCAR_Advocacy.pdf.

———. (2018). *Genital Surgeries in Intersex Children*. Available: https://www.aafp.org/about/policies/all/genital-surgeries.html.

American Academy of Pediatrics. (2018). *Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents*. Available: https://pediatrics.aappublications.org/content/pediatrics/early/2018/09/13/peds.2018-2162.full.pdf.

American College of Nurse Midwives. (2012). *Transgender/Transsexual/Gender Variant Health Care*. Available: http://www.midwife.org/acnm/files/ACNMLibraryData/UPLOADFILENAME/000000000278/Transgender%20Gender%20Variant%20Position%20Statement%20December%202012.pdf.

American College of Obstetricians and Gynecologists. (2011). *Committee Opinion No. 512: Health Care for Transgender Individuals*. Available: https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2011/12/health-care-for-transgender-individuals.

American Medical Association. (2008). *Resolution H-185.950: Removing Financial Barriers to Care for Transgender Patients*. Available: https://policysearch.ama-assn.org/policy-finder/detail/financial%20barriers%20transgender?uri=%2FAMADoc%2FHOD.xml-0-1128.xml.

———. (2018). *Amendment to E-2.2.1: Pediatric Decision Making*. Available: https://www.ama-assn.org/system/files/2018-11/i18-refcomm-conby.pdf.

———. (2019). *Policy Statement H-295.878 on Eliminating Health Disparities: Promoting Awareness and Education of Lesbian, Gay, Bisexual, and Transgender (LGBT) Health Issues in Medical Education*. Available: https://policysearch.ama-assn.org/policyfinder/detail/gender%20identity?uri=%2FAMADoc%2FHOD.xml-0-2177.xml.

Copyright National Academy of Sciences. All rights reserved.

American Medical Association and GLMA: Health Professionals Advancing LGBTQ Equality. (2018). *Issue Brief: LGBTQ Change Efforts ("Conversion Therapy")*. Available: https://www.ama-assn.org/system/files/2019-03/transgender-conversion-issue-brief.pdf.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition*. Washington, DC: American Psychiatric Association.

———. (2018). *Position Statement on Access to Care for Transgender and Gender Diverse Individuals*. Available: www.psychiatry.org/File%20Library/About-APA/Organization-Documents-Policies/Policies/Position-2018-Discrimination-Against-Transgender-and-Gender-Diverse-Individuals.pdf.

American Psychological Association. (2008). *Policy on Transgender, Gender Identity & Gender Expression Non-Discrimination*. Available: https://www.apa.org/about/policy/resolution-gender-identity.pdf.

———. (2009). *Report of the American Psychological Association Task Force on Appropriate Therapeutic Responses to Sexual Orientation*. Available: http://www.apa.org/pi/lgbc/publications/therapeutic-resp.html.

———. (2015). *Resolution on Gender and Sexual Orientation Diversity in Children and Adolescents in Schools*. Available: https://www.apa.org/about/policy/orientation-diversity.

American Society for Reproductive Medicine. (2013). *Access to Fertility Treatment by Gays, Lesbians, and Unmarried Persons: A Committee Opinion*. Available: https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/ethics-committee-opinions/access_to_fertility_treatment_by_gays_lesbians_and_unmarried_persons-pdfmembers.pdf.

Amnesty International. (2017). *First Do No Harm: Ensuring the Right of Children Born Intersex*. Available: https://www.amnesty.org/en/latest/campaigns/2017/05/intersex-rights.

Andréasson, M., Georgas, K., Elander, A., and Selvaggi, G. (2018). Patient-reported outcome measures used in gender confirmation surgery: A systematic review. *Plastic and Reconstructive Surgery*, *141*(4), 1026–1039. doi: 10.1097/PRS.0000000000004254.

Arístegui, I., Radusky, P.D., Zalazar, V., Romero, M., Schwartz, J., and Sued, O. (2017). Impact of the gender identity law in Argentinean transgender women. *International Journal of Transgenderism*, *18*, 446–456.

Bailey, L., Ellis, S.J., and McNeil, J. (2014). Suicide risk in the UK trans population and the role of gender transition in decreasing suicidal ideation and suicide attempt. *Mental Health Review Journal*, *19*(4), 209–220.

Baker, K.E., (2016, June 6). LGBT protections in the Affordable Care Act Section 1557. *Health Affairs Blog*. Available: http://healthaffairs.org/blog/2016/06/06/lgbt-protections-in-affordable-care-act-section-1557.

Baker, K.E., (2017). The future of transgender coverage. *New England Journal of Medicine, 376*(19), 1801–1804. doi: 10.1056/NEJMp1702427.

Baker, K.E., and Durso, L.E. (2017, March 22). Why repealing the Affordable Care Act is bad medicine for LGBT community. *Center for American Progress*. Available: https://www.americanprogress.org/issues/lgbtq-rights/news/2017/03/22/428970/repealing-affordable-care-act-bad-medicine-lgbt-communities/.

Baker, K.E., Durso, L.E., and Cray, A. (2014). *Moving the Needle: The Impact of the Affordable Care Act on LGBT Communities*. Washington, DC: Center for American Progress. Available: https://cdn.americanprogress.org/wp-content/uploads/2014/11/LGBTandACA-report.pdf.

Baker, K.E., Minter, S.P., Wertz, K., and Wood, M. (2012). A new approach to health care equality for transgender people: California's insurance gender non-discrimination act. *LGBTQ Policy Journal at the Harvard Kennedy School, 2*, 35-43. Available: https://lgbtq.hkspublications.org/wp-content/uploads/sites/20/2015/10/LGBTQ_3_29_12.pdf.

Copyright National Academy of Sciences. All rights reserved.

Balzano, F.L., and Hudak, S.J. (2018). Military genitourinary injuries: Past, present, future. *Translational Andrology and Urology, 7*(4), 646–652. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6127528/.

Barone, M., Cogliandro, A., Stefano, N.D., Tambone, V., and Persichetti, P. (2017). A systematic review of patient-reported outcome measures following transsexual surgery. *Aesthetic Plastic Surgery*, 1–14. doi: 10.1007/s00266-017-0812-4.

Becerra-Culqui, T.A., Liu, Y., Nash, R., Cromwell, L., Flanders, W.D., Getahun, D., Giammattei, E., Lash, T., Millman, A., Quinn, V., Robinson B., Roblin, D., Sandberg, D., Silverberg, M., Tangpricha, V., and Goodman, M. (2018). Mental health of transgender and gender nonconforming youth compared with their peers. *Pediatrics, 141*(5). doi: 10.1542/peds.2017-3845.

Berwick, D.M., Nolan, T.W., and Whittington, J. (2008). The triple aim: Care, health and cost. *Health Affairs, 27*(3), 759–769.

Blackless, M., Charuvastra, A., Derryck, A., Fausto-Sterling, A., Lauzanne, K., and Lee, E. (2000). How sexually dimorphic are we? Review and synthesis. *American Journal of Human Biology*, *12*(2), 151–166.

Blosnich, J.R., Hanmer, J., Yu, L., Matthews, D.D., and Kavalieratos, D. (2016). Health care use, health behaviors, and medical conditions among individuals in same-sex and opposite-sex partnerships: A cross-sectional observational analysis of the Medical Expenditures Panel Survey (MEPS), 2003–2011. *Medical Care*, *54*(6), 547–554. doi: 10.1097/MLR.0000000000000529.

Bockting, W., Coleman, E., Deutsch, M. B., Guillamon, A., Meyer, I., Meyer, W., Reisner, S., Sevelius, J., and Ettner, R. (2016). Adult development and quality of life of transgender and gender nonconforming people. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *23*(2), 188–197. doi: 10.1097/MED.0000000000000232.

Bränström, R., and Pachankis, J.E. (2019). Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: A total population study. *American Journal of Psychiatry, 177*(8), 727–734. doi: 10.1176/appi.ajp.2019.19010080.

———. (2020). Toward rigorous methodologies for strengthening causal inference in the association between gender-affirming care and transgender individuals' mental health: Response to letters. *American Journal of Psychiatry, 177*(8), 769–772. doi: 10.1176/appi.ajp.2020.20050599.

Bush, N.C., and Snodgrass, W. (2017). RE: Winship BB, Rushton HG, Pohl HG: In pursuit of the perfect penis: Hypospadias repair outcomes. *Journal of Pediatric Urology, 13*(6), 652–653. doi: 10.1016/j.jpurol.2017.08.011.

Butler, M., McCreedy, E., Schwer, N., Burgess, D., Call, K., Przedworski, J., Rosser, S., Larson, S., Allen, M., Fu, S., and Kane, R.L. (2016). *Improving Cultural Competence to Reduce Health Disparities*. Comparative Effectiveness Review No. 170. Rockville, MD: Agency for Healthcare Research and Quality. Available: https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/cultural-competence_research.pdf.

Cahill, S.R., Baker, K.E., Deutsch, M.B., Keatley, J., and Makadon, H.J. (2016). Inclusion of sexual orientation and gender identity in stage 3 meaningful use guidelines: A huge step forward for LGBT health. *LGBT Health*, *3*(2), 100–102. doi: 10.1089/lgbt.2015.0136.

Canalichio, K.L., Shnorhavorian, M., Oelschlager, A.A., Ramsdell, L., Fisher, C., Adam, M.P., and Fechner, P.Y. (2020). A non-surgical approach to 46,XY differences in sex development through hormonal suppression at puberty: A single-center case series study. *Endocrine, 70*, 170–177. doi: 10.1007/s12020-020-02409-y.

Canner, J.K., Harfouch, O., Kodadek, L.M., Pelaez, D., Coon, D., Offodile, A.C., Haider, A.H., and Lau, B.D. (2018). Temporal trends in gender-affirming surgery among transgender patients in the United States. *JAMA Surgery, 153*(7), 609–616. doi: 10.1001/jamasurg.2017.6231.

Copyright National Academy of Sciences. All rights reserved.

Castellano, E., Crespi, C., Dell'Aquila, C., Rosato, R., Catalano, C., Mineccia, V., Motta, G., Botto, E., and Manieri, C. (2015). Quality of life and hormones after sex reassignment surgery. *Journal of Endocrinological Investigation*, *38*(12), 1373–1381. doi: 10.1007/s40618-015-0398-0.

Center for Consumer Information and Insurance Oversight. (n.d.). *At Risk: Pre-Existing Conditions Could Affect 1 in 2 Americans: 129 Million People Could Be Denied Affordable Coverage without Health Reform*. Centers for Medicare & Medicaid Services. Available: https://www.cms.gov/CCIIO/Resources/Forms-Reports-and-Other-Resources/preexisting.

———. (2014). *Frequently Asked Question on Coverage of Same-Sex Spouses*. Centers for Medicare & Medicaid Services. Available: https://www.cms.gov/CCIIO/Resources/Regulations-and-Guidance/Downloads/frequently-asked-questions-on-coverage-of-same-sex-spouses.pdf.

Centers for Medicare & Medicaid Services. (2015). *Frequently Asked Questions about Affordable Care Act Implementation (Part XXVI)*. Available: https://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/Downloads/aca_implementation_faqs26.pdf.

———. (2016). *Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)*. Available: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=282.

Chertin, B., Natsheh, A., Ben-Zion, I., Prat, D., Kocherov, S., Farkas, A., and Shenfeld, O.Z. (2013). Objective and subjective sexual outcomes in adult patients after hypospadias repair performed in childhood. *Journal of Urology*, *190*(4S), 1556–1560.

Chew, D., Anderson, J., Williams, K., May, T., and Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4), e20173742.

Choi, S.K., Badgett, M.V.L., and Wilson, B.D.M. (2019). *State Profiles of LGBT Poverty in the United States*. Los Angeles, CA: Williams Institute, UCLA School of Law. Available: https://williamsinstitute.law.ucla.edu/wp-content/uploads/State-LGBT-Poverty-Dec-2019.pdf.

Cohen-Kettenis, P.T., and Van Goozen, S. (1998). Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European Child and Adolescent Psychiatry*, *7*, 246–248.

Coleman, E., Bockting, W., Botzer, M., Cohen-Kettenis, P., DeCuypere, G., Feldman, J., Fraser, L., Green, J., Knudson, G., Meyer, W.J., Monstrey, S., Adler, R.K., Brown, G.R., Devor, A.H., Ehrbar, R., Ettner, R., Eyler, E., Garofalo, R., Karasic, D.H., Lev, A.I., Mayer, G., Meyer-Bahlburg, H.F.L., Hall, B.P., Pfäfflin, F., Rachlin, K., Robinson, B., Schechter, L.S., Tangpricha, V., van Trotsenburg, M., Vitale, A., Winter, S., Whittle, S., Wylie, K.R., and Zucker, K. (2012). Standards of care for the health of transsexual, transgender, and gender-nonconforming people. *International Journal of Transgenderism*, *13*(4), 165–232. doi: 10.1080/15532739.2011.70873.

Committee on Health Care Utilization and Adults with Disabilities. (2018). Factors that affect health-care utilization. In *Health-Care Utilization as a Proxy in Disability Determination*. Washington, DC: National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division, Board on Health Care Services. Available: https://www.ncbi.nlm.nih.gov/books/NBK500097/.

Costa, R., and Colizzi, M. (2016). The effect of cross-sex hormonal treatment on gender dysphoria individuals' mental health: A systematic review. *Neuropsychiatric Disease and Treatment*, *12*, 1953–1966. doi: 10.2147/NDT.S95310.

Coursolle, A. (2019). *Protections for LGBTQ People with Behavioral Health Needs*. Available: https://healthlaw.org/resource/protections-for-lgbtq-people-with-behavioral-health-needs.

Dalke, K.B., Baratz, A.B., and Greenberg, J.A. (2020). Protecting children with intersex traits: Legal, ethical, and human rights considerations. In M. Legato (Ed.), *The Plasticity of Sex*. doi: 10.1016/B978-0-12-815968-2.00010-4.

Copyright National Academy of Sciences. All rights reserved.

de Jesus, L.E. (2018). Feminizing genitoplasty: Where are we now? *Journal of Pediatric Urology*, *14*(5), 407–415. doi: 10.1016/j.jpurol.2018.03.020.

de Jesus, L.E., Costa, E.C., and Dekermacher, S. (2019). Gender dysphoria and XX congenital adrenal hyperplasia: How frequent is it? Is male-sex rearing a good idea? *Journal of Pediatric Surgery.* doi: 10.1016/j.jpedsurg.2019.01.062.

de Vries, A.L., McGuire, J.K., Steensma, T.D., Wagenaar, E.C., Doreleijers, T.A., and Cohen-Kettenis, P.T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics, 134*(4), 696–704. doi: 10.1542/peds.2013-2958.

de Vries, A.L., Steensma, T.D., Cohen-Kettenis, P.T., VanderLaan, D.P., and Zucker, K.J. (2016). Poor peer relations predict parent- and self-reported behavioral and emotional problems of adolescents with gender dysphoria: A cross-national, cross-clinic comparative analysis. *European Child and Adolescent Psychiatry, 25*(6), 579–588. doi: 10.1007/s00787-015-0764-7

Dhejne, C., Lichtenstein, P., Boman, M., Johansson, A.L., Langstrom, N., and Landén, M. (2011). Long-term follow-up of transsexual persons undergoing sex reassignment surgery: Cohort study in Sweden. *PLoS One, 6*(2), e16885. doi: 10.1371/journal.pone.0016885.

Dhejne, C., Van Vlerken, R., Heylens, G., and Arcelus, J. (2016). Mental health and gender dysphoria: A review of the literature. *International Review of Psychiatry, 28*(1), 44–57. doi: 10.3109/09540261.2015.1115753.

Diamond, D.A., Burns, J.P., Huang, L., Rosoklija, I., and Retik, A.B. (2011). Gender assignment for newborns with 46XY cloacal exstrophy: A 6-year followup survey of pediatric urologists. *Journal of Urology*, *186*, 1642–1648. doi: 10.1016/j.juro.2011.03.101.

Durwood, L., McLaughlin, K.A., and Olson, K.R. (2017). Mental health and self-worth in socially transitioned transgender youth. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(2), 116–123.e2. doi: 10.1016/j.jaac.2016.10.016.

Dy, G.W., Nolan, I.T., Hotaling, J., and Myers, J.B. (2019). Patient reported outcome measures and quality of life assessment in genital gender confirming surgery. *Translational Andrology and Urology*, *8*(3), 228–240. doi: 10.21037/tau.2019.05.04.

Ehrenfeld, J.M., Zimmerman, D.R., and Gonzales, G. (2018). Healthcare utilization among transgender individuals in California. *Journal of Medical Systems*, *42*(5), 77. doi: 10.1007/s10916-018-0923-8.

Elders, J., Sacher, D., and Armona, R. (2017). *Re-Thinking Genital Surgeries on Intersex Infants*. Palm Center. Available: https://www.palmcenter.org/wp-content/uploads/2017/06/Re-Thinking-Genital-Surgeries-1.pdf.

Endocrine Society. (2017). *Transgender Health*. Available: https://www.endocrine.org/-/media/endocrine/files/advocacy/position-statement/position_statement_transgender_health-updated-august-2020.pdf.

Fagerholm, R., Santtila, P., Miettinen, P. J., Mattila, A., Rintala, R., and Taskinen, S. (2011). Sexual function and attitudes toward surgery after feminizing genitoplasty. *Journal of Urology, 185*(5), 1900–1904. doi: 10.1016/j.juro.2010.12.099.

Fausto-Sterling, A. (2000). *Sexing the Body: Gender Politics and the Construction of Sexuality*. New York: Basic Books.

Finlayson, C., Fritsch, M.K., Johnson, E.K., Rosoklija, I., Gosiengfiao, Y., Yerkes, E., Madonna, M.B., Woodruff, T., and Cheng, E. (2017). Presence of germ cells in disorders of sex development: implications for fertility potential and preservation. *Journal of Urology, 197*(3 Pt 2), 937–943.

Flores, A.R., Herman, J.L., Gates, G.J., and Brown, T.N.T. (2016). How many adults identify as transgender in the United States? Los Angeles, CA: Williams Institute, UCLA School of Law. Available: https://williamsinstitute.law.ucla.edu/wp-content/uploads/How-Many-Adults-Identify-as-Transgender-in-the-United-States.pdf.

Copyright National Academy of Sciences. All rights reserved.

Fredriksen-Goldsen, K.I., Kim, H.-J., and Barkan, S.E. (2012). Disability among lesbian, gay, and bisexual adults: Disparities in prevalence and risk. *American Journal of Public Health*, *102*(1), e16–e21. doi: 10.2105/AJPH.2011.300379.

Freeman, J. (2018). LGBTQ scientists are still left out. *Nature*, *559*(7712), 27–28. doi: 10.1038/d41586-018-05587-y

Gijs, L., and Brewaeys, A. (2007). Surgical treatment of gender dysphoria in adults and adolescents: Recent developments, effectiveness, and challenges. *Annual Review of Sex Research*, *18*(1), 178–224.

Gong, E.M., and Cheng, E.Y. (2017). Current challenges with proximal hypospadias: We have a long way to go. *Journal of Pediatric Urology*, *13*(5), 457–467.

Gonzales, G. (2015). Association of the New York State marriage equality act with changes in health insurance coverage. *Journal of the American Medical Association*, *314*(7), 727–728. doi: 10.1001/jama.2015.7950.

Gonzales, G., and Blewett, L.A. (2013). Disparities in health insurance among children with same-sex parents. *Pediatrics*, *132*(4), 703–711. doi: 10.1542/peds.2013-0988.

———. (2014). National and state-specific health insurance disparities for adults in same-sex relationships. *American Journal of Public Health*, *104*(2), e95–e104. doi: 10.2105/AJPH.2013.301577.

Gonzales, G., and Henning-Smith, C. (2017a). The Affordable Care Act and health insurance coverage for lesbian, gay, and bisexual adults: Analysis of the Behavioral Risk Factor Surveillance System. *LGBT Health*, *4*(1), 62–67. doi: 10.1089/lgbt.2016.0023.

———. (2017b). Barriers to care among transgender and gender nonconforming adults. *The Milbank Quarterly*, *95*(4), 726–748. doi: 10.1111/1468-0009.12297.

Gonzales, G., Driscoll, R., and Quinones, N. (2019). Who are the remaining uninsured sexual minority adults under the Affordable Care Act? *LGBT Health*, *6*(6), 319–325. doi: 10.1089/lgbt.2019.0007.

Gridley, S.J., Crouch, J.M., Evans, Y., Eng, W., Antoon, E., Lyapustina, M., Schimmel-Bristow, A., Woodward, J., Dundon, K., Schaff, R., McCarty, C., Ahrens, K., and Breland, D.J. (2016). Youth and caregiver perspectives on barriers to gender-affirming health care for transgender youth. *Journal of Adolescent Health*, *59*(3), 254–261. doi: 10.1016/j.jadohealth.2016.03.017.

Gruberg, S., and Bewkes, F.J. (2018). *The ACA's LGBTQ Nondiscrimination Regulations Prove Crucial*. Available: https://www.americanprogress.org/issues/lgbtq-rights/reports/2018/03/07/447414/acas-lgbtq-nondiscrimination-regulations-prove-crucial.

Hatzenbuehler, M.L., O'Cleirigh, C., Grasso, C., Mayer, K., Safren, S., and Bradford, J. (2012). Effect of same-sex marriage laws on health care use and expenditures in sexual minority men: A quasi-natural experiment. *American Journal of Public Health*, *102*(2), 285–291. doi: 10.2105.

Health Resources and Services Administration. (n.d.). *SPNS Initiative: Enhancing Engagement and Retention in Quality HIV Care for Transgender Women of Color, 2012-2017*. Available: https://hab.hrsa.gov/about-ryan-white-hivaids-program/spns-transgender-women-color.

Hembree, W.C., Cohen-Kettenis, P.T., Gooren, L., Hannema, S., Meyer, W., Murad, M., Rosenthal, S., Safer, J., Tangpricha, V., and T'Sjoen, G. (2017). Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism*, *102*(11), 3869–3903.

Hollenbach, A.D., Eckstrand, K.L., and Dreger, A.D. (Eds.). (2014). *Implementing Curricular and Institutional Climate Changes to Improve Health Care for Individuals Who Are LGBT, Gender Nonconforming, or Born with DSD: A Resource for Medical Educators*. Washington, DC: Association of American Medical Colleges.

Copyright National Academy of Sciences. All rights reserved.

Horbach, S.E.R., Bouman, M-B., Smit, J.M., Özer, M., Buncamper, M.E., and Mullender, M.G. (2015). Outcome of vaginoplasty in male-to-female transgenders: A systematic review of surgical techniques. *Journal of Sexual Medicine, 12*, 1499–1512.

Hsieh, N., and Ruther, M. (2017). Despite increased insurance coverage, nonwhite sexual minorities still experience disparities in access to care. *Health Affairs*, *36*(10), 1786–1794. doi: 10.1377/hlthaff.2017.0455.

Hughes, I.A., Nihoul-Fékété, C., Thomas, B., and Cohen-Kettenis, P.T. (2007). Consequences of the ESPE/LWPES guidelines for diagnosis and treatment of disorders of sex development. *Best Practice and Research: Clinical Endocrinology and Metabolism*, *21*(3), 351.

Human Rights Campaign Foundation. (2020). *Healthcare Equality Index 2020*. Washington, DC: Human Rights Campaign Foundation. Available: https://hrc-prod-requests.s3-us-west-2.amazonaws.com/resources/HEI-2020-FinalReport.pdf.

Human Rights Watch. (2017). *"I Want to be Like Nature Made Me": Medically Unnecessary Surgeries on Intersex Children in the US*. New York: Human Rights Watch. Available: https://www.hrw.org/sites/default/files/report_pdf/lgbtintersex0717_web_0.pdf.

Institute of Medicine. (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: The National Academies Press. doi: 10.17226/10027.

———. (2011a). *HIV Screening and Access to Care: Exploring the Impact of Policies on Access and Provision of HIV Care*. Washington, DC: The National Academies Press. doi: 10.17226/13057.

———. (2011b). *The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding*. Washington, DC: The National Academies Press. doi: 10.17226/13128.

Jacobs, D.B., and Sommers, B.D. (2015). Using drugs to discriminate—Adverse selection in the insurance marketplace. *New England Journal of Medicine*, *372*(5), 397–399.

James, S.E., Herman, J.L., Rankin, S., Keisling, M., Mottet, L., and Anafi, M. (2016). *The Report of the 2015 U.S. Transgender Survey*. Washington, DC: National Center for Transgender Equality. Available: https://www.transequality.org/sites/default/files/docs/USTS-Full-Report-FINAL.PDF.

Joint Commission. (2011). *Advancing Effective Communication, Cultural Competence, and Patient- and Family Centered Care for the Lesbian, Gay, Bisexual, and Transgender (LGBT) Community: A Field Guide*. Oak Brook, IL: The Joint Commission. Available: www.jointcommission.org/assets/1/18/LGBTFieldGuide.pdf.

Kaiser Family Foundation. (2019). *Medicaid and HIV*. Available: https://www.kff.org/hivaids/fact-sheet/medicaid-and-hiv/#.

Kang, H.J., Imperato-McGinley, J., Zhu, Y.S., and Rosenwaks, Z. (2014). The effect of 5alpha-reductase-2 deficiency on human fertility. *Fertility and Sterility*, *101*(2), 310–316. doi: 10.1016/j.fertnstert.2013.11.128.

Karpman, M., Skopec, L., and Long, S.K. (2015, April 16). QuickTake: Uninsurance rate nearly halved for lesbian, gay, and bisexual adults since mid-2013. *Urban Institute Health Policy Center*. Available: http://hrms.urban.org/quicktakes/Uninsurance-Rate-Nearly-Halved-for-Lesbian-Gay-and-Bisexual-Adults-since-Mid-2013.html.

Kcomt, L. (2019). Profound health-care discrimination experienced by transgender people: Rapid systematic review. *Social Work in Health Care, 58*(2), 201–219. doi: 10.1080/00981389.2018.1532941.

Keith, K. (2019). Trump administration finalizes broad religious and moral exemptions for health care workers. *Health Affairs Blog*. Available: https://www.healthaffairs.org/do/10.1377/hblog20190503.960127/abs/.

———. (2020). Supreme court finds LGBT people are protected from employment discrimination: Implications for the ACA. *Health Affairs Blog*. Available: https://www.healthaffairs.org/do/10.1377/hblog20200615.475537/full/.

Copyright National Academy of Sciences. All rights reserved.

Keo-Meier, C.L., Herman, L.I., Reisner, S.L., Pardo, S.T., Sharp, C., and Babcock, J.C. (2015). Testosterone treatment and MMPI–2 improvement in transgender men: A prospective controlled study. *Journal of Consulting and Clinical Psychology*, *83*(1), 143–156.

Kimberly, L.L., Folkers, K.M., Friesen, P., Sultan, D., Quinn, G.P., Bateman-House, A., Parent, B., Konnoth, C., Janssen, A., Shah, L.D., Bluebond-Langner, R., and Sales-Humara, C. (2018). Ethical issues in gender-affirming care for youth. *Pediatrics*, *142*(6), e20181537.

Kolesinska, Z., Ahmed, S.F., Niedziela, M., Bryce, J., Molinska-Glura, M., Rodie, M., Jiang, J., Sinnott, R., Hughes, I, Darendeliler, F., Hiort, O., van der Zwan, Y., Cools, M., Guran, T., Holterhus, P., Bertelloni, S., Lisa, L., Arlt, W., Krone, N., Ellaithi, M., Balsamo, A., Mazen, I., Nordenstrom, A., Lachlan, K., Alkhawari, M., Chatelain, P., and Weintrob, N. (2014). Changes over time in sex assignment for disorders of sex development. *Pediatrics*, *134*(3), e710–e715.

Krege, S., Eckoldt, F., Richter-Unruh, A., Kohler, B., Leuschner, I., Mentzel, H.J., Moss, A., Schweizer, K., Stein, R., Werner-Rosen, K., Wieacker, P., Wiesemann, C., Wünsch, L., and Richter-Appelt, H. (2019). Variations of sex development: The first German interdisciplinary consensus paper. *Journal of Pediatric Urology*, *15*(2), 114–123. doi: 10.1016/j.jpurol.2018.10.008.

Lambda Legal. (2016). *Creating Equal Access to Quality Health Care for Transgender Patients: Transgender-Affirming Hospital Policies*. New York: Lambda Legal. Available: https://www.lambdalegal.org/know-your-rights/article/trans-affirming-hospital-policies.

———. (2018). *Intersex-Affirming Hospital Policy Guide: Providing Ethical and Compassionate Health Care to Intersex Patients*. New York: Lambda Legal. Available: https://www.lambdalegal.org/sites/default/files/publications/downloads/resource_20180731_hospital-policies-intersex.pdf.

Mahfouda, S., Moore, J.K., Siafarikas, A., Zepf, F.D., and Lin, A. (2017). Puberty suppression in transgender children and adolescents. *Lancet Diabetes and Endocrinology*, *5*(10), 816–826.

Mahfouda, S., Moore, J.K., Siafarikas, A., Hewitt, T., Ganti, U., Lin, A., and Zepf, F.D. (2019). Gender-affirming hormones and surgery in transgender children and adolescents. *Lancet Diabetes and Endocrinology*, *7*(6), 484–498.

Mallory, C., and Tentindo, W. (2019). *Medicaid Coverage for Gender-Affirming Care*. Los Angeles, CA: Williams Institute, UCLA School of Law. Available: https://williamsinstitute.law.ucla.edu/wp-content/uploads/Medicaid-Gender-Care-Oct-2019.pdf.

Mallory, C., Brown, T.N.T., and Conron, K.J. (2019). *Conversion Therapy and LGBT Youth Update*. Los Angeles, CA: Williams Institute, UCLA School of Law. Available: https://williamsinstitute.law.ucla.edu/wp-content/uploads/Conversion-Therapy-Update-Jun-2019.pdf.

Manrique, O.J., Adabi, K., Martinez-Jorge, J., Ciudad, P., Nicoli, F., and Kiranantawat, K. (2018). Complications and patient-reported outcomes in male-to-female vaginoplasty—Where we are today: A systematic review and meta-analysis. *Annals of Plastic Surgery, 80*(6), 684–691. doi: 10.1097/SAP.0000000000001393.

McGeorge, C.R., Carlson, T.S., and Toomey, R.B. (2015). An exploration of family therapists' beliefs about the ethics of conversion therapy: The influence of negative beliefs and clinical competence with lesbian, gay, and bisexual clients. *Journal of Marital and Family Therapy*, *41*(1), 42–56. doi: 10.1111/jmft.12040.

Meyer-Bahlburg, H.F.L. (2005). Gender identity outcome in female-raised 46,XY persons with penile agenesis, cloacal exstrophy of the bladder, or penile ablation. *Archives of Sexual Behavior*, *34*(4), 423–438.

Meyer-Bahlburg, H.F.L., Dalke, K.B., Berenbaum, S.A., Cohen-Kettenis, P.T., Hines, M., and Schober, J.M. (2016). Gender assignment, reassignment and outcome in disorders of sex development: Update of the 2005 Consensus Conference. *Hormone Research in Paediatrics*, *85*, 112–118. doi: 10.1159/000442386.

Copyright National Academy of Sciences. All rights reserved.

Meyer-Bahlburg, H.F.L., Khuri, J., Reyes-Portillo, J., and New, M.I. (2017a). Stigma in medical settings as reported retrospectively by women with congenital adrenal hyperplasia (CAH) for their childhood and adolescence. *Journal of Pediatric Psychology*, (5), 496–503. doi: 10.1093/jpepsy/jsw034.

Meyer-Bahlburg, H.F., Reyes-Portillo, J.A., Khuri, J., Ehrhardt, A.A., and New, M.I. (2017b). Syndrome-related stigma in the general social environment as reported by women with classical congenital adrenal hyperplasia. *Archives of Sexual Behavior*, *46*(2), 341–351. doi: 10.1007/s10508-016-0862-8.

Meyer-Bahlburg, H., Khuri, J., Reyes-Portillo, J., Ehrhardt, A.A., and New, M.I. (2018). Stigma associated with classical congenital adrenal hyperplasia in women's sexual lives. *Archives of Sexual Behavior*, *47*(4), 943–951. doi: 10.1007/s10508-017-1003-8.

Milrod, C., and Karasic, D.H. (2017). Age is just a number: WPATH-affiliated surgeons' experiences and attitudes toward vaginoplasty in transgender females under 18 years of age in the United States. *Journal of Sexual Medicine*, *14*(4), 624–634.

Morrison, S.D., Shakir, A., Vyas, K.S., Kirby, J., Crane, C.N., and Lee, G.K. (2016). Phalloplasty: A review of techniques and outcomes. *Plastic and Reconstructive Surgery*, *138*(3), 594–615. doi: 10.1097/PRS.0000000000002518.

Mouriquand, P.D., Gorduza, D.B., Gay, C.L., Meyer-Bahlburg, H.F., Baker, L., and Baskin, L.S. (2016). Surgery in disorders of sex development (DSD) with a gender issue: If (why), when, and how? *Journal of Pediatric Urology*, *12*(3), 139–149. doi: 10.1016/j.jpurol.2016.04.001.

Movement Advancement Project. (2020a). *Equality Maps: Healthcare Laws and Policies*. Available: https://www.lgbtmap.org/equality-maps/healthcare_laws_and_policies.

———. (2020b). *Equality Maps: Conversion "Therapy" Laws*. Available: https://www.lgbtmap.org/equality-maps/conversion_therapy.

Murad, M.H., Elamin, M.B., Garcia, M.Z., Mullan, R.J., Murad, A., Erwin, P.J., and Montori, V.M. (2010). Hormonal therapy and sex reassignment: A systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clinical Endocrinology, 72*(2), 214–31. doi: 10.1111/j.1365-2265.2009.03625.x.

National LGBT Health Education Center. (2016). *Building Patient-Centered Medical Homes for Lesbian, Gay, Bisexual, and Transgender Patients and Families*. Boston, MA: National LGBT Health Education Center. Available: https://www.lgbthealtheducation.org/wp-content/uploads/Building-PCMH-for-LGBT-Patients-and-Families.pdf.

Nguyen, H.B., Chavez, A.M., Lipner, E., Hantsoo, L., Kornfield, S.L., Davies, R.D, and Epperson, C.N. (2018). Gender-affirming hormone use in transgender individuals: Impact on behavioral health and cognition. *Current Psychiatry Reports*, *20*(12), 110. doi: 10.1007/s11920-018-0973-0.

Nokoff, N.J., Palmer, B., Mullins, A.J., Aston, C.E., Austin, P., Baskin, L., Bernabé, K., Chan, Y., Cheng, E., Diamond, D., Fried, A., Frimberger, D., Galan, D., Gonzalez, L., Greenfield, S., Kolon T., Kropp, B., Lakshmanan, Y., Meyer, S., Meyer, T., Mullins, L., Paradis, A., Poppas, D., Reddy, P., Schulte, M., Scott Reyes, K., Swartz, J., Wolfe-Christensen, C., Yerkes, E., and Wisniewski, A. (2017). Prospective assessment of cosmesis before and after genital surgery. *Journal of Pediatric Urology*, *13*(1), 28.e1–28.e6. doi: 10.1016/j.jpurol.2016.08.017.

Nordenvall, A.S., Frisen, L., Nordenstrom, A., and Lichtenstein, N.A. (2014). Population based nationwide study of hypospadias in Sweden, 1973 to 2009: Incidence and risk factors. *Journal of Urology, 191*, 783–789.

National Public Radio, Robert Wood Johnson Foundation, and Harvard T.H. Chan School of Public Health. (2017). *Discrimination in America: Experiences and Views of LGBTQ Americans*. Available: https://www.npr.org/documents/2017/nov/npr-discrimination-lgbtq-final.pdf.

Copyright National Academy of Sciences. All rights reserved.

Obedin-Maliver, J., Goldsmith, E.S., Stewart, L., White, W., Tran, E., Brenman, S., Wells, M., Fetterman, D.M., Garcia, G., and Lunn, M.R. (2011). Lesbian, gay, bisexual, and transgender–related content in undergraduate medical education. *Journal of the American Medical Association*, *306*(9), 971–977. doi: 10.1001/jama.2011.1255.

Office of Minority Health. (2013). *National Standards for Culturally and Linguistically Appropriate Services in Health and Health Care: A Blueprint for Advancing and Sustaining CLAS Policy and Practice*. Rockville, MD: Author. Available: https://thinkculturalhealth.hhs.gov/assets/pdfs/EnhancedCLASStandardsBlueprint.pdf.

Olson, C.L. (2009). Transgender foster youth: A forced identity. *Texas Journal of Women and the Law, 19*(1), 25–57.

Olson, J., Schrager, S.M., Belzer, M., Simons, L.K., and Clark, L.F. (2015). Baseline physiologic and psychosocial characteristics of transgender youth seeking care for gender dysphoria. *Journal of Adolescent Health, 57*(4), 374–380. doi: 10.1016/j.jadohealth.2015.04.027.

Olson, K.R., Durwood, L., DeMeules, M., and McLaughlin, K.A. (2016). Mental health of transgender children who are supported in their identities. *Pediatrics*, *137*(3), e20153223.

Olson-Kennedy, J., Cohen-Kettenis, P.T., Kreukels, B.P., Meyer-Bahlburg, H.F., Garofalo, R., Meyer, W., and Rosenthal, S.M. (2016). Research priorities for gender nonconforming/transgender youth: Gender identity development and biopsychosocial outcomes. *Current Opinion in Endocrinology, Diabetes, and Obesity*, *23*(2), 172.

Olson-Kennedy, J., Warus, J., Okonta, V., Belzer, M., and Clark, L.F. (2018). Chest reconstruction and chest dysphoria in transmasculine minors and young adults: Comparisons of nonsurgical and postsurgical cohorts. *JAMA Pediatrics, 172*(5), 431–436. doi: 10.1001/jamapediatrics.2017.5440.

Passos, T.S., Teixeira, M.S., and Almeida-Santos, M.A. (2020). Quality of life after gender affirmation surgery: A systematic review and network meta-analysis. *Sexuality Research and Social Policy*, *17*(2), 252–262. doi: 10.1007/s13178-019-00394-0.

Physicians for Human Rights. (2017). *Unnecessary Surgery on Intersex Children Must Stop*. Available: https://phr.org/news/unnecessary-surgery-on-intersex-children-must-stop/.

Progovac, A.M., Mullin, B.O., Creedon, T.B., McDowell, A., Sanchez-Roman, M.J., Hatfield, L.A., Schuster, M.A., and Cook, B.L. (2019). Trends in mental health care use in Medicare from 2009 to 2014 by gender minority and disability status. *LGBT Health, 6*(6), 297–305. doi: 10.1089/lgbt.2018.0221.

Pyle, L.C., and Nathanson, K.L. (2017). A practical guide for evaluating gonadal germ cell tumor predisposition in differences of sex development. *American Journal of Medical Genetics*, *175*(2), 304–314. doi: 10.1002/ajmg.c.31562.

Rafferty, J., Committee on Psychosocial Aspects of Child and Family Health, and Committee on Adolescence. (2018). Ensuring comprehensive care and support for transgender and gender-diverse children and adolescents. *Pediatrics*, *142*(4). doi: 10.1542/peds.2018-2162.

Rebchook, G., Keatley, J., Contreras, R., Perloff, J., Molano, L.F., Reback, C.J., Ducheny, K., Nemoto, T., Lin, R., Birnbaum, J., Woods, T., Xavier, J., and SPNS Transgender Women of Color Study Group. (2017). The Transgender Women of Color Initiative: Implementing and evaluating innovative interventions to enhance engagement and retention in HIV Care. *American Journal of Public Health*, *107*(2), 224–229. doi: 10.2105/AJPH.2016.303582.

Robles, R., Fresán, A., Vega-Ramírez, H., Cruz-Islas, J., Rodríguez-Pérez, V., Domínguez-Martínez, T., and Reed, G. (2016). Removing transgender identity from the classification of mental disorders: A Mexican field study for ICD-11. *Lancet Psychiatry*, *3*, 850–859.

Roen, K. (2019). Intersex or diverse sex development: Critical review of psychosocial health care research and indications for practice. *Journal of Sex Research*, *56*(4-5), 511–528.

Copyright National Academy of Sciences. All rights reserved.

Rolston, A.M., Gardner, M., van Leeuwen, K., Mohnach, L., Keegan, C., Délot, E., Vilain, E., Sandberg, D.E, and members of the DSD-TRN Advocacy, Advisory Network Accord Alliance. (2017). Disorders of sex development (DSD): Clinical service delivery in the United States. *American Journal of Medical Genetics Party C Seminars in Medical Genetics*, *175*(2), 268–278. doi: 10.1002/ajmg.c.31558.

Romao, R.L.P., and Pippi Salle, J.L. (2017). Update on the surgical approach for reconstruction of the male genitalia. *Seminars in Perinatology, 41*(4), 218–226. doi: 10.1053/j.semperi.2017.03.015.

Rooker, S.A., Vyas, K.S., DiFilippo, E.C., Nolan, I.T., Morrison, S.D., and Santucci, R.A. (2019). The rise of the neophallus: A systematic review of penile prosthetic outcomes and complications in gender-affirming surgery. *Journal of Sexual Medicine*, (5), 661–672. doi: 10.1016/j.jsxm.2019.03.009.

Rowniak, S., Bolt, L., and Sharifi, C. (2019). Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: A quantitative systematic review. *JBI Database of Systematic Reviews and Implementation Reports*, *17*(9), 1826–1854. doi: 10.11124/JBISRIR-2017-003869.

Russell, S.T., Pollitt, A.M., Li, G., and Grossman, A.H. (2018). Chosen name use is linked to reduced depressive symptoms, suicidal ideation, and suicidal behavior among transgender youth. *Journal of Adolescent Health*. doi: 10.1016/j.jadohealth.2018.02.003.

Ryan, C., Toomey, R.B., Diaz, R.M., and Russell, S.T. (2018). Parent-initiated sexual orientation change efforts with LGBT adolescents: Implications for young adult mental health and adjustment. *Journal of Homosexuality*, 1–15. doi: 10.1080/00918369.2018.1538407.

Substance Abuse and Mental Health Services Administration. (2015). *Ending Conversion Therapy: Supporting and Affirming LGBTQ Youth*. Rockville, MD: Substance Abuse and Mental Health Services Administration.

———. (2020). *LGBT Training Curricula for Behavioral Health and Primary Care Practitioners*. Available: https://www.samhsa.gov/behavioral-health-equity/lgbt/curricula.

Schulz, S.L. (2018). The informed consent model of transgender care: An alternative to the diagnosis of gender dysphoria. *Journal Humanistic Psychology*, *58*, 72–92.

Shanley, T., Wheeler, D., Cheng, E., and Garofalo, R. (2020). *Intersex Care at Lurie Children's and Our Sex Development Clinic*. Available: https://www.luriechildrens.org/en/blog/intersex-care-at-lurie-childrens-and-our-sex-development-clinic.

Spade, D., Arkles, G., Duran, P., and Gehi, P. (2009). Medicaid policy and gender-confirming healthcare for trans people: An interview with advocates. *Seattle Journal for Social Justice, 8*(1), 497–514. Available: https://digitalcommons.law.seattleu.edu/sjsj/vol8/iss2/4.

Speiser, P.W., Arlt, W., Auchus, R.J., Baskin, L.S., Conway, G.S., Merke, D.P., Meyer-Bahlburg, H., Miller, W., Murad, M., OBerfield, S., and White, P.C. (2018). Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism*, *103*(11), 4043–4088.

Streed, C.G., McCarthy, E.P., and Haas, J.S. (2018). Self-reported physical and mental health of gender nonconforming transgender adults in the United States. *LGBT Health*, *5*(7), 443–448. doi: 10.1089/lgbt.2017.0275.

Streed, C.G., Anderson, J.S., Babits, C., and Ferguson, M.A. (2019a). Changing medical practice, not patients: Putting an end to conversion therapy. *New England Journal of Medicine*, *381*(6), 500.

Streed, C.G., Hedian, H.F., Bertram, A., and Sisson, S.D. (2019b). Assessment of internal medicine resident preparedness to care for lesbian, gay, bisexual, transgender, and queer/questioning patients. *Journal of General Internal Medicine*, *34*(6), 893–898. doi: 10.1007/s11606-019-04855-5.

Tabaac, A.R., Sutter, M.E., Wall, C.S.J., and Baker, K.E. (2018). Gender identity disparities in cancer screening behaviors. *American Journal of Preventive Medicine*, *54*(3), 385–393. doi: 10.1016/j.amepre.2017.11.009.

Copyright National Academy of Sciences. All rights reserved.

Tamar-Mattis, A., Baratz, A., Baratz Dalke, K., and Karkazis, K. (2013). Emotionally and cognitively informed consent for clinical care for differences of sex development. *Psychology and Sexuality*, *5*(1), 44–55.

Tanner, L. (2020). U.S. medical schools boost LGBTQ students, doctor training. *Associated Press*. Available: https://apnews.com/985d50d0a7b1b593acd0dd791e8c3118.

Thyen, U., Lanz, K., Holterhus, P.M, and Hiort, E. (2006). Epidemiology and initial management of ambiguous genitalia at birth in Germany. *Hormone Research*, *66*(4), 195–203.

Timmermans, S., Yang, A., Gardner, M., Keegan, C.E., Yashar, B.M., Fechner, P.Y., Shnorhavorian, M., Vilain, E., and Sandberg, D.E. (2018). Does patient-centered care change genital surgery decisions? The strategic use of clinical uncertainty in disorders of sex development clinics. *Journal of Health and Social Behavior*, *59*(4), 520–535. doi: 10.1177/0022146518802460.

Toler, J., and GLMA Policy and Government Affairs Committee. (2016). *Medical and Surgical Intervention of Patients with Differences in Sex Development*. Available: http://glma.org/index.cfm?fuseaction=document.viewdocument&ID=CEB9FEE4B8DD8B7F4F7575376BD476C3A433379DD853BEA17913AFCCB8270299C0731320B03D2F5E1022F1C15602FBEA.

Tourchi, A., and Hoebeke, P. (2013). Long-term outcome of male genital reconstruction in childhood. *Journal of Pediatric Urology*, *9*(6), 980–989.

Trevor Project. (2019). *National Survey on LGBTQ Mental Health*. Available: https://www.thetrevorproject.org/wp-content/uploads/2019/06/The-Trevor-Project-National-Survey-Results-2019.pdf.

Turban, J.L., Beckwith, N., Reisner, S.L., and Keuroghlian, A.S. (2019). Association between recalled exposure to gender identity conversion efforts and psychological distress and suicide attempts among transgender adults. *JAMA Psychiatry*, 1–9. doi: 10.1001/jamapsychiatry.2019.2285.

UCSF Transgender Care. (2016). *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People* (2nd ed.). M.B. Deutsch (Ed.). San Francisco, CA: Department of Family and Community Medicine, University of California San Francisco. Available: transcare.ucsf.edu/guidelines.

Underhill, K. (2012). Paying for prevention: Challenges to health insurance coverage for biomedical HIV prevention in the United States. *American Journal of Law and Medicine*, *38*(4), 607–666. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4041033.

United Nations General Assembly Human Rights Council. (2013). *Report of the Special Rapporteur on Torture and other Cruel, Inhuman or Degrading Treatment or Punishment*. Available: http://www.ohchr.org/Documents/HRBodies/HRCouncil/RegularSession/Session22/A.HRC.22.53_English.pdf.

U.S. Department of Health and Human Services. (2014). *NCD 140.3, Transsexual Surgery. Docket No. A-13-87, Decision No. 2576*. Available: https://www.hhs.gov/sites/default/files/static/dab/decisions/board-decisions/2014/dab2576.pdf.

van de Grift, T.C., Elaut, E., Cerwenka, S.C., Cohen-Kettenis, P.T., and Kreukels, B.P.C. (2017). Surgical satisfaction, quality of life, and their association after gender-affirming surgery: A follow-up study. *Journal of Sex and Marital Therapy, 44*(2), 138–148. doi: 10.1080/0092623X.2017.1326190.

Van Boerum, M.S., Salibian, A.A., Bluebond-Langner, R., and Agarwal, C. (2019). Chest and facial surgery for the transgender patient. *Translational Andrology and Urology*, *8*(3), 219–227. doi: 10.21037/tau.2019.06.18.

Wernick, J.A., Busa, S., Matouk, K., Nicholson, J., and Janssen, A. (2019). A systematic review of the psychological benefits of gender-affirming surgery. *Urologic Clinics of North America*, *46*(4), 475–486. doi: 10.1016/j.ucl.2019.07.002.

Copyright National Academy of Sciences. All rights reserved.

Case 4:22-cv-00325-RH-MAF Document 133-17 Filed 04/07/23 Page 53 of 54

White Hughto, J.M., and Reisner, S.L. (2016). A systematic review of the effects of hormone therapy on psychological functioning and quality of life in transgender individuals. *Transgender Health*, *1*(1), 21–31. doi: 10.1089/trgh.2015.0008.

Wiepjes, C.M., Nota, N.M., de Blok, C.J.M., Klaver, M., de Vries, A.L.C., Wensing-Kruger, S.A., de Jongh, R.T., Bouman, M.B., Steensma, T.D., Cohen-Kettenis, P., Gooren, L.J.G., Kreukels, B.P.C., and den Heijer, M. (2018). The Amsterdam Cohort of Gender Dysphoria study (1972–2015): Trends in prevalence, treatment, and regrets. *Journal of Sexual Medicine, 15*(4), 582–590. doi: 10.1016/j.jsxm.2018.01.016.

Winship, B.B., Rushton, H.G., and Pohl, H.G. (2017). In pursuit of the perfect penis: hypospadias repair outcomes. *Journal of Pediatric Urology*, *13*(3), 285–288.

Wisniewski, A.B. (2017). Psychosocial implications of DSD treatment for parents. *Current Opinion in Urology*, *27*(1), 11–13. doi: 10.1097/MOU.0000000000000344.

Woo, L.L., Thomas, J.C., and Brock, J.W. (2010). Cloacal exstrophy: A comprehensive review of an uncommon problem. *Journal of Pediatric Urology*, *6*(2), 102–111.

World Health Organization. (n.d.). *Brief—Transgender Health in the Context of ICD-11*. Available: http://www.euro.who.int/en/health-topics/health-determinants/gender/gender-definitions/whoeurope-brief-transgender-health-in-the-context-of-icd-11.

———. (2014). *Eliminating Forced, Coercive and Otherwise Involuntary Sterilization: An Interagency Statement*. Available: http://www.who.int/reproductivehealth/publications/gender_rights/eliminating-forced-sterilization/en.

World Professional Association for Transgender Health. (2016). Position Statement on Medical Necessity of Treatment, Sex Reassignment, and Insurance Coverage in the U.S.A. Available: https://www.wpath.org/media/cms/Documents/Web%20Transfer/Policies/WPATH-Position-on-Medical-Necessity-12-21-2016.pdf.

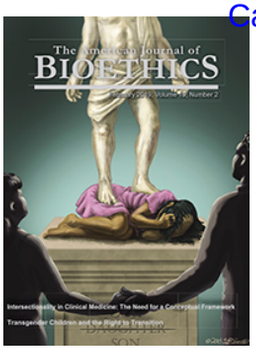
Wright, T., Candy, B., and King, M. (2018). Conversion therapies and access to transition-related healthcare in transgender people: A narrative systematic review. *BMJ Open*, *8*(12), e022425. doi: 10.1136/bmjopen-2018-022425.

Wylie, K., Knudson, G., Khan, S.I., Bonierbale, M., Watanyusakul, S., and Baral, S. (2016). Serving transgender people: Clinical care considerations and service delivery models in transgender health. *Lancet, 388*, 401–411.

Copyright National Academy of Sciences. All rights reserved.

REMAINDER OMITTED

EXHIBIT 17



Taylor & Francis
Taylor & Francis Group

The American Journal of Bioethics

ISSN: 1526-5161 (Print) 1536-0075 (Online) Journal homepage: https://www.tandfonline.com/loi/uajb20

The Right to Best Care for Children Does Not Include the Right to Medical Transition

Michael Laidlaw, Michelle Cretella & Kevin Donovan

To cite this article: Michael Laidlaw, Michelle Cretella & Kevin Donovan (2019) The Right to Best Care for Children Does Not Include the Right to Medical Transition, The American Journal of Bioethics, 19:2, 75-77, DOI: 10.1080/15265161.2018.1557288

To link to this article: https://doi.org/10.1080/15265161.2018.1557288

Published online: 20 Feb 2019.

Submit your article to this journal

Article views: 1323

View related articles

View Crossmark data

Citing articles: 5 View citing articles

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=uajb20

The Right to Best Care for Children Does Not Include the Right to Medical Transition

Michael Laidlaw, Private Practice
Michelle Cretella, American College of Pediatricians
G. Kevin Donovan, Georgetown University Medical Center

Contrary to the suggestion in the article, by Priest (2019) watchful waiting with support for gender-dysphoric children and adolescents up to the age of 16 years is the current standard of care worldwide, not gender affirmative therapy (de Vries and Cohen-Kettenis 2012). The treatment of children and adolescents with sex hormones for a mismatch between their mind's perceived gender and their biological sex—otherwise known as gender dysphoria (GD)—results in unique medical and ethical challenges not present in adults. The main challenge results from stopping normal pubertal development by the use of puberty blocking agents (PBA). These are given as part of a treatment paradigm known as gender affirmative therapy (GAT). After some period of time on PBA, cross-sex hormones are introduced and dosages are increased, and gonads and breasts may be surgically removed. The consequences of PBA/GAT are not trivial and include potential sterility, sexual dysfunction, thromboembolic and cardiovascular disease, osteoporosis, and malignancy (Hembree et al. 2017). The adolescent does not have the intellectual or emotional maturity or judgment to make the decision to undergo PBA/GAT without parental approval.

PUBERTY BLOCKING AGENTS

Gonadotropin-releasing hormone (GnRH) analogues such as leuprolide are being used off label for suppression of normal puberty. These powerful hormones act directly on the pituitary–gonadal axis to inhibit the production of luteinizing hormone (LH)/follicle-stimulating hormone (FSH) and consequently lower testosterone and estrogen to subnormal levels. This pathologic state is known as hypogonadotropic hypogonadism. There are no randomized controlled studies for the use of PBA—including safety—for stopping normal puberty. The Endocrine Society has published revised clinical guidelines in 2017 on the treatment of gender dysphoric persons including adolescents (Hembree et al. 2017). The quality of evidence for PBA is noted to be low. In fact, all of the evidence in the guidelines with regard to treating children/adolescents by GAT is low to very low because of the absence of proper studies.

These same guidelines, however, recommend arresting normal puberty at Tanner stage 2. This is highly significant, because it is the pubertal stage occurring before menarche in girls and before spermarche in boys. Continued suppression of the pituitary gonadal axis by PBA will maintain a state of immaturity of the male and female gonads. As a result, though the child will likely continue to grow in stature, the gonads and entire pelvic genitalia will remain stunted at Tanner stage 2. The addition of cross sex hormones will not change this condition. As a result, the patient will be infertile as an adult. The continued administration of cross-sex hormones may lead to permanent sterility. Gonadectomy, of course, will ensure sterility.

INFERTILITY

Infertility is a major health problem. The literature shows it to be a source of significant psychological distress that reduces quality of life, including "emotional well being, relationships, and sexuality" (Carter et al. 2005). Infertile women even without other health conditions have "depression at twice the rate of the normal population and report levels of psychological distress comparable to the experience of a life threatening illness" (Carter et al. 2005). This is obviously a complex problem that a child, particularly at Tanner stage 2, which may be as young as 8 or 9 years old, does not have the capacity to fully comprehend.

LOW RATES OF FERTILITY PRESERVATION

What about fertility preservation (FP)? An obvious parallel can be found in child and adolescent cancer patients who may lose fertility because of gonadotoxic treatments and surgeries. "From an ethical standpoint, the key

Address correspondence to Michael Laidlaw, Endocrinology, Private Practice, 4770 Rocklin Rd, Ste #1, Rocklin, CA 95677, USA. E-mail: docdrlaidlaw@gmail.com

reason for pursuing fertility protection [in these patients] is to restore personal autonomy to those who might, in the future, become unable to conceive" (Patrizio and Caplan 2010). Unfortunately, studies show that fewer than 5% of adolescents receiving GAT even attempt this process (Chen et al. 2017). Those adolescents who receive PBA at a late stage of puberty may be able to preserve fertility by sperm or oocyte cryopreservation. However, ovarian tissue cryopreservation is still considered experimental in most centers and testicular tissue cryopreservation remains entirely experimental. These experimental forms of FP would be the only options in children blocked prior to spermarche and menarche and are high in cost and limited to specialized centers. Even with FP there is no guarantee of having a child.

IMPAIRED SEXUAL FUNCTION

Another consequence of PBA is impairment of adult sexual function (SF). Again, early blockade of puberty will arrest the genitalia at an early developmental stage with limited to absent functioning as an adult. Normal SF in the male, including erection, orgasm, and ejaculation, will be significantly impaired to absent. In the female, PBA induce a menopausal state with consequent low estradiol and progesterone levels. The pelvic genitalia will acquire a menopausal yet undeveloped state. Consequences will include decreased blood flow to the vagina and vulva, thinning of the vaginal epithelium, and vaginal dryness leading to atrophy. Conditions such as hypoactive sexual desire (HSDD) have been found in naturally menopausal females and to be of even higher prevalence in 20- to 49-year-olds with surgically induced menopause. HSDD is associated with a significant decrease in general health, including aspects of mental and physical health (Leiblum et al. 2006).

Both the male and female will have significantly impaired to absent SF as adults because of the effects of PBA and due to the addition of cross-sex hormones. These effects will be compounded by genital affirmation surgery. The child or adolescent lacks the knowledge, foresight, and in most cases experience of SF to be able to fully comprehend the loss or impairment of SF resulting from the initial step of PBA.

DISRUPTION OF NORMAL BONE DEVELOPMENT

Abnormal bone growth and development is another unique consequence of PBA. Skeletal growth and development is an exquisitely timed and coordinated event involving multiple hormonal interactions, particularly the simultaneous increase in sex hormones and growth hormone. PBA results in very low to absent sex hormone levels during the normal time of increased growth hormone levels. The results and implications of causing this hormonal mismatch are unknown. It has been shown that PBA lead to a decline in the bone mineral density z score (Hembree et al. 2017). This has lifelong implications that may include early-onset osteopenia or osteoporosis.

THE PROBLEM OF ACCURATE DIAGNOSIS AND DESISTANCE

In spite of the previous discussion of risks, one might argue that the benefits of PBA outweigh these risks, and that children and adolescents should have the legal right to access these agents without parental approval. But as in any disease process, how can we be certain that a condition has been properly diagnosed before undergoing life-altering therapies? In the case of cancer, for example, physical evidence and confirmation of the condition would be warranted to both justify and tailor therapy accordingly.

There are no objective tests—laboratory, imaging, or otherwise—to diagnose a "true transgender" child. By adulthood 61–98% will outgrow GD (Ristori and Steensma 2016). There is no known way to predict who will desist and who will remain dysphoric. Furthermore, the recent phenomenon has been described of adolescents, primarily teenage girls, many with neurodevelopmental disorders, suddenly developing GD without prior history, through social contagion (Littman 2018). Therefore, a large number of children and adolescents diagnosed with GD who would otherwise be predicted to desist or who have developed the condition due to social pressures would be irreversibly harmed by PBA/GAT.

PBA compound the problem of natural desistance in a profound way. In a study of 70 adolescents who were followed after receiving PBA, 100% desired to continue on to cross-sex hormones (de Vries et al. 2011). The natural pattern of desistance has been broken, either because of physiologic or psychological effects of PBA or a combination of the two. Adolescents who would have otherwise desisted instead retain the notion that their gender identity and sex do not match and are thereby guaranteed to risk developing the problems addressed in the preceding.

COMORBID PSYCHIATRIC CONDITIONS

An additional issue related to the adolescent's decision to take PBA without parental involvement concerns associated psychological conditions that may affect judgement. A study of the Finnish gender identity service showed that "75% of adolescents [assessed] had been or were currently undergoing child and adolescent psychiatric treatment for reasons other than gender dysphoria" (Kaltiala-Heino et al. 2015). A recent parental survey showed that 62.5% of the affected adolescents had "a psychiatric disorder or neurodevelopmental disability preceding the onset of gender dysphoria" (Littman 2018). These psychiatric conditions compound the problem of immaturity in contemplating the very complex issues that we have addressed.

THE CURRENT STANDARD OF CARE

As stated, watchful waiting with support for GD children and adolescents is the current standard of care worldwide until the age of 16 years, not GAT (de Vries and Cohen-Kettenis 2012). Children referred for psychological therapy or simple watchful waiting have been able to alleviate their GD without the damaging health consequences of GAT. These methods are the obvious and preferred therapy for GD, as they do the least harm with the most benefit for the greatest number.

CONCLUSION

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 pleasure function. To argue that all children who are self-declared as transgendered will be harmed psychologically and physically without puberty blocking treatments is false; the greatest number will be seen to not require this at all. To further argue that these adolescents should receive hormonal therapy without parental approval betrays a poor understanding of adolescent psychology and the role of parents in the family dynamic. Evidence of severe and permanent harm from an appropriate delay for the psychological evaluation and treatment of such children, prior to permanently altering them, does not exist. To argue that such supposed harm rises to the level of denying parental involvement in the care of their gender-dysphoric child is grossly overreaching, and should not be suggested as the standard of care. Rather, it would constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety, for which informed consent therefore would not be possible. ■

ORCID

Michael Laidlaw http://orcid.org/0000-0001-6849-7285
Michelle Cretella https://orcid.org/0000-0002-4264-9911
G. Kevin Donovan https://orcid.org/0000-0002-6115-7840

REFERENCES

Carter, J., K. Rowland, D. Chi, et al. 2005. Gynecologic cancer treatment and the impact of cancer-related infertility. *Gynecologic Oncology* 97(1): 90–95.

Chen, D., L. Simons, E. K. Johnson, B. A. Lockart, and C. Finlayson. 2017. Fertility preservation for transgender adolescents. *The Journal of Adolescent Health* 61(1): 120–123.

de Vries, A. L. C., T. D. Steensma, T. A. H. Doreleijers, and P. T. Cohen-Kettenis. 2011. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. *The Journal of Sexual Medicine* 8(8): 2276–2283. doi: 10.1111/j.1743-6109.2010.01943.x.

de Vries, A. L., and P. T. Cohen-Kettenis. 2012. Clinical management of gender dysphoria in children and adolescents: The Dutch approach. *Journal of Homosexuality* 59(3): 301–320.

Hembree, W. C., P. T. Cohen-Kettenis, L. Gooren, et al. 2017. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism* 102(11): 3869–3903. doi: 10.1210/jc.2017-01658.

Kaltiala-Heino, R., M. Sumia, M. Työläjärvi, and N. Lindberg. 2015. Two years of gender identity service for minors: Overrepresentation of natal girls with severe problems in adolescent development. *Child and Adolescent Psychiatry and Mental Health* 9: 9.

Leiblum, S. R., P. E. Koochaki, C. A. Rodenberg, I. P. Barton, and R. C. Rosen. 2006. Hypoactive sexual desire disorder in postmenopausal women: US results from the women's international study of health and sexuality (WISHeS)). *Menopause* 13(1): 46–56.

Littman, L. 2018. Rapid-onset gender dysphoria in adolescents and young adults: A study of parental reports. *PLoS One* 13(8): e020233016.

Patrizio, P., and A. Caplan. 2010. Ethical issues surrounding fertility preservation in cancer patients. *Clinical Obstetrics and Gynecology* 53(4): 717–726.

Priest, M. 2019. Transgender children and the right to transition: Medical ethics when parents mean well but cause harm. *American Journal of Bioethics* 19(2): 45–59.

Ristori, J., and T. D. Steensma. 2016. Gender dysphoria in childhood. *International Review of Psychiatry (Abingdon, England)* 28(1): 13–20.

EXHIBIT 18

SAHM Response to Dr. Michelle Cretella

More in This Section

The Society for Adolescent Health and Medicine strongly rejects the views of those in the medical community pushing political and ideological agendas not based on science and facts.

Recently, Dr. Michelle Cretella, the president of the American College of Pediatricians, penned a scathing attack on the transgender community thinly veiled as an argument against the dangers of transgender surgery and support; an argument based on medical omissions, circumstantial facts, hateful interpretation and peripheral context.

Earlier this month, the Adolescent Health News Roundup, compiled by Multiview and distributed by SAHM, included the article **"I'm a Pediatrician. How Transgender Ideology Has Infiltrated My Field and Produced Large-Scale Child Abuse"**. While SAHM welcomes opposing views and tries to include other perspectives in its weekly digest of news culled from around the internet, SAHM does not condone misinformation and hurtful, ideological opinion, not rooted in science or evidence-based medicine. The above-referenced article does not meet these standards and was included as "news" in error. It not only promotes a biased agenda, but does so with outright disregard for the facts. We sincerely apologize for including this alongside legitimate news stories and are currently revising our procedures to ensure this does not happen again.

Dr. Cretella begins with "What doctors once treated as a mental illness, the medical community now largely affirms and even promotes as normal." She fails to reference historical medical errors with regard to mental illness such as hysteria, a catch-all diagnosis for outspoken women; nostalgia, an affliction to those who had left their home; or the color purple, once argued to drive people insane. She then lists eight "basic facts" which are anything but, and ends with a conclusion of "Transition-affirming protocol is child abuse."

SAHM is dedicated to fighting this type of misinformation. To combat this hate speech and vitriolic deception, we would like to refute her points one by one.

1) **"Twin studies prove no one is born 'trapped in the body of the wrong sex.'"**

Dr. Cretella's argument here, after citing an article from her own organization, relies on the false premise that DNA determines gender. It determines sex, but not gender. She quickly contradicts herself by citing a 2013 study by Dr. Milton Diamond which reports that 20 percent of identical twin pairs both identify as transgender. Dr. Cretella leaves out two important facts – twins have the same DNA, but assume different

Position Papers
Advocacy Activities
Press Releases

Renew Your Dues
Journal of Adolescent Health
Join the Listserve
Career Center
Contribute to SAHM
Health Info for Parents and Teens
Find an Adolescent Health Professional
SAHM Store

characteristics in the womb after separating, and 20% is far above the gender dysphoria national average of 0.3%, which directly refutes her claim there is a "minimal biological predisposition". She not only cites lackluster science but then makes the leap to "transgenderism will not manifest itself without outside non-biological factors also impacting the individual during his lifetime". She is supporting the archaic argument that gender identity is a choice, contrary to current reputable research.

2) **"Gender identity is malleable, especially in young children."**

Dr. Cretella's post is littered with correlation without causation references, and this is her first such reference. She claims 75 to 95% of pre-pubertal children who were distressed by their biological sex outgrew that distress before widespread promotion of transition affirmation. She also cites an increase in referrals for the Gender Identity Development Service in the UK. Both of these arguments can be explained by the widespread oppression and rejection felt by those who are experiencing gender dysphoria until just recently. As acceptance has grown, suppression and denial has decreased, and requests for help and acceptance has increased. SAHM strongly encourages those who need it to seek specialist treatment and to talk to someone who will listen and support them.

3) **"Puberty blockers for gender dysphoria have not been proven safe."**

The author includes evidence from a report about puberty blockers by the Impact Program, but only highlights the possible negative side effects. She references loss of bone density, without including that bone density loss reverses after puberty. Side effects from cough syrup include blurred vision and confusion, but as is the case with all drugs, the drawbacks must be weighed against the benefits.

4) **"There are no cases in the scientific literature of gender-dysphoric children discontinuing blockers."**

Here, Dr. Cretella suggests that because one study found 100% of pre-pubertal children who were placed on blockers at a young age went on to claim a transgender identity, medical protocol itself may lead children to identify as transgender. Another correlation without causation assumption.

More likely, those children were actually transgender and medical protocol helped them to live their lives. Dr. Cretella does not address this possible explanation.

5) **"Cross-sex hormones are associated with dangerous health risks."**

Membership
Member Benefits
Membership Types and Fees
Getting Involved
Join Now
Membership Application
Become an FSAHM
Log In
Meetings
Future Meetings
2020 Conference
2019 Annual Meeting
Training and CME
Fellowship Training
Adol. Health Curriculum
Continuing Education
Webinars
Clinical Care Resources
Advocacy
Position Statements
Advocacy Activities
Media Center
Awards and Grants
Awards
Award Nominations
Grant Programs
Grants and Funding Opportunities
About SAHM
Mission
Leadership
Chapters
Press Releases
Committees
Headquarters Staff
Our History
Retrieve My Password
Contact SAHM
111 West Jackson Blvd, Suite 1412
Chicago, IL 60604 USA
847-686-2246 p
847-686-2251 f
info@adolescenthealth.org
SAHM LOGIN
©2023 Society for Adolescent Health and Medicine. All Rights Reserved. Registered 501(c)(3). EIN: 23-7035351 Privacy Policy

Again, all drugs have some negative side effects. The author refuses to give any credence to the idea that positive outcomes may be associated with cross-sex hormones. The study she cites gives equal weight to those positive outcomes.

6) **"Neuroscience shows that adolescents lack the adult capacity needed for risk assessment."**

Adolescence is a time of great change, when young people are figuring out who they are, and neuroscience has shown they are fully capable of sound judgement. While risk taking is part of being an adolescent, adolescent brains are wired to ensure a range of exploratory behaviors as part of the developmental process. SAHM supports the field of pediatric psychology, which she has completely undermined with this statement.

7) **"There is no proof that affirmation prevents suicide in children."**

The one study cited showed discrimination *alone* didn't lead to higher rates of suicide for LGBTQ people. However, that same study found that LGBTQ people had higher rates of psychological distress, greater likelihood of diagnosed depression and anxiety and were more likely to report unmet mental healthcare needs.

Meanwhile, she omits the plethora of research which supports affirmation is incredibly important to the LGBTQ community. One study found high levels of social support resulted in an 82% reduction in suicide attempt risk. Another found the attempted suicide rate to be 41% among transgender individuals, well-above the 4.6% overall US population average and cited experiencing discrimination, victimization and rejection by family and friends as causes.

Dr. Cretella offers no proof for a claim that "Many gender dysphoric children simply need therapy to get to the root of their depression, which very well may be the same problem triggering the gender dysphoria," incorrectly assuming gender dysphoria is a treatable mental disorder and dangerously ignoring the causality between gender dysphoria and depression.

8) **"Transition-affirming protocol has not solved the problem of transgender suicide."**

No, it has not, because the transgender community is still working hard to fight against needless and harmful attacks such as this one. SAHM supports all communities fighting discrimination. Acceptance, support and compassion, especially from the medical

community is one way to help solve a complicated condition such as this.

Dr. Cretella's citation of a Swedish study showing adults who undergo sex reassignment have a suicide rate 20 times greater than the general population once again is yet again a case of correlation without causation. We must reject hateful ideology. This is not a battle to be won overnight, but as one study shows, things are improving, and we must continue the fight against discrimination, hate and fear.

SAHM will always look to combat misinformation. One cannot claim to be an unbiased medical professional writing for the greater good when one's entire article is predicated upon gender dysphoria as a choice. It is time to listen to our young people and help them be who they are.

SAHM Executive Committee

EXHIBIT 19

Commentary

CATHOLIC MEDICAL ASSOCIATION

The Linacre Quarterly
2020, Vol. 87(2) 131-137
© Catholic Medical Association 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0024363919875383
journals.sagepub.com/home/lqr
SAGE

Strangers in a Strange Land: How Our Founding Principles and a Bitter Pill Undo the Assimilation of US Catholics

G. Kevin Donovan, MD, MA[1], and Claudia Sotomayor, MD, DBe[1]

Abstract

Most Catholic physicians work with the comfortable assumption that we can practice our profession and our faith, fully assimilated into modern American culture and society. Increasingly, we have come to realize that to be a Catholic Christian is by nature to be countercultural. American culture, ordered by the founding fathers in concepts of liberty and freedom, has been profoundly affected by the introduction and reliance on a contraceptive pill. This has changed the mores and sexual behaviors of society in ways that are antithetical to Catholic values. The consequences of contraception have directly led to an acceptance of a broad number of behaviors and attitudes that society insists must be tolerated. This challenges the commitments of Catholic physicians both personally and professionally.

Keywords

Bioethics, Catholic, Contraception, Happiness, Liberalism, Morality, Physician, Utilitarianism

Despite historical opposition to Catholic emigration in America, the past two or three generations have seen an adjustment of societal attitudes and greater acceptance of Catholics in all walks of life including politics, business, and the professions. At times, we seemed to have achieved a near seamless integration into modern American culture and society. We have grown increasingly comfortable, adopting American principles and traditions as our own. However, in the recent past, cultural flash points have arisen, many of which seem to be a divisive challenge for faithful Catholics in particular. Specifically, we have encountered problems in the practice of medicine more attributable to our role of being both a Catholic and a physician, problems that can make us feel like we are again strangers in a strange land. Why should this be true—why should we not be totally at ease in our society? Perhaps the seeds of our discontent, our present disassociation from mainstream American values, may have been present since our Founding Fathers began the American experiment. It would seem that, like in the parable, they may have sown bad seed with the good (13, Matthew 24:32 RSV). This is not to say they set out to produce anything bad; rather, they certainly aimed for both the good and the true. They began with a description of self-evident truths, "All men are created equal . . . endowed by their Creator with certain inalienable rights, that among these are life, liberty, and the pursuit of happiness" (Declaration of Independence).

How then did our nation devolve from this lofty declaration to present day denigrations, often leaving us feeling like outsiders again? In this essay, we will

[1] Pellegrino Center for Clinical Bioethics, Georgetown University, Washington, DC, USA

Corresponding Author:
G. Kevin Donovan, MD, MA, Pellegrino Center for Clinical Bioethics, Georgetown University, 4000 Reservoir Rd NW, Bldg D #236, Washington, DC 20007, USA.
Email: donovangk@georgetown.edu

argue that there is a link to a succession of present-day actions and behaviors that begins with something small, a contraceptive pill. Temporally, this was juxtaposed to a reworking of the meaning of liberty and happiness that our founding fathers had introduced under the influence of the Enlightenment philosophies but led to a much different activity than they would have envisioned. These behaviors and these actions would have been labeled in previous generations as sins by a majority of our fellow Americans. This can be seen as entirely in keeping with our own church teaching.

Moral Challenges of the Notion of "Liberty and the Pursuit of Happiness" in Today's Context

From the perspective of the Catechism of the Catholic Church (1999, n.1849), sin is seen as "an offense against reason, truth and right conscience . . . love of oneself, even to contempt of God." It is, as it always has been, a preference for our own desires, or our own will, over that of God. There are indeed great many kinds of sin; Scripture provides several lists of them. The letter to the Galatians contrasts the works of the flesh with the fruit of the spirit: "Now the works of the flesh are plain: fornication, impurity, licentiousness . . . selfishness, drunkenness, carousing, and the like" (5 Galatians, 19:21). To most, this would seem like an unequivocal listing of things to avoid, even if they have never been completely avoided throughout history. To some today, it might also look like the unapologetic agenda for many people's weekend. Things seen in the past as moral failings are increasingly practiced openly, even celebrated in contemporary culture. This is where our moral fault lines begin. As a society, we have become increasingly more tolerant—tolerant of contraception, sexual promiscuity, pornography, oral and anal sex, both for heterosexual as well as homosexual couples, and as a consequence, same-sex marriage. Of course, the field of bioethics has matched these issues with moral challenges of its own: abortion, embryo destruction for research, transgender surgeries, physician-assisted suicide, and euthanasia. Although exploring the morality of each of these is beyond our scope, we can look at a few of them as exemplars. If we can identify a common theme that unites them, we may be able to perceive a common explanation for our present predicament. Perhaps this can be identified in those who intended to found our society and its culture on twin pillars of *liberty* and *the pursuit of happiness*.

A contemporary concept for the pursuit of happiness could be defined as "freedom for self-actualization." This was famously stated in a form that pushes the limits of credulity, by Supreme Court Justice Anthony Kennedy: "At the heart of liberty is the right to define one's concept of existence, of meaning, of the universe, and of the mystery of human life" (Planned Parenthood v. Casey 1992, p. 833). The egotism of this stark assertion of the independence of an individual's values from outside moral influences could be traced to the individual rights language of philosophers such as John Locke that was echoed in the Declaration of Independence. Other philosophers, such as Mill (2011) and Comte (1817), emphasized the concept that the only real freedom is to pursue our own good as long as we do not harm others. Old virtues could be swept away in favor of the new, especially that foundational virtue, tolerance. The *liberty* to pursue one's will should then lead to ever-expanding personal *happiness*. In a secular morality, the sin does not disappear, it just gets redefined, but it is actually a tightly constrained freedom, limited to only certain acceptable choices. The tolerance being advocated finds its limits here. Wrong choices don't just threaten the new social order; they signal a problem with the chooser who clearly must be disordered. Those who would oppose the prevalent secular values cannot be considered as merely being in principled opposition. They must be seen as mentally deranged and labeled with a corresponding phobia. An individual can no longer express a principled opposition to homosexual behavior; the only acceptable interpretation of such a position is that it represents an irrational fear of homosexual persons, a homophobia. Such a viewpoint is immediately discounted as impermissible, without further consideration or discussion. Tolerance is thus a one-way street and a narrow one at that.

Such a moral shift has implications for how we live our lives and what we find acceptable or unacceptable. Right and wrong become subjective interpretations, not standards, and are entirely based on personal feelings. One should be free to pursue whatever makes one happy, as long as one doesn't hurt anyone. The fundamentally American pursuit of happiness leads to a moral practice motivated by a form of narcissism, which some studies have shown as the hallmark of this generation of millennials (Stinson, Dawson, and Grant 2008). External authority, particularly moral authority, is largely rejected in favor of the authority of the autonomous self. The primary goal is to seek happiness in order to feel good.

Consequences of the Pill

Mankind's original sin was one of ego, of pride, of wanting to be one's own God. This resulted in grasping a forbidden fruit, with all its deadly consequences. The present generations also want to define their own knowledge of good and evil, but the focal point of sinful rebellion is not a contraband apple, but a contraceptive pill. We argue that the taking of the contraceptive pill, to avoid fruitfulness, has led to as many of the subsequent dire consequences as did the original fruit.

For some, this may be seen as too bizarre, too extreme, proposing a culprit that is too tangential to the more serious transgressions of the modern age. Most millennials and even their parents cannot remember the time when contraception wasn't seen by society as a positive good from which many blessings flow. It is understood as a given that regulation of the timing and number of children in a marriage allows women to pursue careers outside the home and allows unmarried women to prevent having their lives ruined by unexpected and unwanted pregnancies. We can even reassure ourselves that we are limiting excessive growth of world population and helping to save the planet. Given these apparently obvious benefits, many young adults would be surprised if not shocked to find that contraception was not always viewed in this favorable light. Throughout the ages, various attempts at contraception focused on condoms, pessaries, herbals, and coitus interruptus. Although Christian churches traditionally discouraged these, the low level of controversy about their use reflected their low level of effectiveness. Even when feminists in the 1870s argued for "voluntary motherhood" in their desire for women's emancipation, they disapproved of contraception, arguing instead for periodic abstinence, and engaging in sex only for purposes of procreation! (Gordon 2002). In America, the Comstock Act of 1870 made it a federal offense to distribute contraceptives, abortifacients, sex toys and erotica, or information regarding them. Note how the use of contraceptives was linked to the use of erotica and sex toys and other "obscenities" of that time. Both later became closely linked with support for abortion—more about that link later. After the turn of the century, a free love movement arose in opposition, spearheaded by Margaret Sanger in the United States and Marie Stopes in England. Both advocated birth control to liberate women and to decrease overall population, especially of the poor and "inferior" races (Sanger 1919). The Anglican Lambeth Conference of 1930 made them the first major Christian church to break ranks in the opposition to contraception, but many more "mainline" Protestant denominations eventually followed. What is little noted is that the previous Lambeth conference had strongly rejected this position, considering contraception "hostile to the family." Instead, they had emphasized the purposes of marriage to be the begetting of children and "deliberate and thoughtful self-control" (Gore 1930).

This controversy did not effectively explode until effective contraception in the form of a hormone pill became available. In 1957, a hormonal pill was approved by the US Food and Drug Administration for serious menstrual disorders, and by 1960, it was approved as a contraceptive. Even then there were problems including some serious side effects (Nikolev 2010) and resistance by African American activists who charged Planned Parenthood with genocidal intent by pushing it in their neighborhoods. The "pill" has since been joined by a variety of implantable hormonal devices and adjuncts to diaphragms.

When a study of contraception was completed by the Catholic Church, an encyclical letter, *Humanae Vitae*, was issued by Pope Paul VI in 1968. While supporting the concept of birth control, insofar as it applies to the desire or need to space or limit the number of children born to a married couple, it insisted that each marital act must remain "open" to both unitive love and possible procreation. It rejected artificial interference in the latter, including artificial hormonal contraception. A moral decision to limit conception would have to be in accord with natural law, precluding both hormonal drugs and other barriers including sterilization. Of course, abortion also remained unacceptable. Taking advantage of the natural rhythms to both conceive, and to prevent conception, was still seen as morally licit. Humanae Vitae challenged the ideas of "free love" and "sexual liberation" by promoting marital love, chastity, and openness to life. In this Encyclical, social issues such as infidelity, the degradation of morality, the loss of sight of what is right and wrong regarding sexual behavior, and the political uses of contraceptives are foreseen (Klaus 2018). The Pope finished by stating "not everyone will easily accept what has been said."

Only the last statement found a common point of agreement. A storm of controversy ensued from laypersons as well as many clergyman and theologians (Harris 1968). It was rejected by many Catholics "in the pews" who were supported by some of their pastors and teachers. The consequences have been far ranging, with some self-identified Catholics feeling that they should also be able to pick and choose

which other moral teachings of the church they will accept. In a recent study of Catholic college students, not only do a large majority use contraception, but 57 percent support abortion, 71 percent homosexual marriage, and 49 percent casual sex (Gray and Cicade 2010). These discrepancies between what the church teaches as morally acceptable compared to what contemporary Catholics practice are not a random assortment of issues. They flow from one to another, with their own internal logical consistency and their own cultural constituency. Less obvious is the fact that contraception can be seen as the linchpin. The contraceptive pill had become the "sine qua non" of the sexual revolution of the 1960s and 1970s. Cultural attitudes of the time were packed with generational conflict, rebellion toward authority, an unpopular war, and the early onset of radical feminism and the drug culture. The keg was already primed, but it took the pill to light the fuse. The youth of America declared, "If it feels good, do it." Freedom and the pursuit of happiness were taking a sharp turn, but were still on the same road begun by our founding fathers, and subsequently endorsed by Justice Kennedy. It was no surprise that few things fit the "feel good" category better than sex. The pill gave us the ability to indulge ourselves without fear of the consequences. If two people want to do this, who should be able to tell them no, especially if no one gets hurt?

In order to fully examine the myth of sex without harm, we must trace out some of the obvious and inevitable consequences. Because the pill separates sex for pleasure from sex for procreation, young women are expected to be able to exercise their liberty to pursue such happiness. When in the past, they could avoid a decision to relinquish their virginity and shun sexual activity due to a very real fear of pregnancy, any preference for chastity now had no automatic justification or irrefutable argument. The free love of the Boomer generation devolved into the hookup culture of the Gen X and millennials. The pill first separated sex from pregnancy; it now separates sex from love, at least a true and committed love. Sex is sought as something for one's own pleasure or, at best, reciprocal pleasure. Denying one's own pleasure is to deny one's own happiness. The possibility of sexual activity becomes the expectation of sexual activity, with the bar set lower and lower. No longer is the quaint question of kissing on the first date an issue; young women can claim it as a sign of their integrity if they withhold sex until a second or third date, or even later. Dating more than one person at a time with these new expectations of presumptive sexual activity makes a young man apparently a "player" or a young girl presumably promiscuous. This dilemma is eclipsed by forgoing all these quaint rules in order to seek hookups, where nearly complete strangers can couple for pleasure without any supposed emotional involvement, and no supposed harm done. Because these occasions usually arise at parties where large amounts of alcohol are consumed, the only harm to be feared appears to be sex without consent. As a consequence, rather than discouraging the hookups, or the alcohol use that leads to it, college campuses have devised elaborate protocols to assure that consent has occurred ("Code of Student Conduct" 2018–2019). Occasionally, egregious violations are publicized and condemned (Stanford Rape Case 2016). Mostly they are not recognized as such or not investigated (Maloney 2016). The ones who suffer the most are often the young women that the pill was supposed to liberate and make happy.

Clearly, the pill does not solve all the problems that flow from increased sexual activity. While it may prevent pregnancy, there are other consequences from which the pill cannot provide protection. Most obvious, sexually transmitted infections (STIs) have concomitantly taken a sharp upturn in recent years. Antibiotic-resistant infections are an increasing danger, as are viral illnesses such as herpes and genital warts, and chlamydia, for which treatments are imperfect and consequences (such as infertility or chronic HIV) can be devastating. Teenagers make up one-third of the United States population but carry 50 percent of STIs. Depression related to loveless and perfunctory teen sex can also be as devastating as any STI (Meeker 2017). Although teen birth rates and abortion have declined over this time, it is due more to a trend away from condom use toward hormonal birth control. As we have seen, hormonal birth control does not lead to avoidance of sexual activity or avoidance of STIs (Green 2016).

Although the increased sexual activity encouraged by the availability of the pill could lead to significant collateral damage, at least it wasn't supposed to lead to pregnancy. Used with perfect compliance, it is an effective contraceptive in more than 90 percent to 95 percent of cases. Unfortunately, we live in an imperfect world with imperfect people, and unintended pregnancies do occur. The cultural response to this unavoidable fact took two directions. One can indulge in nonprocreative sex, anal or oral, or one can seek an abortion for those

who adamantly refused to accept the results of potentially procreative sex. The former was seen as aberrant and even repugnant in previous generations, particularly by females. However, it became more common after President Clinton finally and publicly admitted his own "nongenital" activity with a young White House intern. He justified his previous denials by asserting that because it wasn't mutually genital, it wasn't really sex (Sanders and Reinisch 1999). This led to numbers of high school girls claiming "technical virginity" while acceding to similar demands from their male companions. This change in sexual practice among heterosexual couples led inevitably to a more tolerant attitude toward those for whom nongenital or nonprocreative sex was the preferred or only option. Negative attitudes toward homosexual activity weakened, in part, because it could be seen that they were only practicing what many heterosexuals were also doing, and how could that then be construed as bad or unnatural?

When homosexuality became more acceptable as an "alternate lifestyle," then the twin principles of toleration and pursuit of pleasure would dictate that related issues should be made culturally acceptable as well. These issues included homosexual marriage, transgender conversion surgeries, and a myriad of bathroom issues and controversies. If we cannot condemn those who merely do what we sometimes do, should we not support them for being like ourselves?

Those who followed the other path and became pregnant despite their use of the pill would not accept such an intolerable consequence. The increased demand for abortion became inevitable for those who felt betrayed by the failure of their contraceptive. Indeed 60 percent of abortions are sought by those who were using contraception at the time they became pregnant (Furendi 2017; British Pregnancy Advisory Service 2017). When your cultural norm assures you that no pregnancy should ever be unintended, then some reliable backup for failed contraception will be seen as both a necessity and a right. **This is the inevitable linkage: a contraceptive culture *requires* a concomitant culture of abortion on demand**. An unrestricted commitment to liberty and the pursuit of happiness has its price. This price is the embryo or fetus. As a result, the field of bioethics has had a hard time objecting to embryo experimentation, genetic manipulation, or any creation or destruction of embryos. If it is acceptable to destroy an embryo by a woman in the pursuit of happiness, it is difficult to deny the liberty to pursue its destruction in the pursuit of science.

Final Remarks

While the chief remaining argument against contraception in our culture has been theological, we have eschewed that approach for the sociological. There appear to be a long list of actions and behaviors that might be considered objectionable or sinful by many who would have *no* objection to the use of contraception. Yet, without making a direct religious objection to the pill and other contraceptives, it can be seen that these behaviors that might be termed sinful can be directly linked to the use of contraception in our culture. Fehring, Bouchard, and Meyers (2018) showed additional correlations between contraceptive use in adolescents and negative sexual outcomes. There are additional arguments that can be made against it, including the deleterious effects of cohabitation on the subsequent marriage and divorce rate, the contamination of the water supply by hormonal drugs, and declining fertility rates. Moreover, some of the most challenging and troublesome ethical questions for Catholic physicians in the current age, such as assisted suicide, euthanasia, and restriction of nutrition/hydration leading to a patient's death, all would seem to have a tenuous connection to the contraception–abortion continuum. However, a cheapening of life, and diminishing respect for life in general, is the necessary substrate for these other attitudes and developments. Their justification often depends on similar arguments based on maximizing liberty and happiness. It appears to be no accident that the most ardent supporters of assisted suicide are frequently ardently pro-choice at the other end of the life continuum as well. These considerations are worthy of exploration but also are beyond the scope of this article. What was intended was to recognize a link to a succession of actions and behaviors that begins with the use of contraception. Contraception is seen by its proponents as justified and necessary when procreative sex is severed from sex for pleasure. Seeking unencumbered sexual pleasure is justified by a misunderstood or misapplied sense of liberty and pursuit of happiness. I do not believe the founding fathers would recognize what we have done with their self-evident truths.

If our modern moral morass and overemphasis on individual rights can be interpreted as a devolution from the founding fathers' principles, perhaps a reinterpretation of their intent may suggest a way out. This interpretation would need to rely on a strong justification for the respect shown to individual liberty. Such a justification could be construed from natural law arguments, buttressed by a Christian concept of the value of the individual. Natural rights and basic human equality are most strongly supported by a

Christian justification, as seen in the belief that all individuals have inherent dignity and value. This value and dignity are found in the individual's status as God's beloved creation, as a child of God made in his image and likeness. When the emphasis on the rights and liberty of the individual is once again linked to this religious principle, rather than enlightenment perspectives, not only are the rights of liberty and pursuit of happiness strengthened, they are appropriately redirected. A more profound understanding of happiness then points us away from shallower material and sexual pleasures to deeper and more satisfying metaphysical ones. Thus, those practices that we examined previously would be superseded by those fostered through the practice of continence, self-discipline, charity toward others, and a true understanding of purity. As Chaput (2017) recently put it,

> Given the hyper sexualized nature of today's culture, when we think of purity, we usually think of sexual purity. And thinking of purity, we typically focus on abstinence. So purity somehow transforms into not experiencing a thing we want to experience. This is a distortion. Purity is about wholeness or integrity. It means that the body, mind, heart, and soul are rightly ordered toward God. Every element of who we are is doing its part to bring us to union with God, which is our ultimate happiness. Given the strength of the sexual desires we all feel, rightly acting on those desires is a key part of maintaining purity. For single people and celibates, it means offering those desires up to God and seeking to channel them in our love and service for others. (p. 126)

Finally, if we accept this chain of events and its consequences, where does that leave us as physicians? We may have started with the comfortable assumption that we can practice our profession and our faith, fully assimilated into modern American culture and society. Increasingly, we have come to realize an age-old truth: to be a Catholic Christian is by nature to be countercultural. Christ did not come to help us assimilate into the world but to help us to seek a better one together. Faced with this, what can we do for our patients and what can we do for ourselves? For our patients, there are measures that can be taken, some simple, some daunting. Can we imagine rejecting the assumption that all our young unmarried patients are sexually active or intend to be? Patients rely on their physicians for contraceptive advice, as well as for referrals for abortion, and instructions in safe sex, the condom cautionary, and so on. How much more time will it take to try to warn them of the adverse effects of a sexually libertine lifestyle, just as we try to warn them against smoking? It might seem to be an impossible task to find ourselves in opposition to a pervasive culture that no longer respects our values. It might seem like trying to empty the ocean with a thimble. But let me remind you of another oceanside parable: after a major storm, when hundreds of starfish were washed up on the beach, a little boy walked along throwing them back into the water before they were fried by the sun. An older man told him to forget about it, the task was too great, he couldn't make a difference. The boy replied, as he threw it back into the water, "Well, it will make a difference to this one." Perhaps developing a one-on-one relationship with our patients has always been the only chance of making a difference for the practitioner as well as for the patient and parents. And in attempting to do this for our patients, for as many patients as possible who are willing to accept it, we are doing something more. We are doing something for ourselves, for the maintenance of our own values, for the strengthening of our own moral character and virtues, and for the preservation of what we find best in our profession. This understanding, this approach, would seem more in keeping with the founding fathers' original intent, who did not appear to seek separation of individual liberty from its Christian foundation or our true happiness.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

G. Kevin Donovan, MD, MA https://orcid.org/0000-0002-6115-7840

References

BPAS (British Pregnancy Advisory Center). 2017. *Women Cannot Control Fertility through Contraception Alone: BPAS Data Shows 1 in 4 Women Having an Abortion Were Using Most Effective Contraception*. https://www.bpas.org/about-our-charity/press-office/press-releases/women-cannot-control-fertility-through-contraception-alone-bpas-data-shows-1-in-4-women-having-an-abortion-were-using-most-effective-contraception/.

Chapman, G. 1999. "Sin. Catechism of the Catholic Church (CCC)." Part Three, Section 1, Chapter 1, Article 8.

Chaput, C. 2017. *Strangers in a Strange Land*. New York: Henry Holt.

Comte, C. 1817. *Du nouveau projet de loi sur la presse*. Paris, France: Au Bureau du Censeur européen.

Code of Student Conduct, Sexual Misconduct Policies and Procedures. 2018–2019. Georgetown University, Section VI, C3, 9–10.

Fehring, R., T. Bouchard, and M. Meyers. 2018. "Influence of Contraception Use on the Reproductive Health of Adolescents and Young Adults." *The Linacre Quarterly* 85:167–77. doi: 10.1177/0024363918770462.

Furendi, A. 2017, July 7. "Women Seeking Abortion after Failed Contraception." *British Pregnancy Advisory Service*.

Gordon, L. 2002. *The Moral Property of Women: A History of Birth Control Politics in America*. University of Illinois press, 55–57.

Gore, C. 1930. *Lambeth on Contraceptives*. London, UK: Mombay.

Gray, M., and M. Cicade. 2010. CARA Report: Catholicism on Campus. *Catholic Education: A Journal of Inquiry and Practice* 14:212–237.

Green, E. 2016. "Condoms Don't Necessarily Help Teen Girls Avoid Pregnancy." *The Atlantic* 46–49.

Harris, P. 1968. *On Humanae Vitae: An Examination of Humanae Vitae*. London, UK: Burns and Oatos.

Klaus, H. 2018. "Rejecting Humanae Vitae: The Social Costs of Denying the Obvious." *The Linacre Quarterly* 85:322–26. doi: 10.1177/0024363918817319.

Maloney, A. 2016. "What the Hookup Culture has Done to Women. *Crisis Magazine* June 14.

Meeker, M. 2017, May 31. Teenagers and the STD Nobody is Talking about. *Blog Entry*.

Mill, J. 2011. *On Liberty*. Bedfordshire, UK: Andrews U.K.

Nikolev, A. 2010. "A Brief History of the Birth Control Pill." *Need to Know*. https://www.pbs.org/wnet/need-to-know/health/a-brief-history-of-the-birth-control-pill/480/.

Pope Paul IV. 1968. *On the Regulation of Birth = Humanae Vitae: Encyclical Letter*. Washington, DC: United States Catholic Conference.

Sanders, S. A., and J. M. Reinisch. 1999. "Would You Say You "Had Sex" If . . . ?" *Journal of the American Medical Association* 281:275–77.

Sanger, M. 1919. "Birth Control and Racial Betterment." In *Society for Constructive Birth Control and Racial Progress, edited by M.* Stopes.

Stanford Rape Case: Inside the Court Documents 2016, June 11, CNN. http://cnn.com/2016/06/10/us/Stanford-rape-case-court-documents/Index.html.

Stinson, F., D. Dawson, and B. Grant. 2008. "Prevalence, Correlates, Disability, and Comorbidity of DSM-IV Narcissistic Personality Disorder: Results from the Wave 2 National Epidemiologic Survey on Alcohol and Related Conditions." *Primary Care Companion to the Journal of Clinical Psychiatry* 69:1033–45.

US Supreme Court. 1992. *Planned Parenthood vs. Casey*.-West Supreme Court Report, vol. 112, 2791–885.

Biographical Notes

G. Kevin Donovan, MD, MA, is the Director of the Pellegrino Center for Clinical Bioethics at Georgetown University Medical School and a professor in the Department of Pediatrics. He is a clinician ethicist with over thirty years experience in the field. He began his training as a visiting scholar with Dr. Edmund Pellegrino at the Kennedy Institute of Ethics of Georgetown University in 1989–1990. It was during this time that he began his studies that led to his earning a master's degree in bioethics from University of Oklahoma. At the request of Dr. Pellegrino, he returned to Georgetown in 2012, as director of the Pellegrino Center. Prior to his return to Georgetown, he had served as section chief, vice chair, interim chair, and professor of pediatrics at the University of Oklahoma College of Medicine—Tulsa, where he was the founding director of the Oklahoma Bioethics Center. He received his undergraduate degree from Notre Dame, his MD from the University of Oklahoma, and his master's in bioethics. He trained in pediatrics at Baylor College of Medicine, completed fellowships in pediatric gastroenterology at the Children's Hospital of Oklahoma and the NIH in Bethesda, Maryland, and is board certified in pediatric gastroenterology. He completed a three-year term as chair of the bioethics section of the American Academy of Pediatrics and was appointed as the first person to serve as liaison from the bioethics section to the Committee on Bioethics of the AAP. He also served on the bioethics committee for the North American Society for pediatric gastroenterology, hepatology, and nutrition, the ethics committee of the Oklahoma State Medical Association and was medical ethics consultant to the Roman Catholic Diocese of Tulsa. He served on the local board of directors for the organ sharing network, the Genetics Advisory Council, and was a founding member and first vice president of the Oklahoma Association for Healthcare Ethics. He also served as chair of the Institutional Review Board at St. Francis Hospital for seventeen years. He has published articles on both pediatrics and bioethics and has spoken extensively on both subjects at the local, national, and international level on four continents.

Claudia Sotomayor, MD, DBe, currently works as clinical ethicist at the Pellegrino Center for Clinical Bioethics and adjunct assistant professor of internal medicine of GUMC. She holds an MD from Universidad Autonoma de Chihuahua in Chihuahua, Mexico. She also graduated with a master's degree in bioethics from Anahuac University in Mexico City, and she graduated with a Doctorate in bioethics from Loyola University in Chicago, Illinois. She also completed a fellowship in clinical bioethics at MD Anderson Cancer Center in Houston, Texas. She has been a research scholar for UNESCO chair in bioethics and human rights since 2012 where she has worked in the area of multiculturalism, bioethics, and religion. She has also served as a member of the Ethics Committee in different hospitals in the United States. Before coming to the United States, she worked in different hospitals in Mexico as a primary care physician and was the health committee coordinator for FUNDESPEN, a nonprofit that provides medical care to Mayan communities in rural areas of Quintana Roo, Mexico.

EXHIBIT 20

AMA *Code of Medical Ethics*

2.1.1 Informed Consent

Informed consent to medical treatment is fundamental in both ethics and law. Patients have the right to receive information and ask questions about recommended treatments so that they can make well-considered decisions about care. Successful communication in the patient-physician relationship fosters trust and supports shared decision making.

The process of informed consent occurs when communication between a patient and physician results in the patient's authorization or agreement to undergo a specific medical intervention. In seeking a patient's informed consent (or the consent of the patient's surrogate if the patient lacks decision-making capacity or declines to participate in making decisions), physicians should:

(a) Assess the patient's ability to understand relevant medical information and the implications of treatment alternatives and to make an independent, voluntary decision.

(b) Present relevant information accurately and sensitively, in keeping with the patient's preferences for receiving medical information. The physician should include information about:

  (i) the diagnosis (when known);

  (ii) the nature and purpose of recommended interventions;

  (iii) the burdens, risks, and expected benefits of all options, including forgoing treatment.

(c) Document the informed consent conversation and the patient's (or surrogate's) decision in the medical record in some manner. When the patient/surrogate has provided specific written consent, the consent form should be included in the record.

In emergencies, when a decision must be made urgently, the patient is not able to participate in decision making, and the patient's surrogate is not available, physicians may initiate treatment without prior informed consent. In such situations, the physician should inform the patient/surrogate at the earliest opportunity and obtain consent for ongoing treatment in keeping with these guidelines.

AMA Principles of Medical Ethics: I,II,V,VIII

EXHIBIT 21

INTERNATIONAL JOURNAL OF UROLOGY

International Journal of Urology (2020) 27, 39–46 doi: 10.1111/iju.14111

Review Article

Effect of antidepressant medications on semen parameters and male fertility

Lauren A Beeder[1] and Mary K Samplaski[2]

[1]Keck School of Medicine, and [2]Institute of Urology, University of Southern California, Los Angeles, California, USA

Abbreviations & Acronyms
BMI = body mass index
FSH = follicle-stimulating hormone
LH = luteinizing hormone
MAOI = monoamine oxidase inhibitor
NDRI = norepinephrine–dopamine reuptake inhibitor
SNRI = serotonin–norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
TCA = tricyclic antidepressant
TUNEL = transferase dUTP nick end labeling

Correspondence: Lauren A Beeder M.D., Keck School of Medicine, University of Southern California, 1975 Zonal Avenue, Los Angeles, CA 90033, USA. Email: beeder@usc.edu

Received 23 April 2019; accepted 25 August 2019. Online publication 21 September 2019

Abstract: Antidepressant medications are commonly used in males of reproductive age for long-term treatment of depression, as well as other disorders. Although antidepressants are known to be associated with sexual side-effects, their effects on semen parameters and other markers of male fertility have been less thoroughly described. The majority of available studies have focused on selective serotonin reuptake inhibitors, which have been shown to negatively impact semen quality in *in vitro*, animal and human studies. Fluoxetine, in particular, has been the subject of multiple studies and has been associated with gonadotoxic effects, including decreased sperm concentration and motility, increased deoxyribonucleic acid fragmentation, and decreased reproductive organ weights. Studies of several other selective serotonin reuptake inhibitors have yielded similar results. Reassuringly, this effect does seem to be reversible. The data regarding serotonin–norepinephrine reuptake inhibitors, norepinephrine–dopamine reuptake inhibitors, tricyclic antidepressants, monoamine oxidase inhibitors and atypical antidepressants are sparse, varied and conflicting. Given the widespread and often long-term use of antidepressant medications, there is a clear need for further data regarding their impact on semen quality and male fertility.

Key words: antidepressant, effects, male infertility, medications, semen.

Introduction

Antidepressants are one of the most commonly used therapeutic drug classes in the USA. While the majority of these medications are taken to treat depression, antidepressants can also be taken to treat other conditions, such as anxiety disorders. The major classes of these are SSRIs, SNRIs, NDRIs, TCAs, MAOIs and atypical antidepressants. Each of these have slightly different mechanisms of action, and therefore can affect sperm in different ways.

According to the National Health and Nutrition Examination Survey, 8.6% of males between the ages of 12 and 18 in the USA took antidepressants between 2011 and 2014.[1] The number of people taking these medications has increased nearly 65% over a 15-year time frame, from 7.7% in 1999–2002 to 12.7% in 2011–2014. Although females are more likely to use these mediations, males have shown a parallel rise in their antidepressant use. Antidepressant use increases with age, from 3.4% among persons aged 12–19 years to 19.1% among persons aged ≥60 years. In addition, these medications are typically taken long term, and between 2011 and 2014, 68.0% of persons aged ≥12 years who took antidepressant medications had been taking these for ≥2 years, and 25% had been taking them for ≥10 years.

There is limited information on the frequency of antidepressant use globally. The Organization for Economic Co-operation and Development has examined this to some degree. Countries with the highest rates of antidepressant use are the USA (110 per 1000 people), Iceland (106 per 1000 people), Australia (89 per 1000 people), Canada (86 per 1000 people) and Denmark (85 per 1000 people). Countries with the lowest reported antidepressant use are Korea (13 per 1000 people), Chile (13 per 1000 people), Estonia (18 per 1000 people), Hungary (27 per 1000 people) and the Slovak Republic (31 per 1000 people).[2] For Japan specifically, although large epidemiological studies are lacking, it is estimated that up to 6 million Japanese suffer from depression, similar to that seen in Western countries.[3]

All classes of antidepressants are known to be associated with some degree of sexual dysfunction in both men and women. In men, the most notable sexual side-effects can include impaired libido, erectile dysfunction, delayed ejaculation or anejaculation. The effects of

© 2019 The Japanese Urological Association

antidepressant medications on semen parameters have been less thoroughly studied, although data do exist for some of the medications in each of the classes of antidepressants. We review all available data (*in vitro*, animal and human studies) regarding the use of antidepressants on semen parameters and male fertility (Table 1).

SSRIs

SSRIs act by inhibiting the reuptake of serotonin, and include citalopram, escitalopram, fluvoxamine, paroxetine, fluoxetine and sertraline. These medications are currently considered first line for the treatment of depression and anxiety disorders. However, SSRIs in particular are known to be associated with significant sexual side-effects, including decreased libido, increased ejaculation latency, alteration of circulating hormones and erectile dyfunction.[4,5] Studies estimate that 25–73% of people treated with an SSRI will experience some type of sexual dysfunction, higher than that of other antidepressants.[4] Studies looking at the impact of these medications on male reproduction and semen parameters are not as robust, but there are some available data. This is the class of antidepressants with the most available data for their effects on semen parameters and male fertility (Table 2).

In vitro studies

There is a single *in vitro* study investigating SSRIs and human sperm. Kumar *et al*. incubated human semen with varying doses of paroxetine, fluoxetine, sertraline, citalopram and fluvoxamine *in vitro*. All SSRIs showed some degree of spermicidal activity, whereas serotonin showed no negative effect on sperm counts. Fluoxetine, which showed the highest spermicidal activity, had a minimal effective concentration comparable to nonoxynol-9, a contraceptive utilized for its spermicidal properties.[6]

Animal studies

Multiple studies carried out in animal models have shown the negative effects of SSRIs on male fertility. Most studies of SSRIs are on fluoxetine, and most do show some degree of gonadotoxic effect. Male rats treated with oral fluoxetine for 60 days were found to have decreased spermatogenesis on histology, as well as significantly decreased sperm density and motility. Treated male rats also had decreased pregnancy and implantation rates with untreated female rats, and had decreased reproductive organ weights, including testes, epididymes, prostates and seminal vesicles.[7] A similar study of rats treated with varying doses of oral fluoxetine for 5 days found a dose-dependent decrease in sperm counts and motility in rats exposed to fluoxetine. At the highest dose (13 mg/kg), sperm count and motility were fourfold less that that observed in controls.[8] Long-term administration of fluvoxamine has also been shown to negatively affect semen parameters, and induce oxidative stress and apoptosis in the testes of rats, which were treated with both low therapeutic doses (9 mg/kg) and high therapeutic doses (27 mg/kg) for 8 weeks.[9] Oxidative stress might mediate and enhance the negative impact that these drugs seem to have on semen parameters. Rats exposed to chronic unpredictable mild stress showed signs of oxidative stress, including increased levels of malondialdehyde and corticosterone, and decreased anti-oxidants, sperm count and motility. These effects were exaggerated in animals treated with

Table 1 Studies carried out on different antidepressant classes

Antidepressant class	*In vitro* studies	Case studies	Animal studies	Human studies
SSRIs	Kumar *et al*.[6]	–	Bataineh and Daradka[7] Alzahrani[8] Galal *et al*.[9] Sakr *et al*.[10] Atli *et al*.[11] Attia and Bakheet[12] Ilgin *et al*.[13] Ayala *et al*.[14] Vieira *et al*.[15]	Tanrikut and Schlegel[16] Elnazer and Baldwin[18] Tanrikut *et al*.[19] Akasheh *et al*.[20] Koyuncu *et al*.[21] Safarinejad[22] Relwani *et al*.[23]
SNRIs	Bandegi *et al*.[24]	–	Bandegi *et al*.[24]	–
NDRIs	–	–	Urra *et al*.[25] Cavariani *et al*.[26] Fazelipour *et al*.[28] Cansu *et al*.[29] Adriani *et al*.[30] Bellentani *et al*.[31]	–
TCAs	Levin *et al*.[32]	–	Bandegi *et al*.[24] Chowdary and Rao[34] Hassanane *et al*.[35]	Levin *et al*.[32] Padrón and Nodarse[33]
MAOIs	–	–	Kalász *et al*.[36] Mihalik *et al*.[37]	–
Atypical antidepressants	Cassidy and Pearson[39]	Elnazer and Baldwin[18]	Ilgin *et al*.[38] El-Sisi *et al*.[40]	–

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2 SSRI effects on semen and other fertility parameters

Drug	*In vivo* effects on semen parameters	Other effects on fertility
SSRIs		
Fluoxetine	*Rats:* Decreased spermatogenesis, sperm density and motility	*Rats:* Decreased pregnancy and implantation rates, decreased reproductive organ weight
Fluvoxamine	*Rats:* Decreased sperm concentration and motility, increased abnormal forms	*Rats:* Oxidative stress and apoptosis in testes, decreased FSH, LH, testosterone and estrogen
Sertraline	*Human case study:* Decreased sperm concentration and motility *Human prospective:* Decreased sperm count, increased abnormal morphology and DNA fragmentation *Rats:* Increased DNA damage and abnormal forms, decreased sperm count	*Rats:* Testicular degeneration, oxidative stress
Citalopram	*Human case study:* Decreased sperm count and motility, increased abnormal morphology *Rats:* Increased DNA strand breaks and oxidative damage, increased abnormal forms	*Rats:* Decreased seminal vesicle mass, decreased volume of seminiferous tubules
Paroxetine	*Human prospective:* Increase in DNA fragmentation	–
Escitalopram	*Human prospective:* Decreased sperm concentration and motility, increased abnormal morphology	–

fluoxetine (10 mg/kg/day for 28 days), and mitigated in groups treated with either resveratrol (20 mg/kg/day for 28 days) or fluoxetine plus resveratrol.[10]

One study examined the effects of sertraline on the reproductive system of rats treated with 5, 10 or 20 mg/kg for 4 weeks. There was a dose-dependent increase in DNA damage (measured using the Comet assay), testicular degeneration and abnormal sperm forms, as well as a decrease in sperm count in treated animals. Decreased levels of glutathione and increased levels of malondialdehyde suggested oxidative stress as a main mechanism for the testicular toxicity observed.[11]

Citalopram has also been shown to exert toxic effects on sperm and testicles, largely through oxidative stress. Attia and Bakheet saw a dose- and duration-dependent increase in DNA strand breaks, oxidative DNA damage, and abnormal primary spermatocytes in male rats treated with citalopram.[12] A study by Ilgin *et al*. found similar results, with citalopram-administered rats showing reduced sperm counts, increased abnormal sperm morphology and increased DNA damage.[13]

These drugs might affect pre- and postpubertal animals differently, and a study examining pre- and postpubertal rats treated with fluoxetine for 30–53 days found that these two populations had different responses. Although all animals had a decrease in LH, FSH, progesterone and testosterone, prepubertal rats were more likely to show decreased sperm membrane integrity, density, motility and morphology versus their adult counterparts.[14] This might have implications for males taking these medications beginning at young ages.

Maternal use of SSRIs during pregnancy and lactation might also impact semen quality in male offspring. Rat offspring exposed to fluoxetine *in utero* and while nursing have been shown to have decreased seminal vesicle mass and sperm counts, as well as reduced height and diameter of seminiferous tubules.[15]

Human studies

Human data consistently support an association between male infertility (semen parameters and sperm DNA fragmentation) and SSRI use. In 2007, Tanrikut and Schlegel described cases of oligospermia, impaired motility and abnormal morphology in two patients taking SSRIs for depression. The first patient presented on citalopram with "marked oligospermia and 1% motility." Semen analysis 1 month after citalopram discontinuation showed a marked improvement in all parameters to within the normal range. Bupropion was started for depression shortly thereafter, and a semen analysis while on bupropion again showed a decrease in sperm concentration to 21 million/mL with 10% motility. After two failed *in vitro* fertilization attempts, the patient was reassessed (still on bupropion). His DNA fragmentation (tested by the sperm chromatin structural assay) was 76%. He was weaned from the bupropion and his follow-up semen analysis 1 month after bupropion discontinuation showed a normal sperm concentration of 41 million/mL with 75% motility. A second semen analysis carried out 2 months after bupropion discontinuation showed normal sperm concentration and motility. A similar pattern (impaired semen parameters on sertraline [sperm concentration of 20 000 with 0% motility]), with dramatic improvement after SSRI discontinuation (3 months after discontinuation 40 million motile sperm) was seen for the second patient described taking sertraline.[16] Human spermatogenesis takes 72 days, and therefore this marked improvement within weeks of antidepressant discontinuation suggests that SSRIs might exert their effects on post-testicular processes rather than spermatogenesis itself.[17] Similarly, Elnazer and Baldwin described a patient with markedly improved sperm concentration, progressive motility and morphology after discontinuation of citalopram.[18]

In a subsequent prospective study, Tanrikut *et al*. examined the effects of paroxetine on semen parameters and DNA fragmentation in 35 healthy male volunteers with normal baseline semen parameters and DNA fragmentation (measured by the TUNEL assay). Study participants (mean age 34 years, range 19–58 years) were treated with therapeutic paroxetine for 5 weeks. Semen parameters and sperm DNA fragmentation were tested before treatment and again post-treatment after a 1-month washout period. Use of paroxetine was associated with a significant increase in DNA fragmentation, from 14% at baseline to 30% post-treatment. In

© 2019 The Japanese Urological Association

addition, the number of men having elevated sperm DNA fragmentation of >30% increased from 10% at baseline to 50% post-treatment (odds ratio 9, confidence interval 2.3–38). In contrast to some other studies, these authors did not identify a change in semen parameters with SSRI use.[19] This suggests that although raw semen parameters might be affected by SSRI use, sperm DNA fragmentation might also be affected even in the absence of changes in semen parameters and could represent an alternative means for impaired male reproductive potential.

Prospective data have also supported a relationship between SSRI use and markers of male infertility. In a randomized, single-blinded clinical trial, 60 men were treated for primary premature ejaculation with either sertraline or non-pharmacological behavioral therapy. The sertraline group was treated with sertraline 25 mg/day for 1 week, followed by 50 mg/day for 3 months. Both sperm concentration (reduction by 10^5/mL) and percent normal morphology were significantly decreased in the sertraline group versus controls. DNA fragmentation (sperm chromatin dispersion method) was also increased in the treatment group (31% *vs* 16%).[20] Another prospective study by Koyuncu *et al*. showed decreased sperm concentration (26.4×10^6/mL *vs* 68.9×10^6/mL), motility (23.4% *vs* 58.2%) and morphology (23.4% *vs* 58.2%) after 3 months of exposure to escitalopram for the treatment of premature ejaculation.[21]

Other factors, including duration of SSRI use and BMI, might synergistically adversely affect semen parameters. One cross-sectional study compared semen parameters and sperm DNA fragmentation in men taking SSRIs versus those of healthy men, and also included an evaluation of the duration of antidepressant use. Men taking SSRIs were found to have significantly lower sperm counts (61 million *vs* 184 million), motility (49% *vs* 66%) and normal morphology (8% *vs* 20%), as well as significantly increased amounts of fragmented sperm DNA versus controls (43% *vs* 21%). All differences in semen parameters and sperm DNA fragmentation correlated with the duration of antidepressant use (6–12 months *vs* 1–2 years), although no differences were observed between specific antidepressants within the SSRI class.[22] Another study of 530 men aged 18–50 years examining the effect of BMI found that use of combination SSRIs was associated with a significant decrease in sperm motility, independent of BMI.[23]

In vitro, animal and human studies all showed a decline in semen quality with SSRI use, as manifested by both impaired semen parameters and increased DNA fragmentation rates. The duration of recovery (<73 days, the time required for spermatogenesis) to baseline semen parameters and DNA fragmentation suggests that these effects might be due to some type of post-testicular process. Given the wide prevalence of the use of this class of medications, there is a clear need for further large-scale, randomized, placebo-controlled trials to further characterize the role of SSRIs in infertility, and their effect on semen parameters and other markers of male fertility.

SNRIs and NDRIs

SNRIs exert their effects by inhibiting the reabsorption of both serotonin and norepinephrine. This class of medications includes desvenlafaxine, duloxetine, levomilnacipran and venlafaxine. The prevalence of sexual dysfunction is 58–70% in patients treated with SNRIs,[4] in general slightly less than that seen for SSRIs. There has only been a single study investigating the effects of any of these medications on semen parameters (Table 3). This group examined 40 adult male mice given oral venlafaxine (2 mg/kg) or venlafaxine (2 mg/

Table 3 Non-SSRI antidepressant effects on semen and other fertility parameters

Drug	*In vivo* effects on semen parameters	Other effects on fertility
SNRIs		
Venlafaxine	*Human prospective:* Improved normal morphology and sperm viability, increased non-progressive motility	–
NDRIs		
Bupropion	*Rats:* Decreased motility at high doses (30 mg/kg)	*Rats:* Increased epididymal duct contractility
Methylphenidate	*Rats:* Increased abnormal sperm tail morphology; increased spermatogonia; reduced round spermatids; increased sperm count	*Rats:* Increased testicular interstitial tissue; decreased germinal epithelium thickness, increased gonadotropins; decreased testicular weight, increase in apoptosis; increased testicular weight
Sibutramine	*Rats:* Decreased sperm number in epididymis, decreased transit time within epididymis	*Rats:* Decreased reproductive organ weight
TCAs		
Desipramine	*Human:* No change in sperm count or motility	–
Amitriptyline	*Human prospective:* Increased ejaculate volume, sperm count and normal morphology; decreased sperm concentration and viability; decreased sperm count and normal forms	*Human prospective:* Increased germ cell mutations
MAOIs		
Selegiline	*Rats:* Increased sperm count and viability	*Rats:* Increase in testis mass
Atypical antidepressants		
Trazodone	*Rats:* Decreased sperm concentration, motility and normal morphology, increased DNA damage	–
Mirtazapine	*Rats:* Protective effect against nitrofurazone-induced decrease in sperm count and viability	–
Agomelatine	*Human case study:* No effect on semen parameters	–

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

kg) plus vitamin C (10 mg/kg) for 35 days. Mice treated with venlafaxine alone had better sperm morphology (58.50% *vs* 43.71%), non-progressive motility (25.50% *vs* 16.25%) and sperm viability (80.25% *vs* 64.62%) compared with controls. This effect is thought to be a result of the anti-oxidant properties of venlafaxine in protecting against lipid peroxidation. There were no significant differences between semen parameters in mice treated with venlafaxine alone and those treated with combination venlafaxine and ascorbic acid.[24]

NDRIs act by blocking the reuptake of norepinephrine and dopamine from the synaptic terminal, thereby increasing their bioavailability. This class includes bupropion, dexmethylphenidate, diphenylprolinol, ethylphenidate, methylenedioxypyrovalerone, methylphenidate, pipradrol, prolintane and sibutramine. In general, the limited available data for these medications show varied effects on semen parameters (Table 3).

Bupropion is commonly used in combination with other medications in the treatment of depression, as well as for smoking cessation. Although the role of dopamine in reproductive physiology has not been clearly established, there are limited data implicating some role in male reproductive function. Urra *et al*. first identified the presence of functional dopamine transporters in equine sperm. In the present study, high levels of dopamine were associated with decreased total and progressive sperm motility, and this effect was partially reversed by the addition of bupropion. Blocking the dopamine transporter reduced uptake of a dopamine analog, thereby decreasing accumulation of the catecholamine in equine sperm.[25] Another study evaluated the effects of bupropion on semen parameters and epididymal duct contractility in rats. At lower doses (15 mg/kg), bupropion increased epididymal duct contractility, but had no effect on semen parameters. At higher doses (30 mg/kg), the drug was shown to impair sperm motility.[26]

Methylphenidate is a psychostimulant that inhibits norepinephrine and dopamine reuptake. It is currently most commonly used in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. In the past it was used as an antidepressant, and there are some conflicting data on its effect on semen parameters. Motagnini *et al*. studied the effects of methylphenidate administration on rats during childhood and young adult development. An increase in abnormal sperm tail morphology was observed, as well as an increase in testicular interstitial tissue in treated animals.[27] A different rat study found that treatment with methylphenidate was associated with decreased germinal epithelium thickness, as well as an increase in the number of spermatogonia, likely secondary to increases in serum gonadotropin levels.[28] Finally, a rat study by Cansu *et al*. showed a dose-dependent association between 90-day exposure to methylphenidate and reduced numbers of round spermatids, decreased testicular weight, and an increase in apoptosis (TUNEL method) and expression of p53.[29] Conversely, Adriani *et al*. found that adolescent rats exposed to methylphenidate had increased testicular weights and increased sperm count as adults.[30] These data are conflicting, and there are no human data, making it difficult to truly know the effect of methylphenidate on semen parameters and male fertility.

Sibutramine, initially developed for use in the treatment of depression, is a monoamine reuptake inhibitor commonly used today for weight loss. There are no human studies for sibutramine, and only a single animal study. Bellentani *et al*. found that exposure to 10 mg/kg of sibutramine for 28 days decreased weights of reproductive organs in male rats, including the ventral prostate and epididymis, although there were no histological changes noted in these organs. The sperm number within the epididymis (180.98×10^6/organ *vs* 276.16×10^6/organ) and transit time within the epididymis (4.73 days *vs* 7.85 days) were also significantly decreased. There was no change in spermatid number within testes, daily sperm production, sperm motility or morphology between groups.[31]

There is a clear lack of data for many of these medications. No studies exist for duloxetine, desvenlafaxine, levomilnacipran, dexmethylphenidate, diphenylprolinol, ethylphenidate, methylenedioxypyrovalerone, pipradrol or prolintane. Scant data exist for venlafaxine, bupropion, methylphenidate and sibutramine. No prospective clinical studies have yet been carried out exploring the effects of SNRIs and NDRIs on semen quality. Given the contradictory results found in preliminary animal studies, there is a clear need for additional research in this area.

TCAs

TCAs, including amitriptyline, nortriptyline, amoxapine, desipramine, doxepin, imipramine, protriptyline and trimipramine, were one of the earliest medications used to treat depression. However, they are generally no longer used as first-line medications because of significant side-effect profiles. The estimated prevalence of sexual dysfunction in men and women taking TCAs is comparatively low, at approximately 30%.[4] Evidence regarding the effects of TCAs on semen quality is scant (Table 3). There is a small number of studies on desipramine and amitriptyline, but no studies on nortriptyline, amoxapine, doxepin, imipramine, protriptyline or trimipramine.

A 1981 study by Levin *et al*. described both *in vitro* and clinical studies examining the effect of desipramine on semen parameters. *In vitro*, desipramine was associated with dose-dependent inhibition of sperm motility. However, *in vivo* clinical evaluation found no difference in sperm count or motility between treatment and control groups. Treatment with desipramine was associated with decreased sperm viability (defined as the percentage of motile spermatozoa, no true viability testing was carried out). Other semen parameters did not significantly differ between treatment and control groups.[32]

There have been four studies examining amitriptyline, yielding conflicting results. A small study on the effects of amitriptyline in 20 infertile men with oligospermia found increased ejaculate volume, sperm count and normal morphology after treatment with amitriptyline. Sperm count was increased in 50% of patients, and motility was increased in 35% of patients.[33] In contrast, Bandegi *et al*. found negative effects of amitriptyline on semen parameters in rats treated with amitriptyline alone versus amitriptyline and ascorbic acid. Rats treated with amitriptyline alone had lower sperm

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

concentration (18.11 million *vs* 22.41 million) and viability (31.25% *vs* 64.62%) compared with controls. These results were also seen when comparing the group receiving amitriptyline plus ascorbic acid and controls, and the addition of ascorbic acid did not seem to mitigate this effect.[24] Two studies suggest that amitriptyline has a mutagenic effect on sperm. A study by Chowdary and Rao showed mutagenic effects of amitriptyline in germ cells of mice treated with various oral doses of the antidepressant.[34] Similar results were obtained in an animal study in which amitriptyline was found to increase chromosome abnormalities, and decrease sperm count and normal morphology.[35]

MAOIs

MAOIs are typically reserved for patients who have failed other first-line medications for the treatment of depression. Medications belonging to this class include selegiline, isocarboxazid, phenelzine and tranylcypromine. Approximately 40% of male and female patients taking MAOIs will experience some degree of sexual dysfunction.[4] Data on semen parameters are scant (Table 3). There have been two rat studies examining the effects of selegiline, but no studies examining the effects of other MAOIs, including isocarboxazid, phenelzine and tranylcypromine, on semen parameters or other markers of male fertility.

Selegiline, used to treat major depressive disorder and parkinsonism, might actually have a favorable effect on male fertility. A small rat study found an increase in testis mass, sperm number and viability (defined as the ratio of live to dead sperm) in rats treated with oral selegiline for 4 weeks.[36] These findings were corroborated in a study of rats treated with intraperitoneal selegiline. Treated rats had significantly higher sperm counts (137.73×10^6/mL *vs* 115.09×10^6/mL on semen analysis) than those receiving intraperitoneal saline.[37] The mechanism for this increase in sperm counts and viability is unclear.

Atypical antidepressants

Atypical antidepressants are those that act by mechanisms separate from those discussed above. These medications include mirtazapine, trazodone, nefazodone, tianeptine, agomelatine, vilazodone and vortioxetine. There are limited data regarding the effects of these medications on fertility through semen parameters, although the available data do suggest a negative effect on semen quality (Table 3).

One study of rats receiving vehicle (control), 5, 10 or 20 mg/kg/day of trazodone for 28 consecutive days found decreased sperm concentration (4.68×10^6/mL, 3.04×10^6/mL, 2.84×10^6/mL and 2.68×10^6/mL, respectively), sperm motility (86.49%, 80.06%, 78.85% and 76.23%, respectively) and normal morphology (18.00%, 28.90%, 31.20% and 37.08% abnormal forms, respectively), as well as increased DNA damage in treated rats. Increased malondialdehyde levels suggested that oxidative stress contributed to the testicular toxicity in these animals.[38] Similarly, Cassidy and Pearson showed that trazodone had an inhibitory effect on motility in *in vitro* samples of human sperm.[39]

Mirtazapine has been shown in one study to have a protective effect against oxidative stress and testicular damage. In that study, testicular damage in rats was induced by administration of nitrofurazone. Rats exposed prophylactically to mirtazapine 1 week before the initiation of nitrofurazone had a significantly less pronounced decline in sperm count and viability than those receiving only nitrofurazone, as well as decreased indicators of oxidative damage.[40]

One case study suggested that agomelatine (*vs* citalopram) does not negatively impact semen quality (at least in one patient). Elnazer and Baldwin described a case of decreased sperm concentration, motility, progressive motility and normal morphology in a patient treated with citalopram for mixed depression and anxiety. These effects resolved after withdrawal of citalopram. The patient was subsequently treated with agomelatine, which was not associated with a decline in semen parameters.[18]

There have been no studies to date regarding the effects of nefazodone, tianeptine, vilazodone or vortioxetine on semen parameters or other markers for male fertility.

Conclusions

Given the relatively common use of antidepressant medications, the limited data on their use is worrisome. This is particularly concerning, given that these medications are taken by young men, generally on a long-term basis. We do not have pregnancy or live birth data on any of these medications. All of them have the potential to affect sexual performance to varying degrees.

The existing data show that SSRIs exert a harmful effect on semen quality and rates of DNA fragmentation, as well as increase oxidative stress within reproductive organs. Most of these effects do seem to be reversible on cessation of treatment with SSRIs, although this might not be possible for all patients who need these medications to control their depression. There is contrasting evidence regarding whether bupropion (an NDRI), negatively or positively impacts sperm motility. Similarly, the available data for methylphenidate is animal only, and conflicting, making it difficult to know its true effect. Studies on amitriptyline have yielded conflicting results, with one small clinical study suggesting improved semen parameters in patients with baseline oligospermia, but three animal studies finding the opposite effect. The only MAOI that has been studied in this arena is selegiline, which has been shown to increase sperm counts and viability in two rat studies.

Evaluations of the effects of treatment with antidepressant medication on semen parameters should consider the effects of untreated depression and anxiety on fertility as well. Shiraishi and Matsuyama showed that comorbid medical conditions negatively impacted spermatogenesis and that treatment of medical comorbidities, including hypertension, hyperlipidemia, hyperuricemia and skin disease, was associated with a significant increase in motile sperm count.[41] In particular, psychosocial stress has been shown to have an inverse effect on testosterone levels.[42] Furthermore, it is not surprising that a diagnosis of major depression appears to affect gonadal

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

function. Men with depressive episodes of moderate-to-severe severity have been shown to have lower levels of testosterone[43] as well as lower sex hormone-binding globulin and DHEA-S, higher secretion of cortisol and prolactin, and lower semen volume and sperm density.[44]

Given the widespread and often long-term use of antidepressant medications, there is a clear need for further data regarding their impact on semen quality and male fertility. The existing data are often based on animal studies or human studies with low numbers of patients. There is a stark absence of prospective data. 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. If possible, a trial of discontinuation of antidepressants is advised, although this should be carried out in conjunction with the patient's mental health provider.

Conflict of interest

None declared.

References

1 Pratt LA, Brody DJ, Gu Q. *Antidepressant Use among Persons Aged 12 and over: United States, 2011–2014*. NCHS data brief, no 283. Hyattsville, MD: National Center for Health Statistics, 2017.

2 Organisation for Economic Co-operation and Development. *OECD Health Statistics*. Paris: Organisation for EconomicCo-operation and Development, 2015.

3 Berger D. Antidepressant drug development in Japan: current & future horizons. *Clin. Res. Focus* 2005; **16**: 32–5.

4 Higgins A, Nash M, Lynch AM. Antidepressant-associated sexual dysfunction: impact, effects, and treatment. *Drug Healthc. Patient Saf.* 2010; **2**: 141–50.

5 Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the study of psychotropic-related sexual dysfunction. *J. Clin. Psychiatry* 2001; **62** (Suppl 3): 10–21.

6 Kumar VS, Sharma VL, Tiwari P *et al*. The spermicidal and antitrichomonas activities of SSRI antidepressants. *Bioorg. Med. Chem. Lett.* 2006; **16**: 2509–12.

7 Bataineh HN, Daradka T. Effects of long-term use of fluoxetine on fertility parameters in adult male rats. *Neuro. Endocrinol. Lett.* 2007; **28**: 321–5.

8 Alzahrani HA. Sister chromatid exchanges and sperm abnormalities produced by antidepressant drug fluoxetine in mouse treated in vivo. *Eur. Rev. Med. Pharmacol. Sci.* 2012; **16**: 2154–61.

9 Galal AA, Alam RT, Abd El-Aziz RM. Adverse effects of long-term administration of fluvoxamine on haematology, blood biochemistry and fertility in male albino rats: a possible effect of cessation. *Andrologia* 2016; **48**: 914–22.

10 Sakr HF, Abbas AM, Elsamanoudy AZ, Ghoneim FM. Effect of fluoxetine and resveratrol on testicular functions and oxidative stress in a rat model of chronic mild stress-induced depression. *J. Physiol. Pharmacol.* 2015; **66**: 515–27.

11 Atli O, Baysal M, Aydogan-Kilic G *et al*. Sertraline-induced reproductive toxicity in male rats: evaluation of possible underlying mechanisms. *Asian J. Androl.* 2017; **19**: 672–9.

12 Attia SM, Bakheet SA. Citalopram at the recommended human doses after long-term treatment is genotoxic for male germ cell. *Food Chem. Toxicol.* 2013; **53**: 281–5.

13 Ilgin S, Kilic G, Baysal M *et al*. Citalopram induces reproductive toxicity in male rats. *Birth Defects Res.* 2017; **109**: 475–85.

14 Ayala ME, Gonzáles A, Olivarez RM, Aragón-Martínez A. Fluoxetine treatment of prepubertal male rats uniformly diminishes sex hormone levels and in a subpopulation of animals, negatively affects sperm quality. *Reprod. Fertil. Dev.* 2018; **30**: 1329–41.

15 Vieira ML, Hamada RY, Gonzaga NI *et al*. Could maternal exposure to the antidepressants fluoxetine and St. John's Wort induce long-term reproductive effects on male rats? *Reprod. Toxicol.* 2013; **35**: 102–7.

16 Tanrikut C, Schlegel PN. Antidepressant-associated changes in semen parameters. *Urology* 2007; **69**: 185.e5–e7.

17 Drobnis EZ, Nangia AK. Psychotropics and male reproduction. In: Drobnis EZ, Nangia AK (eds). *Impacts of Medications on Male Fertility*, 1034th edn. Springer, 2017; 64–78.

18 Elnazer HY, Baldwin DS. Treatment with citalopram, but not with agomelatine, adversely affects sperm parameters: a case report and translational review. *Acta Neuropsychiatr.* 2014; **26**: 125–9.

19 Tanrikut C, Feldman AS, Altemus M, Paduch DA, Schlegel PN. Adverse effect of paroxetine on sperm. *Fertil. Steril.* 2010; **94**: 1021–6.

20 Akasheh G, Sirati L, Noshad Kamran AR, Sepehrmanesh Z. Comparison of the effect of sertraline with behavioral therapy on semen parameters in men with primary premature ejaculation. *Urology* 2014; **83**: 800–4.

21 Koyuncu H, Serefoglu EC, Yencilek E, Atalay H, Akbas NB, Sarıca K. Escitalopram treatment for premature ejaculation has a negative effect on semen parameters. *Int. J. Impot. Res.* 2011; **23**: 257–61.

22 Safarinejad MR. Sperm DNA damage and semen quality impairment after treatment with selective serotonin reuptake inhibitors detected using semen analysis and sperm chromatin structure assay. *J. Urol.* 2008; **180**: 2124–8.

23 Relwani R, Berger D, Santoro N *et al*. Semen parameters are unrelated to BMI but vary with SSRI use and prior urological surgery. *Reprod. Sci.* 2011; **18**: 391–7.

24 Bandegi L, Anvari M, Vakili M, Khoradmehr A, Mirjalili A, Talebi AR. Effects of antidepressants on parameters, melondiadehyde, and diphenyl-2-picryl-hydrazyl levels in mice spermatozoa. *Int. J. Reprod. Biomed.* 2018; **16**: 365–72.

25 Urra JA, Villaroel-Espíndola F, Covarrubias AA, Rodríguez-Gil JE, Ramírez-Reveco A, Concha II. Presence and function of dopamine transporter (DAT) in stallion sperm: dopamine modulates sperm motility and acrosomal integrity. *PLoS One* 2014; **9**: e112834.

26 Cavariani MM, de Almeida Kiguti LR, de Lima RJ *et al*. Bupropion treatment increases epididymal contractility and impairs sperm quality with no effects on the epididymal sperm transit time of male rats. *J. Appl. Toxicol.* 2015; **35**: 1007–16.

27 Montagnini BG, Silva LS, dos Santos AH *et al*. Effects of repeated administration of methylphenidate on reproductive parameters in male rats. *Physiol. Behav.* 2014; **133**: 122–9.

28 Fazelipour S, Tootian Z, Saremi ZG *et al*. Evaluation of histopathologic and histomorphometric changes of testicular tissue and gonadotropin levels following consumption of methylphenidate in male mice. *Turk. J. Med. Sci.* 2014; **44**: 554–9.

29 Cansu A, Ekinci O, Serdaroglu A, Erdogan D, Coskun ZK, Gürgen SG. Methylphenidate has dose-dependent negative effects on rat spermatogenesis: decreased round spermatids and testicular weight and increased p53 expression and apoptosis. *Hum. Exp. Toxicol.* 2011; **30**: 1592–600.

30 Adriani W, Leo D, Guarino M *et al*. Short-term effects of adolescent methylphenidate exposure on brain striatal gene expression and sexual/endocrine parameters in male rats. *Ann. N. Y. Acad. Sci.* 2006; **1074**: 52–73.

31 Bellentani FF, Fernandes GS, Perobelli JE *et al*. Acceleration of sperm transit time and reduction of sperm reserves in the epididymis of rats exposed to sibutramine. *J. Androl.* 2011; **32**: 718–24.

32 Levin RM, Amsterdam JD, Winokur A, Wein AJ. Effects of psychotropic drugs on human sperm motility. *Fertil. Steril.* 1981; **36**: 503–6.

33 Padrón RS, Nodarse M. Effects of amitriptyline on semen of infertile men. *Br. J. Urol.* 1980; **52**: 226–8.

34 Chowdary PS, Rao MS. Cytogenetic effects of amitriptyline hydrochloride in somatic and germ cells of mice. *Toxicol. Lett.* 1987; **39**: 199–204.

35 Hassanane MS, Hafiz N, Radwan W, El-Ghor AA. Genotoxic evaluation for the tricyclic antidepressant drug, amitriptyline. *Drug Chem. Toxicol.* 2012; **35**: 450–5.

36 Kalász H, Thuróczy J, Karvaly G *et al*. Effects on sperms' quality of selegiline in aged rats. *Open Med. Chem. J.* 2017; **11**: 138–45.

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

37 Mihalik J, Mašlanková J, Solár P *et al*. The effect of R-(-)-deprenyl administration on reproductive parameters of rat males. *Eur. J. Pharmacol.* 2015; **754**: 148–52.
38 Ilgın S, Aydoğan-Kılıç G, Baysal M *et al*. Toxic effects of trazodone on male reproductive system via disrupting hypothalamic-pituitary-testicular axis and inducing testicular oxidative stress. *Oxid. Med. Cell Longev.* 2018; **2018**: 7196142.
39 Cassidy SL, Pearson RM. Effects of trazodone and nadolol upon human sperm motility. *Br. J. Clin. Pharmacol.* 1986; **22**: 119–21.
40 El-Sisi AE, El-Sayad ME, Abdelsalam NM. Protective effects of mirtazapine and chrysin on experimentally induced testicular damage in rats. *Biomed. Pharmacother.* 2017; **95**: 1059–66.
41 Shiraishi K, Matsuyama H. Effects of medical comorbidity on male infertility and comorbidity treatment on spermatogenesis. *Fertil. Steril.* 2018; **110**: 1006–11.e2.
42 Nilsson PM, Møller L, Solstad K. Adverse effects of psychosocial stress on gonadal function and insulin levels in middle-aged males. *J. Intern. Med.* 1995; **237**: 479–86.
43 Schweiger U, Deuschle M, Weber B *et al*. Testosterone, gonadotropin, and cortisol secretion in male patients with major depression. *Psychosom. Med.* 1999; **61**: 292–6.
44 Wdowiak A, Bień A, Iwanowicz-Palus G, Makara-Studzińska M, Bojar I. Impact of emotional disorders on semen quality in men treated for infertility. *Neuro. Endocrinol. Lett.* 2017; **38**: 50–8.

Editorial Comment

Editorial Comment to Effect of antidepressant medications on semen parameters and male fertility

The paper by Beeder and Samplaski is a review article of antidepressant medications and male fertility.[1]

Antidepressant medications are widely applied for patients in the psychological field. As the authors mentioned, it is well known that antidepressant medications cause male sexual dysfunction, including erectile dysfunction and late-onset hypogonadism syndrome.

A few previous studies have reported a relationship between male fertility factors and antidepressants, mainly in basic research besides the references in this article.[2–4] The authors concluded that the existing data show that selective serotonin reuptake inhibitors exert harmful effects on semen quality and rates of DNA fragmentation. This conclusion might almost be acceptable. However, at present, there are insufficient data to clearly show relationships between male fertility factors and antidepressants, because we did not find adequate and decisive results from previous reports. The effects of antidepressants on male infertility are still equivocal and the mechanisms are unclear. In addition, there are so many variations of antidepressants, and each selective serotonin reuptake inhibitor might have their own mechanisms and characteristics, as mentioned in this review.

Although there is still not enough evidence in the content of this review to generally and widely accept the influence of antidepressants on male infertility, this article is significant in that it raises urologists' concerns about the risks of antidepressants in regard to male infertility.

Another interesting point is that this harmful effect seems to be reversible upon cessation. In clinical practice, we sometimes experience reversible testicular function (spermatogenesis) in patients with male hypogonadotropic hypogonadism. Spermatogenesis is often observed in male hypogonadotropic hypogonadism patients when luteinizing hormone and follicle-stimulating hormone treatment are commenced, even after testosterone replacement therapy. A normal to nearly normal testis itself seems to have a high potential for spermatogenesis function.

It is almost impossible to clarify which antidepressants affect which level of spermatogenesis. It is most important that we pay attention to the risks posed to male infertility by antidepressants, and avoid overprescribing antidepressants.

Toshiyasu Amano M.D., Ph.D.
Department of Urology, Nagano Red Cross Hospital, Nagano, Japan
amanot@nagano-med.jrc.or.jp

DOI: 10.1111/iju.14126

Conflict of interest

None declared.

References

1 Beeder LA, Samplaski MK. Effect of antidepressant medications on semen parameters and male fertility. *Int. J. Urol.* 2020; **27**: 39–46.
2 Câmara ML, Almeida TB, de Santi F *et al*. Fluoxetine-induced androgenic failure impairs the seminiferous tubules integrity and increases ubiquitin carboxyl-terminal hydrolase L1 (UCHL1): Possible androgenic control of UCHL1 in germ cell death? *Biomed. Pharmacother.* 2019; **109**: 1126–39.
3 Prasad P, Ogawa S, Parhar IS. Serotonin reuptake inhibitor citalopram inhibits GnRH synthesis and spermatogenesis in the male zebrafish. *Biol. Reprod.* 2015; **93**: 102.
4 Erdemir F, Atilgan D, Firat F, Markoc F, Parlaktas BS, Sogut E. The effect of sertraline, paroxetine, fluoxetine and escitalopram on testicular tissue and oxidative stress parameters in rats. *Int. Braz. J. Urol.* 2014; **40**: 100–8.

© 2019 The Japanese Urological Association

14422042, 2020, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/iju.14111, Wiley Online Library on [06/04/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

EXHIBIT 22

GYNECOLOGY

The effect of antidepressants on fertility

Marianne M. Casilla-Lennon, BS; Samantha Meltzer-Brody, MD; Anne Z. Steiner, MD, MPH

BACKGROUND: Information on the effects of different pharmaceuticals on fertility is sparse. Human and animal models indicate that antidepressant use could have a negative effect on fertility through alteration of levels of the neurosteroid, allopregnanolone.

OBJECTIVE: The objective of this study is to assess the effects of antidepressants on the natural fertility in women.

STUDY DESIGN: A secondary analysis of data from Time to Conceive, a prospective cohort study, was conducted. Women ages 30 to 44 years without a history of infertility, early in their attempts to conceive, were followed with standardized pregnancy testing until pregnancy was detected. Medication use was assessed at enrollment, daily for up to 4 months, and then monthly. For this analysis, discrete time regression models were created to calculate the association between antidepressant use and fecundability. Potential confounders—age, body mass index, caffeine, alcohol use, and education—were included in all models.

RESULTS: Ninety-two (9.6%) of 957 women reported antidepressant use while attempting to conceive. Women taking antidepressants were more likely to be non-Hispanic Caucasian (91% vs 75%, $P < .01$) and to consume alcoholic beverages (74% vs 61%, $P < .01$). Antidepressant use at enrollment had an adjusted fecundability ratio (FR) of 0.86 (95% confidence interval [CI], 0.63—1.20). However, time-varying analyses suggested that antidepressant use in a given cycle is associated with a reduced probability of conceiving in that cycle (adjusted FR, 0.75; 95% CI, 0.53—1.06). After adjusting for history of depression or restricting the analysis to women who reported a history of depression, the association between antidepressant use and decreased fecundability remained [adjusted FR, 0.66 (95% CI, 0.45—0.97) and (adjusted FR, 0.64; 95% CI, 0.43—0.94), respectively].

CONCLUSION: Our data suggest that 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.

Key words: antidepressants, depression, fertility, fecundability

Antidepressants are the first line of treatment for unipolar major depression[1] and a number of other psychiatric disorders, such as obsessive compulsive disorder.[2] In 2011, antidepressants were the most dispensed drug in the United States, accounting for over 260 million prescriptions.[3] Antidepressants were disproportionately used by women,[4] the majority of reproductive age, compared with men.[5] Although there has been significant research on the teratogenicity of antidepressants, little is known about their direct impact on fertility.

The three most commonly prescribed classes of antidepressants increase allopregnanolone,[6] a progesterone derivative considered a neurosteroid that is produced and is neuroactive in the brain. Allopregnanolone is a positive allosteric modulator of the gamma aminobutyric acid ($GABA_A$) receptor. Its presence enhances the activity of GABA, which is the main inhibitory neurotransmitter in the central nervous system, including the hypothalamus.

Research on rodents suggests that an antidepressant-induced increase in allopregnanolone levels could lead to dysregulation of the hypothalamic-pituitary-ovarian (HPO) axis. Incubation of hypothalamic tissue with allopregnanolone suppresses GnRH release in a concentration-dependent manner. The effects are blocked with the addition of a GABA-antagonist, suggesting that allopregnanolone increases GABA activity, suppressing GnRH release.[7] Accordingly, injection of allopregnanolone into the hypothalamus of rats has been shown to decrease circulating LH levels and result in fewer oocytes at oestrus.[6] The results of animal models have been consistent in humans. Intravenous administration of allopregnanolone in healthy, fertile women decreases follicle-stimulating hormone (FSH) and LH levels[8] and subsequently decreases rates of ovulation. This dysregulation in allopregnanolone could inhibit the pulsatile action of GnRH needed to sustain proper synchronization of ovulation, resulting in infertility.

The above evidence suggests that antidepressants may contribute to changes in the HPO axis through their GABAergic action. HPO axis dysfunction can manifest in numerous ways, including anovulation or luteal phase defects, which can negatively affect a woman's ability to conceive. We hypothesized that antidepressant use would impair natural fertility, which we examined by analyzing the effect of antidepressants on fecundability, the probability of conceiving in a menstrual cycle.

Materials and Methods

This study is a secondary analysis of Time to Conceive (TTC), an ongoing prospective time-to-pregnancy cohort study approved by the institutional review board at the University of North Carolina. A detailed description of the TTC study has been published previously.[9] In brief, women were recruited to the study via community-based fliers, informational emails, internet, radio, television and print advertising, and community blogs. English-speaking women 30 to 44 years old, who had been attempting to conceive for less than 3 months, were eligible to participate.

Cite this article as: Casilla-Lennon MM, Meltzer-Brody S, Steiner AZ, et al. The effect of antidepressants on fertility. Am J Obstet Gynecol 2016;215:314.e1-5.

0002-9378/$36.00
Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.ajog.2016.01.170

Women with a history of infertility, polycystic ovary syndrome, pelvic inflammatory disease, endometriosis, pelvic radiation, or a partner with a history of infertility were excluded. Our analysis includes women enrolled between April 2008 and July 2015. Information was collected via web-based questionnaires and daily diaries. At enrollment, women provided demographic information, medical and surgical history, obstetric, gynecologic, and menstrual history, information on behaviors, height and weight, and pregnancy history, as well as partner demographics. Women were asked if they had a history of anxiety or depression (yes/no). The question was not restricted to any specific type of depression or anxiety. The Cerner Multum drug database system was embedded to identify and record over-the-counter and prescription medication use. This comprehensive database included dosing information and drug names, both generic and brand names.

While attempting to conceive, women completed an online daily diary for 4 months or until pregnancy was detected. The daily diary collected information on vaginal bleeding, intercourse, pregnancy test results, and medication use. If the woman did not conceive in the first 4 months of enrollment, she completed an online questionnaire monthly thereafter, which also collected information on medication use. The women were followed for twelve months or until pregnancy was achieved. Pregnancy tests (sensitivity = 20 mIU hCG/mL) were provided with standardized instructions. For this analysis, a positive pregnancy test was our primary outcome of interest.

Antidepressants were categorized by class via mechanism of action. A comprehensive list of traditional antidepressants was constructed. Our list included selective serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors, serotonin antagonist and reuptake inhibitors, norepinephrine reuptake inhibitors, norepinephrine/dopamine reuptake inhibitors, tri and tetracyclic antidepressants (TCAs), monoamine oxidase inhibitors, and other antidepressants. Adjunct antidepressants and other psychotropic medications with antidepressant action were excluded.

Statistical analysis

Women were categorized by antidepressant use (yes/no). Antidepressant use was categorized by 1) use at enrollment, 2) use at any given time during the study, and 3) use in a given menstrual cycle. Bivariate analyses, with χ^2 tests, were used to compare demographics and potential covariates (age, race, education level, pregnancy history, menstrual cycle regularity and length, frequency of intercourse, previous contraceptive use, body mass index [BMI], partner age, smoking status, alcohol use, and caffeine use) between the antidepressant users (at any given time in the study) and non-users.

Discrete-time survival models were constructed to assess the relationship between 1) antidepressant use at enrollment and fecundability and, as antidepressant use of an individual woman could vary over time, 2) antidepressant use in a given cycle and fecundability in that given cycle. All analyses were restricted to the first nine cycles of attempt, due to few women remaining after that time. All models accounted for both the right censoring and left truncation (due to women enrolling in cycles 1, 2, 3, or 4 of their pregnancy attempt) present in the data. In these models, a fecundability ratio (FR) less than 1.0 suggested reduced fecundability.

In all adjusted models we included both the covariates strongly associated with fecundability or antidepressants and those identified in multiple prior studies as related to fecundability. These covariates were age, Caucasian race (yes/no), BMI, education level, and alcohol use (yes/no). Maternal age was collapsed into three categories (30–34, 35–37, and 38–44 years of age), and BMI was categorized into 4 groups ($\leq$18.4, 18.5–24.9, 25.0–29.9, and $\geq$30 kg/m^2). Additional analyses adjusted for history of anxiety/depression as reported in the baseline questionnaire and restricted analysis to those women, who reported a history of anxiety/depression. In an attempt to explore the extent to which underlying anxiety/depression may play a role in the relationship between antidepressants and fertility, we analyzed the relationship between history of anxiety/depression, as reported in the baseline questionnaire and fecundability.

Results

A total of 957 women and 3355 menstrual cycles were included in this analysis. Of the analysis cohort, 70% of women were 30 to 34 years old, 18% were 35 to 37 years old, and 12% were 38 to 44 years old. Participants tended to be Caucasian (76%), highly educated (72% with some graduate education or more), and normal weight (62%). Six hundred twenty-two (65%) of subjects conceived during their first 9 cycles of attempt. Analysis was restricted to the first nine cycles due to high levels of drop-out past this point.

Ninety-two (9.6%) women reported antidepressant use at some point during enrollment. Antidepressant use was reported by 7.6% of women in the first cycle of attempt, 9.0% in the second, 8.9% in the third, 8.2% in the sixth, and 11.0% in the eighth. The most frequently used antidepressants were SSRIs and all antidepressants, except one report of TCAs, were reuptake inhibitors. Women taking antidepressants were more likely to be non-Hispanic Caucasian (91% vs 75%, $P < .01$) and to consume alcoholic beverages (74% vs 61%, $P < .01$). There were no differences in other variables analyzed (Table 1). Menstrual cycle length and history of regular menstrual cycles did not differ at baseline by antidepressant use. Antidepressant users at enrollment reported on average 2.18 [standard deviation (SD) 1.25] acts of intercourse per week, which did not differ significantly from non-users at that time with 2.38 (SD 1.59) act per weeks ($P = .27$. Women reporting a history of depression had similar fecundability to those who did not (adjusted FR, 1.03; 95% CI, 0.82–1.24).

Initial models suggested minimal to no effect of antidepressants on fecundability (Figure 1) when analyzing baseline antidepressant use; women who were taking antidepressants at enrollment had an adjusted FR of 0.86 (95%

CI, 0.63−1.20). When analyzing cycles individually, time varying analyses suggested that antidepressant use in a given cycle was associated with a reduced probability of conceiving in that cycle (adjusted FR, 0.75; 95% CI, 0.53−1.06). After adjusting for a history of anxiety/depression as reported on the baseline questionnaire, the association between antidepressant use and fecundability remained [adjusted FR, 0.66 (95% CI, 0.45−0.97)]. When the analyses were restricted to women with a history of anxiety/depression, the association also remained (adjusted FR, 0.64; 95% CI, 0.43−0.94).

Discussion

In this prospective cohort study we found that 9.6% of women took antidepressants while trying to conceive. Almost all antidepressants used in our study were reuptake inhibitors, sharing a similar mechanism of action. Women in our study who took antidepressants tended to be non-Hispanic Caucasian and more likely to consume alcoholic beverages. History of depression or anxiety was not associated with fecundability. Antidepressant use within a given menstrual cycle was associated with a lower probability of conceiving among women who reported a history of anxiety or depression.

Antidepressant use in our cohort was similar to that in previous studies. A cross-sectional study of 12,637 Americans found antidepressant use in women ages 18 to 39 years to be 9.2%.[4] Another study found similar rates of antidepressant use in this age group at 9.9%.[10] In addition, a study of antidepressant use during pre-conception and early pregnancy reported a rate of 10.0% and was similar in regard to age and race.[11] Retrospective studies relying on reported antidepressant use in IVF recipients reported significantly lower rates than prospective studies.[11-14]

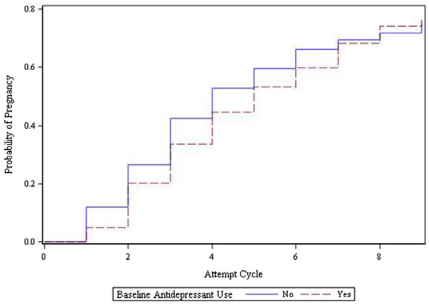
Prior studies reported higher rates of antidepressant use in older women and women of Caucasian race.[4,10] In our study antidepressant users did not differ from non-users by race or age. The age distribution did not significantly differ by antidepressant use. Regarding race distribution, 79% of antidepressant users were Non-Hispanic Caucasian, whereas 76% of non-users were non-Hispanic Caucasian. Our inability to detect previously observed associations may be due to the relatively narrow age range and underrepresentation of minorities in this study.

TABLE 1
Baseline characteristics of women taking antidepressants

Characteristic	Category	Antidepressant taken during study: No (%) $n = 865$	Antidepressant taken during study: Yes (%) $n = 92$	P
Age (years)	30−34	611 (70)	64 (69)	.46
	35−37	157 (18)	14 (15)	
	38 and over	97 (11)	14 (15)	
Race	Non-Hispanic Caucasian	652 (75)	84 (91)	<.01
	Other	213 (25)	8 (8)	
Education level	Less than college degree	71 (8)	5 (5)	.77
	College degree	174 (20)	17 (18)	
	Some graduate/masters	79 (9)	11 (12)	
	Completed postgraduate	541 (63)	59 (64)	
Nulligravid	Previous pregnancy	445 (51)	53 (58)	.26
	Never been pregnant	420 (49)	30 (42)	
Regular menstrual cycles	No	122 (14)	13 (14)	1.00
	Yes	742 (86)	79 (86)	
Body mass index (kg/m^2)	Less than 18.5	23 (3)	1 (1)	.50
	18.5−24.9	538 (62)	54 (59)	
	25−29.9	175 (20)	24 (26)	
	30 and over	128 (15)	13 (14)	
Current smoker	No	852 (99)	91 (99)	.75
	Yes	13 (1)	1 (1)	
Partner age (years)	<50	853 (99)	92 (100)	.28
	50 or more	11 (1)	0 (0)	
Past year hormonal contraceptive use	No	474 (55)	44 (48)	.20
	Yes	391 (45)	48 (52)	
Caffeinated beverage consumption	No	163 (19)	15 (16)	.04
	Yes	701 (81)	77 (84)	
Alcohol consumption	No	335 (39)	24 (26)	.01
	Yes	526 (61)	67 (74)	
Average menstrual cycle length (days)	25 or fewer	75 (9)	12 (13)	.28
	26−30	618 (72)	61 (67)	
	30−35	126 (15)	16 (18)	
	36 or more	42 (5)	2 (2)	

Casilla-Lennon et al. The effect of antidepressants on fertility. Am J Obstet Gynecol 2016.

FIGURE 1
Unadjusted Kaplan-Meier curves of time to pregnancy, according to baseline antidepressant use



Casilla-Lennon et al. The effect of antidepressants on fertility. Am J Obstet Gynecol 2016.

We did not find any differences in the reported regularity or length of menstrual cycles between women using and not using antidepressants. If menstrual cycle characteristics had been different between groups, this may have suggested HPO axis dysfunction. However, menstrual cycles tend to be highly variable,[15] and a lack of these findings does not exclude the possibility of HPO axis dysregulation leading to anovulation or luteal phase defects.

Our study found lower fecundability in cycles in which a woman took an antidepressant. This finding was statistically significant after adjusting for history of anxiety or depression or restricting the analysis to those that reported a history of anxiety or depression. To our knowledge, this is the first prospective study to look at the effect of antidepressants on fertility. In a case control study, Grodstein et al[19] found that women who took antidepressants for more than 6 months had 2.9 times the odds of infertility (95% CI, 0.9−8.3). This finding was based on 5 cases who took antidepressants.[19] Klock et al[12] performed a retrospective study to analyze the effect of SSRIs on the success of IVF treatments, reporting that the group of women using SSRIs had a lower pregnancy rate than non-users (40% vs 51%). Their findings were limited by a small sample size and were not statistically significant.[12]

The observed association between antidepressants and fecundability could be due to the antidepressants itself or the underlying fertility. This study was not designed to look at the relationship between depression and fecundability. There was a single question on the enrollment questionnaire that queried about history of underlying depression or anxiety. This simple measure was not associated with fecundability. However, we are unable to determine the extent to which antidepressants users or non-users suffered from depression or residual depressive symptoms. Therefore, this study is unable to truly differentiate the effect of the underlying depression from the antidepressant. Future studies could use validated questionnaires to assess anxiety and depression symptoms.

The true relationship between depression and fertility is unknown. Odegard found in a study of 30,438 married or previously married women in Norway hospitalized for psychiatric disorders, that women with affective psychoses had a similar number of observed children as expected for the general population.[16] This study assessed severe psychiatric conditions and did not specifically stratify the differences in mood disorders alone. Harlow et al[17] found, in a prospective cohort of women going through menopause, that women with a history of depression reported fewer live births. Neither of these studies account for desires to conceive. In a prospective time-to-pregnancy study, Lynch et al[18] used the Hospital Anxiety and Depression Scale to assess the association between depression and fecundability. They did not find an association between depression scores and fecundability. However, depression scores for their cohort were within the normal range; thus they were not able to assess the impact of depressive disorders.[18]

Confounding by indication, in which a disease is associated with the use of a medication and the outcome, is a problem in may many pharmacological studies.[20] A recent study by Andersen et al[21] examined the relationship between antidepressant use and miscarriage using a pharmacy database. The authors found an increased risk of miscarriage in those women taking antidepressants during the first trimester (1.27 HR; 95% CI, 1.22−1.33) compared with women who did not. However, they found a similarly increased risk of miscarriage in those women who stopped the antidepressant prior to conceiving (1.24 HR; 95% CI, 1.18−1.30). This would suggest a potential for confounding by indication with this class of medication. To try to account for the possibility of confounding by indication, we restricted our analysis to women who reported a history of anxiety/depression. However, we did not account for current disease or severity of disease. Future studies may need to collect more information to allow the use of propensity scores (to predict probability of using antidepressants) in analyses.

Our study is not without limitations. By design it includes older reproductive-aged women. While this increases the prevalence of antidepressant use, it may decrease generalizability. Although we identified numerous variables known to affect both depression and fertility, the nature of an observational study precludes us from adjusting for all possible confounders. The outcome we used was an epidemiological measure of fecundability, not incidence of infertility, and the outcome was pregnancy, not live birth. One would presume, however, that decreased fecundability would result in increased rates of infertility. Because our study was not originally designed to assess depression, we relied on a self-report of a history of depression/anxiety. As discussed above, this study cannot differentiate between active or past depression nor between anxiety and depression.

Our study design was the most important strength of our study. A prospective cohort provides the strongest evidence when assessing pharmaceuticals on women attempting to conceive, as randomized controlled trials are not done in this context.[20] Cross-sectional studies are limited by their inability to determine temporal causality. The online self-reported daily diaries allowed for accuracy, as well as privacy, compared with face-to-face interviews, which may be especially important when

assessing sensitive information.[22] To further improve accuracy by avoiding misclassification and monitoring adherence of antidepressants, the Center Multum drug database was used.

In conclusion, antidepressants are among the most widely used medications in reproductive-aged women in the United States. Our study suggests that antidepressant use in women with a history of anxiety or depression diminishes natural fertility. While this is concerning, it is possible that the indication for the antidepressant is the causal factor. Thus, this study alone cannot be used as justification for women to stop their antidepressants when attempting to conceive. ■

References

1. Davidson JRT. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry 2010;71(Suppl E1):e04.

2. Kellner M. Drug treatment of obsessive-compulsive disorder. Dialogues Clin Neurosci 2010;12:187-97.

3. Lindsley CW. The top prescription drugs of 2011 in the United States: antipsychotics and antidepressants once again lead CNS therapeutics. ACS Chem Neurosci 2012;3:630-1.

4. Pratt L, Brody D, Gu Q. Antidepressant use in persons aged 12 and over: United States, 2005–2008. NCHS data brief, No. 76. Hyattsville, MD: National Center for Health Statistics. 2011 [Internet]. [cited 2014 Jul 15]. Available from: http://www.cdc.gov/nchs/data/databriefs/db76.htm.

5. Farr SL, Bitsko RH, Hayes DK, Dietz PM. Mental health and access to services among US women of reproductive age. Am J Obstet Gynecol 2010;203:542.e1-9.

6. Uzunova V, Wrynn AS, Kinnunen A, Ceci M, Kohler C, Uzunov DP. Chronic antidepressants reverse cerebrocortical allopregnanolone decline in the olfactory-bulbectomized rat. Eur J Pharmacol 2004;486:31-4.

7. Calogero AE, Palumbo MA, Bosboom AM, et al. The neuroactive steroid allopregnanolone suppresses hypothalamic gonadotropin-releasing hormone release through a mechanism mediated by the gamma-aminobutyric acid A receptor. J Endocrinol 1998;158:121-5.

8. Timby E, Hedström H, Bäckström T, Sundström-Poromaa I, Nyberg S, Bixo M. Allopregnanolone, a GABAA receptor agonist, decreases gonadotropin levels in women: a preliminary study. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol 2011;27:1087-93.

9. Steiner AZ, Herring AH, Kesner JS, et al. Antimüllerian hormone as a predictor of natural fecundability in women aged 30-42 years. Obstet Gynecol 2011;117:798-804.

10. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry 2009;66:848-56.

11. Cooper WO, Willy ME, Pont SJ, Ray WA. Increasing use of antidepressants in pregnancy. Am J Obstet Gynecol 2007;196:544.e1-5.

12. Klock SC, Sheinin S, Kazer R, Zhang X. A pilot study of the relationship between selective serotonin reuptake inhibitors and in vitro fertilization outcome. Fertil Steril 2004;82:968-9.

13. Friedman BE, Rogers JL, Shahine LK, Westphal LM, Lathi RB. Effect of selective serotonin reuptake inhibitors on in vitro fertilization outcome. Fertil Steril 2009;92:1312-4.

14. Van Gelder MMHJ, van Rooij IALM, de Walle HEK, Roeleveld N, Bakker MK. Maternal recall of prescription medication use during pregnancy using a paper-based questionnaire: a validation study in the Netherlands. Drug Saf 2013;36:43-54.

15. Münster K, Schmidt L, Helm P. Length and variation in the menstrual cycle: a cross-sectional study from a Danish county. Br J Obstet Gynaecol 1992;99:422-9.

16. Odegård O. Fertility of psychiatric first admissions in Norway 1936-1975. Acta Psychiatr Scand 1980;62:212-20.

17. Harlow BL, Wise LA, Otto MW, Soares CN, Cohen LS. Depression and its influence on reproductive endocrine and menstrual cycle markers associated with perimenopause: the Harvard Study of Moods and Cycles. Arch Gen Psychiatry 2003;60:29-36.

18. Lynch CD, Sundaram R, Buck Louis GM, Lum KJ, Pyper C. Are increased levels of self-reported psychosocial stress, anxiety, and depression associated with fecundity? Fertil Steril 2012;98:453-8.

19. Grodstein F, Goldman MB, Ryan L, Cramer DW. Self-reported use of pharmaceuticals and primary ovulatory infertility. Epidemiol Camb Mass 1993;4:151-6.

20. Koren G, Nickel S. Sources of bias in signals of pharmaceutical safety in pregnancy. Clin Investig Med Online 2010;33:E349-55.

21. Andersen JT, Andersen NL, Horwitz H, Poulsen HE, Jimenez-Solem E. Exposure to selective serotonin reuptake inhibitors in early pregnancy and the risk of miscarriage. Obstet Gynecol 2014;124:655-61.

22. Perlis TE, Des Jarlais DC, Friedman SR, Arasteh K, Turner CF. Audio-computerized self-interviewing versus face-to-face interviewing for research data collection at drug abuse treatment programs. Addict Abingdon Engl 2004;99:885-96.

Author and article information

From the Department of Obstetrics and Gynecology, University of North Carolina School of Medicine, Chapel Hill, North Carolina (Ms. Casilla-Lennon and Dr. Steiner); Department of Psychiatry, University of North Carolina, Chapel Hill, North Carolina (Dr. Meltzer-Brody).

Received Oct. 26, 2015; revised Jan. 4, 2016; accepted Jan. 20, 2016.

The authors report no conflict of interest.

Supported by grants T35-DK007386 and R01067683 from the NIH/NICHD.

Presented at the 63rd Annual Meeting of the Pacific Coast Reproductive Society; Palm Springs, California, March 2015.

Corresponding author: Anne Z. Steiner, MD, MPH, University of North Carolina, CB#7570, 4001 Old Clinic Bldg., Chapel Hill, NC 27599. asteiner@med.unc.edu