FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

ADREE EDMO, AKA Mason Edmo, *Plaintiff-Appellee*, v. CORIZON, INC.; SCOTT ELIASON; MURRAY YOUNG; CATHERINE WHINNERY, *Defendants-Appellants*, and IDAHO DEPARTMENT OF CORRECTIONS; HENRY ATENCIO; JEFF ZUMDA; HOWARD KEITH YORDY; AL RAMIREZ, Warden; RICHARD CRAIG; RONA SIEGERT, *Defendants.*	No. 19-35017 D.C. No. 1:17-cv-00151-BLW

ADREE EDMO, AKA Mason Edmo, *Plaintiff-Appellee*, v. IDAHO DEPARTMENT OF CORRECTIONS; HENRY ATENCIO; JEFF ZUMDA; HOWARD KEITH YORDY; AL RAMIREZ, Warden; RICHARD CRAIG; RONA SIEGERT, *Defendants-Appellants*, and CORIZON, INC.; SCOTT ELIASON; MURRAY YOUNG; CATHERINE WHINNERY, *Defendants.*	No. 19-35019 D.C. No. 1:17-cv-00151-BLW ORDER

Filed February 10, 2020

Before: M. Margaret McKeown and Ronald M. Gould, Circuit Judges, and Robert S. Lasnik,* District Judge.

Order;
Statement by Judge O'Scannlain;
Dissent by Judge Collins;
Dissent by Judge Bumatay

* The Honorable Robert S. Lasnik, United States District Judge for the Western District of Washington, sitting by designation.

SUMMARY**

Prisoner Civil Rights

The panel denied a petition for panel rehearing and denied a petition for rehearing en banc on behalf of the court, in a case in which the panel affirmed the district court's entry of a permanent injunction in favor of an Idaho state prisoner, but vacated the injunction to the extent it applied to certain defendants in their individual capacities, in the prisoner's action seeking medical treatment for gender dysphoria.

Respecting the denial of rehearing en banc, Judge O'Scannlain, joined by Judges Callahan, Bea, Ikuta, R. Nelson, Bade, Bress, Bumatay and VanDyke, stated that with its decision not to rehear this case en banc, this court became the first federal court of appeals to mandate that a State pay for and provide sex-reassignment surgery to a prisoner under the Eighth Amendment. Judge O'Scannlain stated that the three-judge panel's conclusion—that any alternative course of treatment would be "cruel and unusual punishment"—is as unjustified as it is unprecedented. To reach such a conclusion, the court created a circuit split, substituted the medical conclusions of federal judges for the clinical judgments of prisoners' treating physicians, redefined the familiar "deliberate indifference" standard, and, in the end, constitutionally enshrined precise and partisan treatment criteria in what is a new, rapidly changing, and highly controversial area of medical practice.

** This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

Dissenting from the denial of rehearing en banc, Judge Collins stated that whether the defendant doctor was negligent or not (a question on which Judge Collins expressed no opinion), his treatment decisions did not amount to "cruel and unusual punishment," and the court thus strayed far from any proper understanding of the Eighth Amendment.

Dissenting from the denial of rehearing en banc, Judge Bumatay, joined by Judges Callahan, Ikuta, R. Nelson, Bade and VanDyke, and by Judge Collins as to Part II, stated that by judicially mandating an innovative and evolving standard of care, the panel effectively constitutionalized a set of guidelines subject to ongoing debate and inaugurated yet another circuit split. And by diluting the requisite state of mind from "deliberate indifference" to negligence, the panel effectively held that—contrary to Supreme Court precedent—medical malpractice does become a constitutional violation merely because the victim is a prisoner.

ORDER

The full court was advised of the petition for rehearing en banc. A judge requested a vote on whether to rehear the matter en banc. The matter failed to receive a majority of the votes of nonrecused active judges in favor of en banc consideration. Fed R. App. P. 35.

The petition for rehearing en banc is **DENIED**. An opinion respecting denial of rehearing en banc, prepared by Judge O'Scannlain, and dissents from denial of rehearing en banc prepared by Judge Collins and Judge Bumatay are filed concurrently with this order.

O'SCANNLAIN, Circuit Judge,[*] with whom CALLAHAN, BEA, IKUTA, R. NELSON, BADE, BRESS, BUMATAY, and VANDYKE, Circuit Judges, join, respecting the denial of rehearing en banc:

With its decision today, our court becomes the first federal court of appeals to mandate that a State pay for and provide sex-reassignment surgery to a prisoner under the Eighth Amendment. The three-judge panel's conclusion—that any alternative course of treatment would be "cruel and unusual punishment"—is as unjustified as it is unprecedented. To reach such a conclusion, the court creates a circuit split, substitutes the medical conclusions of federal

[*] As a judge of this court in senior status, I no longer have the power to vote on calls for rehearing cases en banc or formally to join a dissent from failure to rehear en banc. *See* 28 U.S.C. § 46(c); Fed. R. App. P. 35(a). Following our court's general orders, however, I may participate in discussions of en banc proceedings. *See* Ninth Circuit General Order 5.5(a).

judges for the clinical judgments of prisoners' treating physicians, redefines the familiar "deliberate indifference" standard, and, in the end, constitutionally enshrines precise and partisan treatment criteria in what is a new, rapidly changing, and highly controversial area of medical practice.

Respectfully, I believe our court's unprecedented decision deserved reconsideration en banc.

I

A

In 2012, Adree Edmo (then known as Mason Dean Edmo) was incarcerated for sexually assaulting a sleeping 15-year-old boy. By all accounts, Edmo is afflicted with profound and complex mental illness. She[1] suffers from major depressive disorder, anxiety, alcohol addiction, and drug addiction. At least two clinicians have concluded that she shares the traits of borderline personality disorder. She abused alcohol and methamphetamines every day for many years, stopping only upon her incarceration. A victim of sexual abuse at an early age, she attempted suicide three times before her arrest for sexual assault—twice by overdose and once by cutting.

A new diagnosis was added in 2012: gender dysphoria. Two months after being transferred to the Idaho State Correctional Institution (a men's prison), Edmo sought to speak about hormone therapy with Dr. Scott Eliason, the Board-certified director of psychiatry for Corizon, Inc. (the prison's medical care provider). In Dr. Eliason's view,

[1] Though Edmo was born a male, Edmo has legally changed the sex listed on her birth certificate to female. I therefore use feminine pronouns throughout, just as the panel does.

Edmo met the criteria for gender dysphoria.[2] After the diagnosis was confirmed by another forensic psychiatrist and the prison's Management and Treatment Committee, Edmo was prescribed hormone therapy. She soon changed her legal name and the sex listed on her birth certificate. As a result of four years of hormone therapy, Edmo experienced physical changes, including breast development, redistribution of body fat, and a change in body odor. She now has the same circulating hormones as a typical adult female.

In April 2016, at Edmo's request, Dr. Eliason evaluated her for sex-reassignment surgery.[3] Ultimately, Dr. Eliason decided to maintain the current course of hormones and supportive counseling instead of prescribing surgery. He staffed Edmo's case with Dr. Jeremy Stoddart (a psychiatrist) and Dr. Murray Young (a physician who served as the Regional Medical Director for Corizon), as well as Jeremy Clark, a clinical supervisor and member of the World Professional Association for Transgender Health ("WPATH"). He also presented the evaluation and vetted it

[2] Gender dysphoria is a diagnosis introduced in the latest, fifth edition of the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders*. It replaces the now-obsolete "gender identity disorder" used in the previous edition. The gender dysphoric patient experiences "clinically significant distress or impairment in social, occupational, or other important areas of functioning" that is associated with the feeling of incongruence between perceived gender identity and phenotypic sex. *See* Am. Psychiatric Ass'n, *Diagnostic and Statistical Manual of Mental Disorders* 453 (5th ed. 2013).

[3] The panel adopts the question-begging term "gender confirmation surgery," which is preferred by Edmo and her lawyers. I will continue to use the neutral "sex-reassignment surgery."

before the regular meeting of the multidisciplinary Management Treatment Committee.

Dr. Eliason, supported by Dr. Stoddart, Dr. Young, and Clark, opted not to recommend sex-reassignment surgery for several reasons, some of which are described in his chart notes and others of which were elaborated in their testimony. First, Dr. Eliason noted that Edmo reported that the hormone therapy had improved her dysphoria and Eliason "did not observe significant dysphoria." In the absence of more severe distress, Dr. Eliason could not justify the risks of pursuing the most aggressive—and permanent—treatment through surgery. Second, Dr. Eliason observed that Edmo's comorbid conditions—major depressive disorder and alcohol use disorder, among others—were not adequately controlled. Edmo had refused to attend therapy consistently in prison. She also engaged in self harm (including cutting and attempted castration) and exhibited co-dependency and persistently poor sexual boundaries with other prisoners. In Dr. Eliason's view, Edmo's other mental health disorders were not sufficiently stabilized to handle the stressful process of surgery and transition. Finally, Dr. Eliason observed that Edmo—who was parole-eligible and due to be released in 2021—had not lived among her out-of-prison social network as a woman. He noted the high suicide rates for postoperative patients and was concerned that Edmo might be at greater risk of suicide given the potential lack of support from family, friends, coworkers, and neighbors during her transition. Dr. Eliason did not rule out the possibility of Edmo receiving sex-reassignment surgery at some later point. As Dr. Eliason put it in his notes on his consultation with Edmo, "Medical Necessity for Sexual Reassignment Surgery is not very well defined and is constantly shifting." Citing the changing nature of the

science and the contingent nature of his evaluation of Edmo, his recommendations were merely "for the time being."

B

About a year after her evaluation, Edmo filed this § 1983 lawsuit against Dr. Eliason, the Idaho Department of Corrections, Corizon, and several other individuals, alleging that the prison doctors' treatment choice violated her right to be free from cruel and unusual punishment under the Eighth and Fourteenth Amendments. She then moved for a preliminary injunction to require the prison to provide her with sex-reassignment surgery.

The district court held an evidentiary hearing on the motion. At the outset of the hearing, the court commented that it was hard "to envision" how a request to mandate sex-reassignment surgery could be granted through anything other than a permanent injunction. Nonetheless, the district court evaluated Edmo's motion under the preliminary injunction standard and, only out of "an abundance of caution," provided a footnote evaluating whether an injunction was merited under the more demanding standard for a permanent injunction (which the court erroneously described as "no more rigorous than that applicable to a claim for preliminary mandatory relief"). *Edmo v. Idaho Dep't of Corr.*, 358 F. Supp. 3d 1103, 1122 n.1 (D. Idaho 2018); *see Edmo v. Corizon, Inc.*, 935 F.3d 757, 784 n.13 (9th Cir. 2019) ("[T]he standard for granting permanent injunctive relief is higher (in that it requires actual success on the merits) . . . .").

In addition to testimony from Edmo, Dr. Eliason, and Jeremy Clark, the evidentiary hearing featured testimony from four expert witnesses. Edmo presented Dr. Randi Ettner, a psychologist, and Dr. Ryan Gorton, an emergency

room physician. Dr. Ettner is one of the authors of the World Professional Association of Transgender Health's Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People and chairs WPATH's Committee for Institutionalized Persons. Dr. Gorton serves on that committee too. WPATH—formerly the Harry Benjamin International Gender Dysphoria Association—describes itself as a "professional association" devoted "to developing best practices and supportive policies worldwide that promote health, research, education, respect, dignity, and equality for transsexual, transgender, and gender nonconforming people in all cultural settings." World Prof'l Ass'n for Transgender Health, *Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People* 1 (7th ed. 2011) ("WPATH Standards"). One of WPATH's central functions is to promulgate Standards of Care, which offer minimalist treatment criteria for several possible approaches to gender dysphoria, from puberty-blocking hormones to sex-reassignment surgery.

In addition to Dr. Eliason and Mr. Clark, the State presented Dr. Keelin Garvey, the Chief Psychiatrist of the Massachusetts Department of Corrections and chair of its Gender Dysphoria Treatment Committee, and Dr. Joel Andrade, a clinical social worker who served as clinical director for the Massachusetts Department of Corrections and served on its Gender Dysphoria Treatment Committee. Each set of experts had gaps in their relevant experience. Edmo's experts had never treated *inmates* with gender dysphoria, while the State's experts had never conducted long-term follow-up care with a patient who had undergone sex-reassignment surgery.

Edmo's experts testified that, in their opinion, Edmo needs sex-reassignment surgery. They based their conclusion on the latest edition of WPATH Standards of Care, which contain six criteria for sex-reassignment surgery:

(1) "persistent, well documented gender dysphoria,"

(2) "capacity to make a fully informed decision and to consent for treatment,"

(3) "age of majority,"

(4) "if significant medical or mental health concerns are present, they must be well controlled,"

(5) "12 continuous months of hormone therapy as appropriate to the patient's gender goals,"

(6) "12 continuous months of living in a gender role that is congruent with their gender identity."

Id. at 60. In the opinion of Edmo's experts, Edmo met all six criteria and was unlikely to show further improvement in her gender dysphoria without such surgery.

The State's experts disagreed on three main grounds. First, they did not regard the WPATH Standards as definitive treatment criteria, let alone medical consensus. In their analysis, the evidence underlying the WPATH Standards is not sufficiently well developed, particularly when it comes to the treatment of gender dysphoric prisoners. Therefore, they opined that a prudent, competent doctor might rely on clinical judgment that differs from the (already ambiguous) WPATH Standards. Second, the State's experts testified that, even under WPATH, Edmo failed to meet the fourth

criterion for surgery, which requires that the patient's other mental health concerns be well controlled in order to reduce the risks associated with transitioning. In the view of the State's experts, her mental health raised the concern that she would have trouble transitioning. For their part, Edmo's experts argued that Edmo's depression and addiction were controlled enough for surgery and that some current symptoms (such as self-cutting) stem from her gender dysphoria and therefore can be alleviated with surgery. Finally, the State's experts testified that Edmo also failed to meet the WPATH Standards' sixth criterion for surgery, which requires that Edmo live as a woman for twelve months before surgery. In their view, it was essential that Edmo live those twelve months outside of prison—that is, within her social network—in order to be adequately sure that she and her social network are ready for the challenges posed by transitioning. Edmo's experts disagreed, noting that WPATH says treatment in prisons should "mirror" treatment outside of prisons.

C

Although this appeal is from a grant of a preliminary injunction, at some point the evidentiary hearing on the motion for a preliminary injunction was consolidated into a final bench trial on the merits. It is hard to know when (or if) the parties were given the requisite "clear and unambiguous notice" of consolidation. *See Isaacson v. Horne*, 716 F.3d 1213, 1220 (9th Cir. 2013); *see also Univ. of Tex. v. Camenisch*, 451 U.S. 390, 395 (1981).

The district court applied the Supreme Court's oft-cited rule that "deliberate indifference to serious medical needs of prisoners constitutes the 'unnecessary and wanton infliction of pain' proscribed by the Eighth Amendment." *Estelle v. Gamble*, 429 U.S. 97, 104 (1976) (quoting *Gregg v.*

Georgia, 428 U.S. 153, 173 (1976)). The State agreed that gender dysphoria is a serious medical need, so the only question on the merits is whether Dr. Eliason and his team were "deliberately indifferent" as a matter of law.

The district court concluded that the State's experts were "unconvincing" and gave their opinions "virtually no weight." *Edmo*, 358 F. Supp. 3d at 1125–26. Once such expert testimony was set aside, the district court held that any decision not to prescribe sex-reassignment surgery would be "medically unacceptable under the circumstances" and would therefore violate the Eighth Amendment. *Id.* at 1127. Accordingly, the district court entered an injunction ordering the State to "take all actions reasonably necessary to provide Ms. Edmo gender confirmation surgery as promptly as possible." *Id.* at 1129.

D

The panel has now affirmed the injunction. *See Edmo*, 935 F.3d at 803. Concluding that sex-reassignment surgery was "medically necessary" and that the prison officials chose a different course of treatment "with full awareness of the prisoner's suffering," the panel holds that Dr. Eliason and the other prison officials "violate[d] the Eighth Amendment's prohibition on cruel and unusual punishment." *Id.*

To reach its conclusion that sex-reassignment surgery was medically necessary, the panel spends most of its lengthy opinion extolling and explaining the WPATH Standards of Care. Because Dr. Eliason failed to "follow" or "reasonably deviate from" the WPATH Standards, the panel concluded that his treatment choice was "medically unacceptable under the circumstances." *Id.* at 792. To reach the ultimate conclusion—that Dr. Eliason had a deliberately

indifferent state of mind and was consequently in violation of the Eighth Amendment—the panel posited that Dr. Eliason's awareness of the risks that Edmo would attempt to castrate herself or feel "clinically significant" distress "demonstrates that Dr. Eliason acted with deliberate indifference." *Id.* at 793. Each conclusion was legal error.

II

"Deliberate indifference is a high legal standard." *Toguchi v. Chung*, 391 F.3d 1051, 1060 (9th Cir. 2004). It is, after all, under governing precedent one form of the "unnecessary and wanton infliction of pain" that is the sine qua non of an Eighth Amendment violation. *Estelle*, 429 U.S. at 104 (quoting *Gregg v. Georgia*, 428 U.S. 153, 173 (1976)). Simply put, Edmo must prove that Dr. Eliason's chosen course of treatment was the doing of a criminally reckless—or worse—state of mind. *Farmer v. Brennan*, 511 U.S. 825, 839 (1994).

We have stated that a deliberately indifferent state of mind may be inferred when "the course of treatment the doctors chose was medically unacceptable under the circumstances" and "they chose this course in conscious disregard of an excessive risk to plaintiff's health." *Jackson v. McIntosh*, 90 F.3d 330, 332 (9th Cir. 1996). Yet even most objectively unreasonable medical care is not deliberately indifferent. "[M]ere 'indifference,' 'negligence,' or 'medical malpractice'" is not enough to constitute deliberate indifference. *Lemire v. Cal. Dep't of Corr. & Rehab.*, 726 F.3d 1062, 1082 (9th Cir. 2013) (quoting *Broughton v. Cutter Labs.*, 622 F.2d 458, 460 (9th Cir. 1980)). "Even gross negligence is insufficient to establish deliberate indifference . . . ." *Id.* Likewise, "[a] difference of opinion between a physician and the prisoner—or between medical professionals—concerning what

medical care is appropriate does not amount to deliberate indifference." *Snow v. McDaniel*, 681 F.3d 978, 987 (9th Cir. 2012) (citing *Sanchez v. Vild*, 891 F.2d 240, 242 (9th Cir. 1989)), *overruled on other grounds by Peralta v. Dillard*, 744 F.3d 1076, 1083 (9th Cir. 2014) (en banc). Although the panel organizes its opinion according to the dictum we first articulated in *Jackson*, it so contorts the standard as to render deliberate indifference exactly what we have said it is not: a constitutional prohibition on good-faith disagreement between medical professionals.

A

The panel first, and fundamentally, errs by misunderstanding what it means for a chosen treatment to be medically "unacceptable" for purposes of the Eighth Amendment. As did the district court, the panel concludes that the decision to continue hormone treatment and counseling instead of sex-reassignment surgery for Edmo was "medically unacceptable under the circumstances" because, in short, Dr. Eliason failed to "follow" or "reasonably deviate from" the WPATH Standards of Care. *Edmo*, 935 F.3d at 792. Yet such an approach to the Eighth Amendment suffers from three essential errors. First, contrary to the panel's suggestion, constitutionally acceptable medical care is not defined by the standards of one organization. Second, the panel relies on standards that were promulgated by a controversial self-described advocacy group that dresses ideological commitments as evidence-based conclusions. Third, once the WPATH Standards are put in proper perspective, we are left with a "case of dueling experts," compelling the conclusion that Dr. Eliason's treatment choice was indeed medically acceptable.

1

A mere professional association simply cannot define what qualifies as constitutionally acceptable treatment of prisoners with gender dysphoria. In *Bell v. Wolfish*, 441 U.S. 520 (1979), the Supreme Court rejected the argument that prison conditions must reflect those set forth in the American Public Health Association's Standards for Health Services in Correctional Institutions, the American Correctional Association's Manual of Standards for Adult Correctional Institutions, or the National Sheriffs' Association's Handbook on Jail Architecture. *Id.* at 543 n.27. According to the Court, "the recommendations of these various groups may be instructive in certain cases, [but] they simply do not establish the constitutional minima." *Id.* After all, even acclaimed, leading treatment criteria only represent the "goals recommended by the organization in question" and the views of the promulgating physicians,[4] and so, without more, a physician's disagreement with such criteria is simply the "'difference of medical opinion' . . . [that is] insufficient, as a matter of law, to establish deliberate indifference." *Id.*; *Jackson*, 90 F.3d at 332 (quoting *Sanchez*, 891 F.2d at 242); *accord Snow*, 681 F.3d at 987; *see also Long v. Nix*, 86 F.3d 761, 765 (8th Cir. 1996) ("[N]othing in the Eighth Amendment prevents prison doctors from exercising their independent medical judgment.").

In its discussion of the role of treatment standards, the panel fails to cite a single case in which a professional organization's standards of care defined the line between medically acceptable and unacceptable treatment. Instead, the panel cites two cases, one from the Seventh Circuit and

[4] Although, as we will see, only half of the committee that promulgates the WPATH Standards are physicians.

one from the Eighth, for the proposition that professional organizations' standards of care are "highly *relevant* in determining what care is medically acceptable and unacceptable." *Edmo*, 935 F.3d at 786 (emphasis added). That may be. But as those two cases demonstrate, the range of medically acceptable care is defined by *qualities* of that care (or of its opposite) and not by professional associations. Medically unacceptable care is "*grossly incompetent* or inadequate care," *Allard v. Baldwin*, 779 F.3d 768, 772 (8th Cir. 2015), or care that constitutes "such a substantial departure from accepted professional judgment to demonstrate that the person responsible did not base the decision on . . . [accepted professional] judgment," *Henderson v. Ghosh*, 755 F.3d 559, 566 (7th Cir. 2014) (original parenthetical) (quoting *McGee v. Adams*, 721 F.3d 474, 481 (7th Cir. 2013) (stipulating that "medical professionals . . . are 'entitled to deference in treatment decisions unless no minimally competent professional would have so responded'")). For its part, the First Circuit holds in its own sex-reassignment-surgery case that medical care does not violate the Eighth Amendment so long as it is "reasonably commensurate with the medical standards of prudent professionals." *Kosilek v. Spencer*, 774 F.3d 63, 90 (1st Cir. 2014) (en banc). The panel is alone in its insistence that a professional association's standards add up to the constitutional minima.[5]

[5] Far from countering such assertions, the panel's concession that "deviation from [WPATH] standards does not alone establish an Eighth Amendment claim" is just a truism that recognizes that the Eighth Amendment also contains a subjective element. *Edmo*, 935 F.3d at 789. Moreover, such a statement serves simply to repeat the panel's faulty premise that the WPATH Standards are the appropriate reference point in any analysis of medical acceptability.

2

In the words of the panel, speaking for our court, the WPATH Standards are "the gold standard," the "established standards" for evaluations of the necessity of sex-reassignment surgery, the "undisputed starting point in determining the appropriate treatment for gender dysphoric individuals." *Edmo*, 935 F.3d at 787–88, 788 n.16. But such overwrought acclaim is just the beginning of the panel's thorough enshrinement of the WPATH Standards. The district court chose which expert to rely on by looking at which expert hewed most closely to the WPATH Standards of Care. *See Edmo*, 358 F. Supp. 3d at 1124–26. And the panel uncritically approves such an approach, calling the WPATH Standards "a useful starting point for analyzing the credibility and weight to be given to each expert's opinion." *Edmo*, 935 F.3d at 788 n.16. By rejecting any expert not (in the court's view) appropriately deferential to WPATH, the district court and now the panel have effectively decided ab initio that only the WPATH Standards could constitute medically acceptable treatment.[6]

[6] In enshrining the WPATH Standards as the "gold standard" for determining when to provide surgery to a prisoner with gender dysphoria, the panel makes much of the State's comment in its opening statement before the evidentiary hearing that the WPATH Standards are the "best standards out there." *Edmo*, 935 F.3d at 769, 788 n.16. The panel even goes so far as to insist that "[b]oth sides . . . agree that the appropriate benchmark regarding treatment for gender dysphoria is the World Professional Association of Transgender Health Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People." *Id.* at 767. But, contrary to the panel's suggestion, the State's admission that the WPATH Standards are more refined than any alternative hardly means that the State agrees—or the Eighth Amendment requires—that a medical provider must base treatment decisions on WPATH's criteria. Indeed, before the district

One would be forgiven for inferring from the panel's opinion that its bold assertions about the WPATH Standards are uncontroverted truths. But, as the Fifth Circuit has recognized, "the WPATH Standards of Care reflect not consensus, but merely one side in a sharply contested medical debate over sex reassignment surgery." *Gibson v. Collier*, 920 F.3d 212, 221 (5th Cir. 2019). For its part, the First Circuit, sitting en banc, has likewise held that "[p]rudent medical professionals . . . do reasonably differ in their opinions regarding [WPATH's] requirements." *Kosilek*, 774 F.3d at 88. Our court should have done the same.

The WPATH Standards are merely criteria promulgated by a controversial private organization with a declared point of view. According to Dr. Stephen Levine, author of the WPATH Standards' fifth version, former Chairman of WPATH's Standards of Care Committee, and the court-appointed expert in *Kosilek*, WPATH attempts to be "both a scientific organization and an advocacy group for the transgendered. These aspirations sometimes conflict." *Id.* at 78. Sometimes the pressure to be advocates wins the day. As Levine put it, "WPATH is supportive to those who want sex reassignment surgery. . . . Skepticism and strong alternate views are not well tolerated. Such views have been known to be greeted with antipathy from the large numbers of nonprofessional adults who attend each [of] the organization's biennial meetings . . . ." *Id.* (ellipses and

court and before our court, the State clearly rejected the notion that any particular treatment criteria defines what is medically acceptable, stating that Dr. Eliason's choice "should be ratified as long as it is a reasonable choice." The panel erroneously construes the State's refusal to concede that it violated the WPATH Standards as a concession that such standards are the "benchmark" of legally acceptable medical care.

brackets original). WPATH's own description of its drafting process makes this clear. Initially, the sections of the sixth version were each assigned to an individual member of WPATH who then published a literature review with suggested revisions. WPATH Standards, *supra*, at 109. The suggested revisions were then discussed and debated by a thirty-four-person Revision Committee, all before a subcommittee drafted the new document. *Id.* at 109–11. Only about half of the Revision Committee possesses a medical degree. The rest are sexologists, psychotherapists, or career activists, with a sociologist and a law professor rounding out the group. *Id.* at 111.

The pressure to be advocates appears to have won the day in the WPATH Standards' recommendations regarding institutionalized persons. Recall that one central point of contention between the State's witnesses and Edmo's was over whether Edmo's time undergoing hormone therapy in prison provides sufficient guarantee that she could live well outside of prison as a woman without having ever done so before. The district court resolved the debate by citing the WPATH Standards' section on institutionalized persons, *see Edmo*, 358 F. Supp. 3d at 1125, which tersely stipulates that institutionalized persons should not be "discriminated against" on the basis of their institutionalization, WPATH Standards, *supra*, at 67. Such a recommendation is not supported by any research about the similarity between prisoners' experiences with sex-reassignment surgery and that of the general public. Indeed, as Edmo's expert witness and WPATH author, Dr. Randi Ettner, admits, there is only one known instance of a person undergoing sex-reassignment surgery while incarcerated—leaving medical knowledge about how such surgery might differ totally undeveloped.

Instead, WPATH's recommendation for institutionalized persons merely expresses a policy preference. The article from which the recommendations are adapted stipulates upfront that, because WPATH's "mission" is "to advocate for nondiscriminatory" care, it presumes that treatment choices should be the same for all "demographic variables, unless there is a clinical indication to provide services in a different fashion." George R. Brown, *Recommended Revisions to the World Professional Association for Transgender Health's* Standards of Care *Section on Medical Care for Incarcerated Persons with Gender Identity Disorder*, 11 Int'l J. of Transgenderism 133, 134 (2009). Unable to make an evidentiary finding from a sample size of one, the article concludes that its presumption should set the standard of care and then proceeds to recommend revisions with the express purpose of influencing how courts review gender dysphoria treatments under the Eighth Amendment. *Id.* at 133, 135. As a later peer-reviewed study by Dr. Cynthia Osborne and Dr. Anne Lawrence put it, WPATH's institutionalized-persons recommendations follow from an "ethical principle," not "extensive clinical experience." Cynthia S. Osborne & Anne A. Lawrence, *Male Prison Inmates With Gender Dysphoria: When Is Sex Reassignment Surgery Appropriate?*, 45 Archives of Sexual Behav. 1649, 1651 (2016).

Even apart from the concerns over WPATH's ideological commitments, its evidentiary basis is not sufficient to justify the court's reliance on its strict terms. The WPATH Standards seem to suggest as much. In its own words, the WPATH Standards are simply "*flexible* clinical guidelines," which explicitly allow that "individual health professionals and programs may modify them." WPATH Standards, *supra*, at 2. Indeed, the most recent WPATH Standards "represents a significant departure from previous

versions" in part due to significant changes in researchers' conclusions over the preceding decade. *Id.* at 1 n.2. Moreover, the WPATH Standards lack the evidence-based grading system that characterizes archetypal treatment guidelines, such as the Endocrine Society's hormone therapy guidelines. Lacking evidence-based grading, the WPATH Standards leave practitioners in the dark about the strength of a given recommendation. *See* William Byne et al., *Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder*, 41 Archives of Sexual Behav. 759, 783 (2012) (concluding that "the level of evidence" supporting WPATH's Standards' criteria for sex-reassignment surgery "was generally low"). For these reasons, the Centers for Medicare & Medicaid Services, an agency of the United States Department of Health and Human Services, decided, "[b]ased on a thorough review of the clinical evidence," that providers may consult treatment criteria other than WPATH, including providers' own criteria. Ctrs. for Medicare & Medicaid Servs, *Proposed Decision Memo for Gender Dysphoria and Gender Reassignment Surgery* (June 2, 2016); Ctrs. for Medicare & Medicaid Servs, *Decision Memo for Gender Dysphoria and Gender Reassignment Surgery* (Aug. 30, 2016).

3

The panel's disposition results from its failure to put the WPATH Standards in proper perspective. Had the district court understood that Edmo's experts' role in WPATH marks them not with special insight into the legally acceptable care, but rather as mere participants in an ongoing medical debate, they would have acknowledged this case for what it is: a "case of dueling experts." *Edmo*, 935 F.3d at 787. Instead of giving Drs. Garvey and Andrade (to say nothing of Dr. Eliason) "no weight" due to their insufficient

fealty to WPATH, the district court should have recognized them as legitimate, experienced participants in that debate. And had the State's experts' criticisms of and interpretation of the WPATH Standards been given proper weight—any weight at all—the district court would have had to conclude that the State's disagreement with Edmo's experts was a mere "difference of medical opinion," not a constitutional violation. *Jackson*, 90 F.3d at 332.

So too with its assessment of Dr. Eliason's treatment choice. It is instructive that the worst the district court can say about Dr. Eliason is that he "did not apply the WPATH criteria." *Edmo*, 358 F. Supp. 3d at 1126. Focusing the analysis not on whether Dr. Eliason applied the standards of a professional association but rather on whether the treatment choice was within that of a prudent, competent practitioner, the cautious treatment selected by Dr. Eliason is plainly constitutionally acceptable.

As Drs. Garvey and Andrade explain, it is medically acceptable to offer Edmo a treatment of hormone therapy and psychotherapy but not sex-reassignment surgery. The practitioners' fear that sex-reassignment surgery would exacerbate Edmo's other mental illnesses and increase the risk of surgery was a genuine and sound fear. As Dr. Garvey put it, "[b]ased on her current coping strategies, I would be concerned about her suicide risk after surgery." Although the measured "regret rate," which refers to the proportion of postoperative patients who regret their surgery, is "low," *see Edmo*, 935 F.3d at 771, the district court and the panel failed to acknowledge detailed testimony that those studies neglected to follow up with such a high proportion of the observed sample that the stated figure does not "represent the full picture." In Dr. Andrade's opinion, "I think there are things she needs to work out in therapy in the short and long

term before she can make a really well-informed decision about surgery." He raised the concern that Edmo is particularly at risk because of "unresolved trauma" that may stem, not from gender dysphoria, but instead from past sexual abuse.

Dr. Eliason's view that Edmo needed to have lived as a woman outside of prison in order to ensure that she would be able to adapt well after the surgery was also legitimate. Indeed, under the peer-reviewed treatment criteria developed by Drs. Osborne and Lawrence, Edmo was not eligible for sex-reassignment surgery for these exact reasons. Acknowledging the lack of evidence concerning the effects of sex-reassignment surgery on inmates, the unique challenges imposed by the correctional setting, and the significant risk of patient regret, Drs. Osborne and Lawrence proposed criteria that require a prospective patient have "a satisfactory disciplinary record and demonstrated capacity to cooperate" and "a long period of expected incarceration after [surgery]," among others. Osborne & Lawrence, *supra*, at 1661. This latter criterion helps to ensure that male-to-female patients have "a longer period of time to consolidate one's feminine gender identity and gender role." *Id.* at 1660; *see also id.* at 1656 ("[I]nmates with [gender dysphoria] who attempt to live in female-typical gender roles within men's prisons . . . could not effectively prepare" for life after surgery.) The district court disregarded such additional, peer-reviewed treatment criteria because they "are not part of the WPATH criteria and are in opposition to the WPATH Standards of Care." *Edmo*, 358 F. Supp. 3d at 1126. Had the district court taken a step back and considered not whether Osborne and Lawrence were WPATH-compliant but rather whether a competent physician could rely on their reasoning, it would have had to conclude that Dr. Eliason's treatment choice was that of a competent, prudent physician.

Perhaps recognizing such problems with the district court's definition of medical unacceptability, the panel concludes its medical-unacceptability analysis by changing the subject. Instead of considering whether Dr. Eliason's choice of *treatment* was medically unacceptable, the panel fixates on Dr. Eliason's chart notes, which sets forth three general categories in which he believes sex-reassignment surgery may be required: (1) "Congenital malformation or ambiguous genitalia," (2) "Severe and devastating dysphoria that is primarily due to genitals," (3) or "Some type of medical problem in which endogenous sexual hormones were causing severe physiological damage." According to the panel, such categories "bear little resemblance" to the WPATH Standards and therefore "Dr. Eliason's evaluation was not an exercise of medically acceptable professional judgment." *Edmo*, 935 F.3d at 791–92. In the first place, Dr. Eliason's categories are not meant to substitute for treatment standards. Such categories describe three broad pools of eligible patients; whether a particular patient belongs in a certain pool—by having dysphoria sufficiently severe to require sex-reassignment surgery, for instance—would be resolved by more detailed evaluative criteria. In the second place, conformity to WPATH is not the test of constitutionally acceptable treatment of gender dysphoria. But more broadly, the panel simply asks the wrong question. Deliberate indifference may be inferred when "the *course of treatment* the doctors chose was medically unacceptable under the circumstances," not when the doctors' contemporaneous explanation of the choice is incomplete. *Jackson*, 90 F.3d at 332 (emphasis added); *see also Snow*, 681 F.3d at 988; *Toguchi*, 391 F.3d at 1058; *Hamby v. Hammond*, 821 F.3d 1085, 1092 (9th Cir. 2016) (all referring to the "course of treatment," not the rationale). It does not matter that Dr. Eliason's testimony justifies his treatment choice in ways not explicit in his chart notes such that the

panel calls his testimony a "post hoc explanation." *Edmo*, 935 F.3d at 791. So long as the ultimate treatment *choice* was medically acceptable, our precedents tell us, we cannot infer "the unnecessary and wanton infliction of pain" that violates the Eighth Amendment.

B

Even were the panel correct that the only medically acceptable way to approach a gender dysphoric patient's request for sex-reassignment surgery is to apply the WPATH Standards of Care, we still could not infer a constitutional violation from these facts. As the Supreme Court has explained, the Eighth Amendment simply proscribes categories of punishment, and punishment is "a deliberate act intended to chastise or deter." *Wilson v. Seiter*, 501 U.S. 294, 299–300 (1991). "[O]nly the 'unnecessary *and wanton* infliction of pain' implicates the Eighth Amendment." *Id.* at 297 (quoting *Estelle*, 429 U.S. at 104) (emphasis original). Hence the commonplace deliberate-indifference inquiry, which is a culpability standard equivalent to criminal recklessness. *Farmer*, 511 U.S. at 839–40. Simply put, unless the official "knows of and disregards an excessive risk to inmate health and safety," he does not violate the Eighth Amendment. *Id.* at 837.

1

With little explanation, the panel castigates Dr. Eliason for having "disregarded" risks that he directly and forthrightly addressed. *Edmo*, 935 F.3d at 793. Far from disregarding the risk that Edmo would attempt to castrate herself, Dr. Eliason investigated the causes of such a risk and took concrete steps to mitigate it. Edmo's self-harm (including her castration attempts) followed closely after her disciplinary infractions and other severe stressors.

Identifying this causal connection, Dr. Eliason prescribed and encouraged regular counseling to address Edmo's acting out and her ability to cope. Dr. Eliason also sought to further deter self-castration by explaining to Edmo that she will need to have intact genitals for any eventual surgery, something Edmo now understands and articulated in her testimony. Likewise, contrary to the panel's conclusion that he disregarded the risk of continued distress, Dr. Eliason opted for a treatment of continued hormone therapy and more regular supportive counseling precisely because hormone therapy had already substantially ameliorated the distress from the dysphoria.

Furthermore, the panel errs by fixating on such individual risks. Physicians ministrate to whole individuals with whole diseases. Thus, individual risks may—and frequently do—persist for the sake of the overall health of the person. Dr. Eliason and his staff clearly believed their treatment choice would mitigate *overall risk*, including grave risks the panel downplays. Given Edmo's long-term struggles with severe depression and addiction, coupled with the fact that she had not lived as a woman within her social network, Eliason and the other doctors with whom he staffed the evaluation were concerned that she would have trouble adjusting after surgery, which could lead to regret, relapse, or new mood disorders. Ultimately, they worried that she might attempt suicide again. Such risks are not trifling and, in light of them, Dr. Eliason's willingness to accept some risk that Edmo would try to castrate herself or would continue to feel the distress of gender dysphoria (while taking steps to mitigate such risks) is anything but deliberately indifferent.

2

None of this is to acquiesce in the straw-man argument set up by the panel: that, so long as officials provide some care, they are immunized from an Eighth Amendment claim. One may assume that some medical care is indeed so obviously inadequate that, without any direct evidence of the defendant's state of mind, we may infer that the defendant was deliberately indifferent. *See Farmer*, 511 U.S. at 842 (remarking that deliberate indifference is "subject to demonstration in the usual ways, including inference from circumstantial evidence" and may be inferred "from the very fact that the risk was obvious").[7] But that is not this case.

Even in a legal universe in which the WPATH Standards define adequate care, Dr. Eliason's deviations were not deliberately indifferent. He selected a course of treatment that, in light of the complex of diagnoses, the grave risks, and the rapidly evolving nature of the medical research, was

[7] It should, however, be noted that the panel fails to identify a precedent of ours in which we have inferred a physician's deliberate indifference solely from the inadequate nature of the treatment and the persistence of known risks. In the nearest cases, some other circumstantial evidence has suggested the obviousness of the inadequacy such that the physician must have been aware of the inadequacy. *E.g.*, *Snow*, 681 F.3d at 988 (non-specialist refused the recommendation of a treating specialist); *Hamilton v. Endell*, 981 F.2d 1062, 1067 (9th Cir. 1992) (same); *Lopez v. Smith*, 203 F.3d 1122, 1132 (9th Cir. 2000) (same); *Hunt v. Dental Dep't*, 865 F.2d 198, 201 (9th Cir. 1989) (refusal to replace the dentures prisoner had been prescribed); *Jett v. Penner*, 439 F.3d 1091, 1098 (9th Cir. 2006) (prisoner not referred to specialist for reasons unrelated to the prisoner's medical needs and medical records were manipulated); *Colwell v. Bannister*, 763 F.3d 1060, 1070 (9th Cir. 2014) (reliance on arbitrary prison policy). I do not doubt that mere inadequacy may raise the inference of deliberate indifference, but we seem to leave such an inference for cases of genuine quackery.

not obviously inadequate. *Cf. Lemire*, 726 F.3d at 1075 ("A prison official's deliberately indifferent conduct will generally 'shock the conscience' so long as the prison official had time to deliberate before acting . . . ."). He subjected his assessment to a review process intended to surface any possibility he was not considering, a review process that included several doctors and a full committee. And far from being an "unjustifiable" or "gross" deviation from the WPATH Standards, he departed from WPATH by raising the Standards' own concerns for the presence of comorbid conditions and the patient's limited experience as a woman. *See Farmer*, 511 U.S. at 839 (incorporating the Model Penal Code's definition of criminal recklessness); Model Penal Code § 2.02(2)(c) (1985) (stating that the criminally reckless individual "disregards a substantial and unjustifiable risk" and that such disregard "involves a gross deviation from the standard of conduct that a law-abiding person would observe in the actor's situation."). Indeed, the panel concludes that his deviations were simply not "reasonable"—the test for negligent malpractice, not deliberate indifference. *Edmo*, 935 F.3d at 792. "Eighth Amendment liability requires 'more than ordinary lack of due care . . . .'" *Farmer*, 511 U.S. at 835 (quoting *Whitley v. Albers*, 475 U.S. 312, 319 (1986)).

III

The panel's novel approach to Eighth Amendment claims for sex-reassignment surgery conflicts with every other circuit to consider the issue. The panel acknowledges such a circuit split with the Fifth Circuit's opinion in *Gibson v. Collier*, 920 F.3d 212 (5th Cir. 2019), but tries—and fails—to distinguish the First Circuit's en banc opinion in *Kosilek v. Spencer*, 774 F.3d 63 (1st Cir. 2014). *See Edmo*, 935 F.3d at 794–95. The panel does not even address a third

decision: the Tenth Circuit's opinion in *Lamb v. Norwood*, 899 F.3d 1159 (10th Cir. 2018).

Just as in this case, the First Circuit considered an appeal of an injunction mandating sex-reassignment surgery. But, unlike our court, the First Circuit reversed. Though the panel attempts to downplay the direct conflict between its opinion and *Kosilek* by pointing to minor differences between the factual circumstances in each case,[8] the decisive differences are matters of law. As to whether the care was medically unacceptable, the First Circuit held that medically acceptable treatment of gender dysphoric prisoners is not synonymous with the demands of WPATH. *Kosilek* first reversed the district court's finding that one of the State's experts was "illegitimate" because the district court "made a significantly flawed inferential leap: it relied on its own—non-medical—judgment" and put too much "weight" on the WPATH Standards. *Kosilek*, 774 F.3d at 87–88. With that expert now taken seriously, the First Circuit held that the denial of Kosilek's sex-reassignment surgery was medically

[8] The differences between the circumstances in *Kosilek* and those in this case are not substantial enough to distinguish the holdings. The clinical judgments in each case were motivated by concerns about coexisting mental health conditions and the risk of suicide. *Kosilek*, 774 F.3d at 72. Just as in this case, *Kosilek* surfaced expert opinions that the WPATH Standards are best applied flexibly, that in-prison experience in the newly assigned gender is not a sufficient guarantee of ability to transition, and that practitioners face a "dearth of empirical research" on sex-reassignment surgery. *Id.* at 72–73, 76. The "security concerns" over how to house a potential postoperative Kosilek, which the panel considers the foremost difference between the two cases, was not even essential to *Kosilek*'s holding. *See Edmo*, 935 F.3d at 794; *Kosilek*, 774 F.3d at 91–92 (concluding that the officials' "choice of a medical option . . . does not exhibit a level of inattention or callousness to a prisoner's needs rising to a constitutional violation" before even analyzing the security concerns).

acceptable because it was within the bounds of "the medical standards of prudent professionals." *Id.* at 90. On the question of deliberate indifference, the First Circuit applied a test, which, unlike the panel's inference from the practitioners' mere knowledge that a course of treatment carried risks, asked whether the practitioners "knew or should have known" that course of treatment was *medically unacceptable*. *Id.* at 91.

For its part, the Fifth Circuit has held that good faith denial of sex-reassignment surgery *never* violates the Eighth Amendment. Recognizing "large gaps" in medical knowledge and a "robust and substantial good faith disagreement dividing respected members of the expert medical community," the Fifth Circuit concluded that "there can be no claim [for sex-reassignment surgery] under the Eighth Amendment." *Gibson*, 920 F.3d at 220, 222. Indeed, Texas's refusal to even evaluate the inmate for sex-reassignment surgery is, in the words of the Fifth Circuit, not "so unconscionable as to fall below society's minimum standards of decency" and permit an Eighth Amendment claim. *Id*. at 216 (quoting *Kosilek*, 774 F.3d at 96).

Finally, the Tenth Circuit has upheld the entry of summary judgment against a prisoner's Eighth Amendment claim for sex-reassignment surgery. *See Lamb*, 899 F.3d at 1163. As in this case, the doctor who evaluated the prisoner in *Lamb* determined that "surgery is impractical and unnecessary in light of the availability and effectiveness of more conservative therapies." *Id.* Adopting *Kosilek*'s subjective standard—that an Eighth Amendment violation would take place "only if prison officials had known or should have known" that "sex reassignment surgery [was] the only medically adequate treatment"—the Tenth Circuit held that "prison officials could not have been deliberately

indifferent by implementing the course of treatment recommended by a licensed medical doctor." *Id.* at 1163 & n.11 (citing *Kosilek*, 774 F.3d at 91).

Although I am not aware of any other circuits to have directly addressed the questions posed in this case,[9] for its part, the Seventh Circuit has held that it is at least not "clearly established" that there is a constitutional right to gender-dysphoria treatment beyond hormone therapy. *Campbell v. Kallas*, 936 F.3d 536, 549 (7th Cir. 2019). Nor is it "clearly established" that a prison medical provider is prohibited from denying sex-reassignment surgery on the basis of the patient's status as an institutionalized person. *Id.* at 541, 549.

With this decision, our circuit sets itself apart.

IV

I do not know whether sex-reassignment surgery will ameliorate or exacerbate Adree Edmo's suffering. Fortunately, the Constitution does not ask federal judges to put on white coats and decide vexed questions of psychiatric medicine. The Eighth Amendment forbids the "unnecessary and wanton infliction of pain," not the "difference of opinion between a physician and the prisoner—or between medical

[9] The Seventh and Fourth Circuits (along with our own circuit) have also held that arbitrary blanket bans on certain gender dysphoria treatments can violate the Eighth Amendment—an issue not presented here because Idaho evaluates prisoner requests for sex-reassignment surgery on a case-by-case basis. *See Rosati v. Igbinoso*, 791 F.3d 1037, 1040 (9th Cir. 2015); *De'lonta v. Johnson*, 708 F.3d 520, 526 (4th Cir. 2013); *Fields v. Smith*, 653 F.3d 550, 556 (7th Cir. 2011).

professionals." *Snow*, 681 F.3d at 985, 987 (quoting *Estelle*, 429 U.S. at 104).

Yet today our court assumes the role of Clinical Advisory Committee. Far from rendering an opinion "individual to Edmo" that "rests on the record," *Edmo*, 935 F.3d at 767, the panel entrenches the district court's unfortunate legal errors as the law of this circuit. Instead of permitting prudent, competent patient care, our court enshrines the WPATH Standards as an enforceable "medical consensus," effectively putting an ideologically driven private organization in control of every relationship between a doctor and a gender dysphoric prisoner within our circuit. Instead of reserving the Eighth Amendment for the grossly, unjustifiably reckless, the panel infers a culpable state of mind from the supposed inadequacy of the treatment.

We have applied the traditional deliberate-indifference standard to requests for back surgery, kidney transplant, hip replacement, antipsychotic medication, and hernia surgery. Yet suddenly the request for sex-reassignment surgery—and the panel's closing appeal to what it calls the "increased social awareness" of the needs and wants of transgender citizens—effects a revolution in our law! *Id.* at 803. The temptation to stand at what we are told is society's next frontier and to invent a constitutional right to state-funded sex-reassignment surgery does not justify the revision of previously universal principles of Eighth Amendment jurisprudence.

Dr. Eliason and the State's other practitioners were not deliberately indifferent—far from it. And they certainly were not guilty of violating the Eighth Amendment. They confronted the serious risks to Edmo's health, especially the gravest one. They considered the knotty quandary posed by her overlapping illnesses and the vicissitudes of her life.

Mindful of the dictate "first do no harm," these doctors determined that the appropriate treatment would be more cautious and more reversible than the one the patient desired. And they did so in the shadow of the ongoing debate about when the surgical replacement of the genitals is curative and when it is not.

Surely this was not cruel and unusual punishment.

COLLINS, Circuit Judge, dissenting from the denial of rehearing en banc:

The Supreme Court has held that a prisoner claiming that his or her medical treatment is so inadequate that it constitutes "cruel and unusual punishment" in violation of the Eighth Amendment must make the demanding showing that prison officials acted with "deliberate indifference" to the prisoner's "serious medical needs." *Estelle v. Gamble*, 429 U.S. 97, 104 (1976). As judges of an "inferior Court[]," *see* U.S. Const. art. III, § 1, we are bound to apply that standard, but as Judge Bumatay explains, the panel here effectively waters it down into a "mere negligence" test. *See infra* at 47–48 (Bumatay, J., dissenting from denial of rehearing en banc). That is, by narrowly defining the range of "medically acceptable" options that the court believes a prison doctor may properly consider in a case such as this one, and by then inferring deliberate indifference from Dr. Eliason's failure to agree with that narrow range, the district court and the panel have applied standards that look much more like negligence than deliberate indifference. *Id.* at 45–48. Whether Dr. Eliason was negligent or not (a question on which I express no opinion), his treatment decisions do not amount to "cruel and unusual punishment," and we have thus strayed far from any proper understanding

of the Eighth Amendment. I therefore join Part II of Judge Bumatay's dissent, and I respectfully dissent from our failure to rehear this case en banc.

BUMATAY, Circuit Judge, with whom CALLAHAN, IKUTA, R. NELSON, BADE, and VANDYKE, Circuit Judges, join, and with whom COLLINS, Circuit Judge, joins as to Part II, dissenting from the denial of rehearing en banc:

Like the panel and the district court, I hold great sympathy for Adree Edmo's medical situation. And as with all citizens, her constitutional rights deserve the utmost respect and vigilant protection. As the district court rightly stated,

> The Rule of Law, which is the bedrock of our legal system, promises that all individuals will be afforded the full protection of our legal system and the rights guaranteed by our Constitution. This is so whether the individual seeking that protection is black, white, male, female, gay, straight, or, as in this case, transgender.[1]

Adree Edmo is a transgender woman suffering from gender dysphoria—a serious medical condition. While incarcerated in Idaho's correctional facilities, she asked that her gender dysphoria be treated with sex-reassignment

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[1] *Edmo v. Idaho Dep't of Corr.*, 358 F. Supp. 3d 1103, 1109 (D. Idaho 2018), *order clarified*, No. 1:17-CV-00151-BLW, 2019 WL 2319527 (D. Idaho May 31, 2019), *and aff'd in part, vacated in part, remanded sub nom. Edmo v. Corizon, Inc.*, 935 F.3d 757 (9th Cir. 2019).

surgery ("SRS"). After consultation with a prison doctor, her request was denied. She then sued under the Eighth Amendment.[2]

I respect Edmo's wishes and hope she is afforded the best treatment possible. But whether SRS is the optimal treatment for Edmo's gender dysphoria is not before us. As judges, our role is not to take sides in matters of conflicting medical care. Rather, our duty is to faithfully interpret the Constitution.

That duty commands that we apply the Eighth Amendment, not our sympathies. Here, in disregard of the text and history of the Constitution and precedent, the panel's decision elevates innovative and evolving medical standards to be the constitutional threshold for prison medical care. In doing so, the panel minimizes the standard for establishing a violation of the Eighth Amendment.

After today's denial of rehearing en banc, the Ninth Circuit stands alone in finding that a difference of medical opinion in this debated area of treatment amounts to "cruel and unusual" punishment under the Constitution. While this posture does not mean we are wrong, it should at least give us pause before embarking on a new constitutional trajectory. This is especially true given the original meaning of the Eighth Amendment.

Because the panel's opinion reads into the Eighth Amendment's Cruel and Unusual Clause a meaning in conflict with its text, original meaning, and controlling

[2] Because Judge O'Scannlain thoroughly recites the relevant facts in his opinion respecting the denial of the rehearing en banc, which I join in full, I do not reiterate them here.

precedent, I respectfully dissent from the denial of rehearing en banc.

I.

In holding that Idaho[3] violated the Eighth Amendment, the panel opined that the Constitution's text and original meaning merited "little discussion." *See Edmo*, 935 F.3d at 797 n.21. I disagree.

As inferior court judges, we are bound by Supreme Court precedent. Yet, in my view, judges also have a "duty to interpret the Constitution in light of its text, structure, and original understanding." *NLRB v. Noel Canning*, 573 U.S. 513, 573 (2014) (Scalia, J., concurring). While we must faithfully follow the Court's Eighth Amendment precedent as articulated in *Estelle v. Gamble*, 429 U.S. 97 (1976), and its progeny, "[w]e should resolve questions about the scope of those precedents in light of and in the direction of the constitutional text and constitutional history." *Free Enter. Fund v. Public Co. Accounting Oversight Bd.*, 537 F.3d 667, 698 (D.C. Cir. 2008) (Kavanaugh, J., dissenting), *aff'd in part, rev'd in part and remanded*, 561 U.S. 477 (2010).

Accordingly, the Eighth Amendment's history and original understanding are of vital importance to this case.

A.

The Eighth Amendment provides that "[e]xcessive bail shall not be required, nor excessive fines imposed, nor cruel and unusual punishments inflicted." U.S. Const. amend.

[3] For simplicity, I collectively refer to Defendants below and Appellants here as "Idaho."

VIII. Even just a cursory review of the amendment's original meaning shows that Edmo's claims fall far below a constitutional violation as a matter of text and original understanding.

At the time of the Eighth Amendment's ratification, "cruel" meant "[p]leased with hurting others; inhuman; hard-hearted; void of pity; wanting compassion; savage; barbarous; unrelenting." *Bucklew v. Precythe*, 139 S. Ct. 1112, 1123 (2019) (citing 1 Samuel Johnson, *A Dictionary of the English Language* (4th ed. 1773); 1 Noah Webster, *An American Dictionary of the English Language* (1828) ("Disposed to give pain to others, in body or mind; willing or pleased to torment, vex or afflict; inhuman; destitute of pity, compassion or kindness."). Even today, "cruel" punishments have been described as "inhumane," *Farmer v. Brennan*, 511 U.S. 825, 838 (1994), involving the "unnecessary and *wanton* infliction of pain," *Whitley v. Albers*, 475 U.S. 312, 319 (1986) (emphasis added) (citations omitted), or involving the "*superadd[ition]* of terror, pain, or disgrace." *Bucklew*, 139 S. Ct. at 1124 (emphasis added) (internal quotation marks and citations omitted).

In the 18th Century, a punishment was "unusual" if it ran contrary to longstanding usage or custom, or had long fallen out of use. *Bucklew*, 139 S. Ct. at 1123 (citing 4 William Blackstone, *Commentaries on the Laws of England* 370 (1769); Stuart Banner, *The Death Penalty: An American History* 76 (2002); *Baze v. Rees*, 553 U.S. 35, 97 (2008) (Thomas, J., concurring); John F. Stinneford, *The Original Meaning of "Unusual": The Eighth Amendment as a Bar to Cruel Innovation*, 102 Nw. U. L. Rev. 1739, 1770–71, 1814 (2008)). This early understanding comports with the plain meaning of "unusual," which has changed little from our

Nation's founding. *See Harmelin v. Michigan*, 501 U.S. 957, 976 (1991) (comparing Webster's American Dictionary (1828) definition of "unusual" as that which does not "occu[r] in ordinary practice" with Webster's Second International Dictionary 2807 (1954) as that which is not "in common use.").

Conversely, customs enjoying a long history of usage were described as "usual" practices. Stinneford, *supra*, at 1770. James Wilson, a key contributor to the Constitution, stated that "long customs, approved by the consent of those who use them, acquire the qualities of a law." 2 James Wilson, *Collected Works of James Wilson* 759 (Kermit L. Hall & Mark David Hall eds., Indianapolis, Liberty Fund 2007); *see also* Stinneford, *supra*, at 1769. Likewise, early American courts construing the term "cruel and unusual" (generally, as used in state constitutions) upheld punishments that were not "unusual" in light of common law usage. Stinneford, *supra*, at 1810–11 (citing *Barker v. People*, 20 Johns. 457, 459 (N.Y. Sup. Ct. 1823), *aff'd*, 3 Cow. 686 (N.Y. 1824); *Commonwealth v. Wyatt*, 27 Va. 694, 701 (Va. Gen. Ct. 1828); *People v. Potter*, 1 Edm. Sel. Cas. 235, 245 (N.Y. Sup. Ct. 1846)). Thus, "[u]nder the plain meaning of the term, a prison policy cannot be 'unusual' if it is widely practiced in prisons across the country." *Gibson v. Collier*, 920 F.3d 212, 226 (5th Cir. 2019).

Finally, various views have been proposed with respect to the original meaning of "punishment" in the Eighth Amendment. Some view the word as being inapplicable to conditions of confinement. *See, e.g.*, *Farmer*, 511 U.S. at 837 ("The Eighth Amendment does not outlaw cruel and unusual 'conditions'; it outlaws cruel and unusual 'punishments.'") (Souter, J.). Some have even suggested

that "punishment" refers only to sentences imposed by a judge or jury. *See Hudson v. McMillian*, 503 U.S. 1, 18 (1992) (Thomas, J., dissenting); *but see Helling v. McKinney*, 509 U.S. 25, 40 (1993) (Thomas, J., dissenting) (recognizing that the "evidence is not overwhelming" on this question). Others believe the term was originally understood to encompass more than sentences called for by statute or meted out from the bench or jury box, but it required deliberate intent. *See, e.g.*, *Wilson v. Seiter*, 501 U.S. 294, 300 (1991) ("The infliction of punishment is a deliberate act intended to chastise or deter. This is what the word means today; it is what it meant in the eighteenth century.") (Scalia, J.) (quoting *Duckworth v. Franzen*, 780 F.2d 645, 652 (7th Cir. 1985)); *see also* Celia Rumann, *Tortured History: Finding Our Way Back to the Lost Origins of the Eighth Amendment*, 31 Pepp. L. Rev. 661, 675, 677 (2004) (presenting historical evidence that the word punishment was "understood at the time to include torturous interrogation") (citing 4 William Blackstone, *Commentaries on the Laws of England*; 3 Jonathan Elliot, The Debates in the Several State Conventions on the Adoption of the Federal Constitution 447–48).

B.

While the foregoing overview does not provide the full contours of the original understanding of the Cruel and Unusual Clause, it demonstrates that Idaho's actions are far from a constitutional violation based on the clause's text and original meaning. Idaho's actions simply do not amount to the "barbarous" or "inhuman" treatment so out of line with longstanding practice as to be forbidden by the Eighth Amendment.

No longstanding practice exists of prison-funded SRS.[4] Indeed, the medical standards at the heart of Edmo's claim are innovative and evolving. The standards of care relied on by Edmo were promulgated by the World Professional Association for Transgender Health ("WPATH") in 2011—only about five years before Edmo's lawsuit. WPATH, *Standard of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People* (7th ed. 2011) ("WPATH standards"). As the standards themselves note, this "field of medicine is evolving." The WPATH standards also call for flexibility, individual tailoring, and wide latitude in treatment options.

Likewise, as recognized by numerous federal courts, the WPATH standards are not accepted as medical consensus. The first circuit court to address the issue ruled that the WPATH standards did not foreclose alternative treatment options, and that a doctor's decision to choose a non-WPATH treatment did not violate the Eighth Amendment. *Kosilek v. Spencer*, 774 F.3d 63, 90 (1st Cir. 2014). The Fifth Circuit also found that the WPATH standards remained controversial and did not reflect a consensus. *Gibson*, 920 F.3d at 223. Similarly, after reciting the WPATH standard's recommended treatment options for gender dysphoria, the Tenth Circuit rejected a claim that prison officials acted with deliberate indifference "by implementing [an alternative] course of treatment recommended by a licensed medical doctor," rather than

[4] *See, e.g.*, *Quine v. Beard*, No.14-cv-02726-JST, 2017 WL 1540758, at *1 (N.D. Cal. Apr. 28, 2017), *aff'd in part, vacated in part, rev'd in part sub nom. Quine v. Kernan*, 741 F. App'x 358 (9th Cir. 2018); Kristine Phillips, *A Convicted Killer Became the First U.S. Inmate to Get State-Funded Gender-Reassignment Surgery*, Wash. Post (Jan. 10, 2017), https://wapo.st/2S21zP3.

SRS. *Lamb v. Norwood*, 899 F.3d 1159, 1163 (10th Cir. 2018), *cert. denied*, 140 S. Ct. 252 (2019).[5]

The debate about the WPATH standards continues even outside prison walls. The Centers for Medicare and Medicaid Services ("CMS") declined to adopt the WPATH standards due to inadequate scientific backing, and instead gives providers discretion to apply either the WPATH standards or their own standards. CMS, Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (August 30, 2016), available at https://go.cms.gov/36yMrx X. Similarly, the American Psychiatric Association expressed concern about the scientific evidence undergirding the WPATH standards. And as recently as 2017, WPATH requested that Johns Hopkins University conduct an evidence-based review of the standards, a review that, at the time of Edmo's lawsuit, was ongoing.

Idaho's actions reflect the uncertainty regarding the WPATH standards throughout the medical field, and do not, under the record, reflect a want of compassion. *See supra* O'Scannlain, J., dissenting at 22–29. Given the lack of medical consensus, Dr. Eliason's decision to pursue an alternative treatment, rather than SRS, cannot constitute the "barbarous" or "inhuman" conduct prohibited by the Eighth Amendment. *See Bucklew*, 139 S. Ct. at 1123. Nothing in the record reflects that Dr. Eliason's diagnosis and treatment of Edmo was tainted by malice or animosity. Notably, Dr. Eliason concluded that Edmo had coexisting mental

[5] In the non-SRS context, the Tenth Circuit also found no Eighth Amendment violation where a doctor prescribed lower hormonal treatment levels for a gender dysphoric inmate than those suggested by the WPATH standards. *Druley v. Patton*, 601 F. App'x 632, 635 (10th Cir. 2015).

health issues that required treatment and counseling prior to considering SRS. The district court itself found Edmo's reluctance to address those issues "troubling." *Edmo*, 358 F. Supp. 3d at 1121. Additionally, Idaho had no blanket policy prohibiting SRS, and Dr. Eliason never definitively ruled it out. Dr. Eliason committed to monitoring Edmo's candidacy for SRS after deciding that Edmo did not meet the criteria for the procedure in 2016. In sum, Dr. Eliason's decision to pursue an alternative treatment to SRS suggests a tailored evaluation of potential risks and does not reflect the hard-hearted or barbarous treatment proscribed by the text of the Constitution.

Given the facts of this case, Dr. Eliason's treatment cannot rise to the infliction of cruel and unusual punishment—not in a sense that bears any resemblance to the original meaning of that phrase. This is not to say that the WPATH standards are not *a* medically acceptable standard. But the innovative, contested, and evolving nature of the WPATH standards, the lack of medical consensus, and the particular circumstances of this case make clear that no constitutional violation occurred under the Constitution's text and original understanding.

II.

In addition to being inconsistent with the original understanding of the Eighth Amendment, I, like Judge O'Scannlain, believe that the panel decision departs from precedent.

A.

Since *Estelle v. Gamble*, the Supreme Court has recognized claims for inadequate medical treatment under the Eighth Amendment when prison officials act with

"deliberate indifference to serious medical needs of prisoners." 429 U.S. at 104. The test for such a claim involves "both an objective standard—that the deprivation was serious enough to constitute cruel and unusual punishment—and a subjective standard—deliberate indifference." *Snow v. McDaniel*, 681 F.3d 978, 985 (9th Cir. 2012), *overruled on other grounds by Peralta v. Dillard*, 774 F.3d 1076 (9th Cir. 2014). Under Ninth Circuit precedent, if a defendant's treatment decision was "medically acceptable," then the court need go no further: the plaintiff cannot show deliberate indifference as a matter of law. *Jackson v. McIntosh*, 90 F.3d 330, 332 (9th Cir. 1996) (citing *Estelle*, 429 U.S. at 107–08).

Deliberate indifference is a high bar, involving an "unnecessary and wanton infliction of pain" or conduct that is "repugnant to the conscience of mankind." *Estelle*, 429 U.S. at 104, 105–06 (citations omitted). An inadvertent failure to provide adequate medical care is neither, so it cannot support an Eighth Amendment claim. *Id*; *see also Farmer*, 511 U.S. at 835 (explaining that deliberate indifference requires "more than ordinary lack of due care for the prisoner's interests or safety") (citation omitted).

A prison official acts with deliberate indifference only where he "knows of and disregards an *excessive* risk to inmate health or safety." *Farmer*, 511 U.S. at 837 (emphasis added). As Justice Thomas describes it, this is the second-highest standard of subjective culpability under the Court's Eighth Amendment jurisprudence—short only of "malicious and sadistic action for the very purpose of causing harm." *Id*. at 861 (Thomas, J., concurring) (internal quotation marks and citations omitted). Such a stringent culpability requirement "follows from the principle that 'only the unnecessary and wanton infliction of pain implicates the

Eighth Amendment.'" *Id.* at 834 (quoting *Wilson*, 501 U.S. at 294).

Our precedent has consistently emphasized the challenging threshold for showing deliberate indifference.[6] Rightfully so, too. In the 44 years since *Estelle*, an unbroken line of Supreme Court cases reaffirmed that mere negligence, inadvertence, or good-faith error cannot establish an Eighth Amendment claim.[7]

B.

The panel's decision here dilutes the otherwise stringent deliberate indifference standard. The panel begins by finding Edmo's gender dysphoria to be a "serious medical

[6] *See Hamby v. Hammond*, 821 F.3d 1085, 1092 (9th Cir. 2016) (explaining that "[a] difference of opinion between a physician and the prisoner—or between medical professionals—concerning what medical care is appropriate does not amount to deliberate indifference," and reiterating the "high legal standard" for showing an Eighth Amendment violation) (citations omitted); *Toguchi v. Chung*, 391 F.3d 1051, 1060 (9th Cir. 2004); *Hallett v. Morgan*, 296 F.3d 732, 745 (9th Cir. 2002); *Wood v. Housewright*, 900 F.2d 1332, 1334 (9th Cir. 1990).

[7] *See Minneci v. Pollard*, 565 U.S. 118, 130 (2012) (noting that "to show an Eighth Amendment violation a prisoner must typically show that a defendant acted, not just negligently, but with 'deliberate indifference'") (citing *Farmer*, 511 U.S. at 825, 834); *Ortiz v. Jordan*, 562 U.S. 180, 190 (2011) (restating *Farmer*'s articulation of the deliberate indifference standard); *Wilson*, 501 U.S. at 297 ("[A]llegations of 'inadvertent failure to provide adequate medical care,' or of a 'negligent . . . diagnosis,' simply fail to establish the requisite culpable state of mind.") (internal citations and alterations omitted); *Whitley*, 475 U.S. at 319 ("To be cruel and unusual punishment, conduct that does not purport to be punishment at all must involve more than ordinary lack of due care . . . . It is obduracy and wantonness, not inadvertence or error in good faith, that characterize the conduct prohibited by the Cruel and Unusual Punishments Clause[.]").

need." *Edmo*, 935 F.3d at 785. It then determines, based solely on the WPATH standards, that Dr. Eliason's failure to recommend SRS was medically unacceptable. *Id.* at 786–92. From there, the panel leaps to conclude that Dr Eliason was "deliberately indifferent" precisely because it viewed his treatment as "ineffective" and "medically unacceptable" under the panel's reading of the WPATH standards. *Id.* at 793. Thus, under the panel's approach, compliance with the court-preferred medical standards (in this case, the WPATH standards) is the beginning and the end of the inquiry. This is not the deliberate indifference inquiry required by precedent.

As an initial matter, and as Judge O'Scannlain aptly points out, the panel errs in holding up *one* medically accepted standard, i.e., the WPATH guidelines, as the constitutional "gold standard," thereby precluding any further debate on the matter. *See supra* O'Scannlain, J., dissenting at 15–22. As discussed above, the WPATH standards do not establish a definitive medical consensus and judges applying Eighth Amendment standards should not and need not take sides in this debate.

More fundamentally though, the panel's analysis effectively erases the subjective deliberate indifference requirement with its circular reasoning. Nowhere does the panel consider any direct evidence of Dr. Eliason's subjective mental state. *Cf. Jett v. Penner*, 439 F.3d 1091, 1098 & n.2 (9th Cir. 2006) (concluding that a doctor's medical note stating "I reviewed xrays which showed no obvious fracture malalignment," written after reviewing a radiology report which specifically indicated a deformity, could evidence deliberate indifference) (alteration in original). Nor does the panel consider the many reasons underlying Dr. Eliason's decision to decline SRS treatment.

See supra O'Scannlain, J., dissenting at 15–22. Once those reasons are swept aside, the panel circularly *infers* deliberate indifference based on its prior determination that Dr. Eliason's treatment plan was "ineffective" or "medically unacceptable" under the WPATH standards. *See Edmo*, 935 F.3d at 793–94 (finding Dr. Eliason deliberately indifferent because his treatment "stopped short of what was medically necessary").

Such an approach is particularly troublesome because, if replicated, deliberate indifference could be inferred solely from a finding of a "medically unacceptable" treatment. For Eighth Amendment claims like Edmo's, a plaintiff must first show the "medically unacceptable" treatment of a "serious medical need[]" and, second, that the doctor's treatment decision reflected "deliberate indifference" to the medical need. *Jackson*, 90 F.3d at 332. The panel's analysis collapses this two-part inquiry into one circular step. If courts follow the panel's reasoning, in every case of medically unacceptable treatment, courts could automatically infer deliberate indifference.

Worse still, because "medical acceptability" is an objective negligence inquiry, the ultimate effect of the panel's analysis is to dilute the heightened, subjective culpability required for deliberate indifference, *see Farmer*, 511 U.S. at 839–40, into mere negligence, which the Supreme Court has repeatedly warned falls short of an Eighth Amendment violation. *See, e.g.*, *Estelle*, 429 U.S. at 105–06. By denying rehearing en banc in this case, we relegate federal judges to the role of referee in medical disputes. This is not what the Constitution or precedent envisions.

* * *

The Eighth Amendment's history and text entreat us to hold the line on the heightened standards for a constitutional deprivation found in our precedent. As Justice Thomas rightly observed, "[t]he Eighth Amendment is not, and should not be turned into, a National Code of Prison Regulation." *Hudson*, 503 U.S. at 28 (Thomas, J., dissenting). By judicially mandating an innovative and evolving standard of care, the panel effectively constitutionalizes a set of guidelines subject to ongoing debate and inaugurates yet another circuit split. And by diluting the requisite state of mind from "deliberate indifference" to negligence, the panel effectively holds that—contrary to Supreme Court precedent—"[m]edical malpractice [*does*] become a constitutional violation merely because the victim is a prisoner." *Estelle*, 429 U.S. at 106 (altered). I respectfully dissent from the denial of rehearing en banc.

A convicted killer became the first U.S. inmate to get state-funded gender-reassignment surgery

washingtonpost.com/news/post-nation/wp/2017/01/10/a-transgender-inmate-became-first-to-get-state-funded-surgery-advocates-say-fight-is-far-from-over

By Kristine Phillips Reporter

After a lengthy legal battle, a California transgender woman became the first inmate in the United States to receive a government-funded gender-reassignment surgery.

Convicted murderer Shiloh Quine, who is serving a life sentence for her role in a deadly 1980 incident in Los Angeles, is currently recovering from the surgery, according to the Transgender Law Center, which represented Quine in a federal civil rights lawsuit against California prison officials.

Advocates say it's a significant step that sets a precedent in recognizing transgender people's constitutional rights behind bars, particularly on issues of medical treatment. But they also caution that the fight for transgender rights in prisons is far from over.

"The work is in no way finished," attorney Flor Bermudez, detention project director for the Transgender Law Center, told The Washington Post.

While Quine's case led to the creation of transgender-friendly policies in California prisons, implementing those policies in a way that benefits transgender inmates is another matter, Bermudez said. Quine's success also makes her a minority, as transgender inmates who request gender-reassignment surgeries still often get denied, advocates say.

“Medical needs for trans people are rejected out of hand, or not even treated as medical issues; they’re treated as a political issue,” said Harper Jean Tobin, director of policy for the National Center for Transgender Equality.

In what advocates called a historic settlement, the California Department of Corrections and Rehabilitation agreed in 2015 to pay for Quine’s gender-reassignment surgery and to transfer her to a women’s facility. The agency also agreed to change its policies so that transgender inmates can wear clothes and have commissary items consistent with their gender identity.

“For too long, institutions have ignored doctors and casually dismissed medically necessary and life-saving care for transgender people just because of who they are — with devastating consequences to our community,” Kris Hayashi, executive director for the Northern California-based Transgender Law Center, said in a statement. “With this surgery, the state is fulfilling one part of a landmark settlement that was a victory not only for Shiloh and transgender people in prison, but for all transgender people who have ever been denied the medical care we need.”

A spokeswoman for the California Correctional Health Care Services declined to say where and when Quine had her surgery, citing medical privacy laws. The 57-year-old inmate’s attorneys told the Associated Press that the procedure was performed at a San Francisco hospital.

Quine, currently listed as an inmate at Mule Creek State Prison in Ione, Calif., about 50 miles southeast of Sacramento, is serving a life sentence without parole for murder. She sued prison officials in federal court in 2014 after her requests for surgery and a transfer to a women’s facility were denied. A settlement was reached in August 2015.

Terry Thornton, a spokeswoman for the California Department of Corrections and Rehabilitation, told the AP that the state is constitutionally required to provide inmates, including those who have been diagnosed with gender dysphoria, with “medically necessary treatment for medical and mental health conditions.”

Quine, who was born in Los Angeles and grew up in Northern California and Arizona, has identified as a female since she was 9 and has been taking hormones since adolescence, according to court records. Raised as a man, Quine was married — and divorced — twice and had two daughters with her second wife.

Quine said in court records that she attempted suicide multiple times in the past, once by slitting her wrist and again by attempting to hang herself. In 1978, she said she tried to castrate herself.

While in prison, she was receiving treatment for depression and was diagnosed with gender dysphoria, formerly called gender identity disorder, which manifests in feelings of distress, anxiety and depression. A psychologist who examined her determined her to be a good candidate for gender-reassignment surgery “on the basis of medical necessity,” and that the procedure is “reasonable and necessary to alleviate severe pain,” according to the psychologist’s report.

In an interview with the Transgender Law Center after the 2015 ruling, Quine said allowing her to have the surgery meant she was “getting closer to being comfortable” with herself.

“It shows the world is evolving, and starting to understand different viewpoints and perspectives better than in the past,” she said. “People are learning to recognize the humanity in everybody. It’s been a long time coming.”

But Bermudez, the Transgender Law Center’s detention project director, said that while Quine’s success in court was a step toward the right direction, she has received at least 30 letters from other transgender people who said they’ve been denied surgery.

Liz Gransee, a spokeswoman for the California Correctional Health Care Services, said the state has so far received 64 requests from prisoners for gender-reassignment surgery. Of those requests, two male-to-female and two female-to-male surgery requests have been approved.

Thirteen are still waiting for decisions, while 51 — about 80 percent of the requests — have been denied, Gransee said.

There are 475 transgender inmates in California prisons.

Quine was arrested and charged with robbery, kidnapping and murder in 1980, after she and an accomplice killed 33-year-old

Shahid Ali Baig, a father of three, in downtown Los Angeles, the AP reported.

Baig's daughter, who fought Quine's request in court, said knowing that taxpayers funded surgery for her father's killer was "a slap in the face."

"My dad begged for his life," Farida Baig told the AP. "It just made me dizzy and sick. I'm helping pay for his surgery; I live in California."

The cost of Quine's surgery is unknown.

Gransee, the California Correctional Health Care Services spokeswoman, said she could not discuss an inmate's health care. But depending on individual circumstances, she said, costs for gender-reassignment surgery could reach up to $100,000, including counseling and other treatments and medications before, during and after a procedure.

The Transgender Law Center, however, said that figure is an overestimation.

Marci Bowers, a transgender obstetrician and gynecologist in California, and Fred Ettner, an Illinois physician who works with people going through the transition, told The Post's Lenny Bernstein in 2015 that a male-to-female surgery costs between $40,000 and $50,000. A female-to-male procedure costs at least $75,000.

One of the highest-profile cases in California involved a transgender inmate named Michelle-Lael Norsworthy, who was abruptly released from prison in 2015 after a federal judge granted her request for gender-reassignment surgery, the Los Angeles Times reported.

Last year, the U.S. Army agreed to pay for hormone treatments for Chelsea Manning, the former intelligence analyst who was imprisoned in 2013 for leaking government files to WikiLeaks, the AP reported. Manning's lawyers announced in September that they'd been assured the government will provide gender-reassignment surgery, according to USA Today.

In 2012, a judge ordered Massachusetts to pay for the surgery of an inmate, but that decision was overturned on appeal, the AP reported.

Tobin, of the National Center for Transgender Equality, said she believes there will be more cases in which the government will "resist" paying for gender-reassignment surgeries.

"More courts will have to step in and remind the government of those responsibilities," Tobin said.

Decision Memo for GENDER Dysphoria and GENDER REASSIGNMENT SURGERY (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

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
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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.

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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

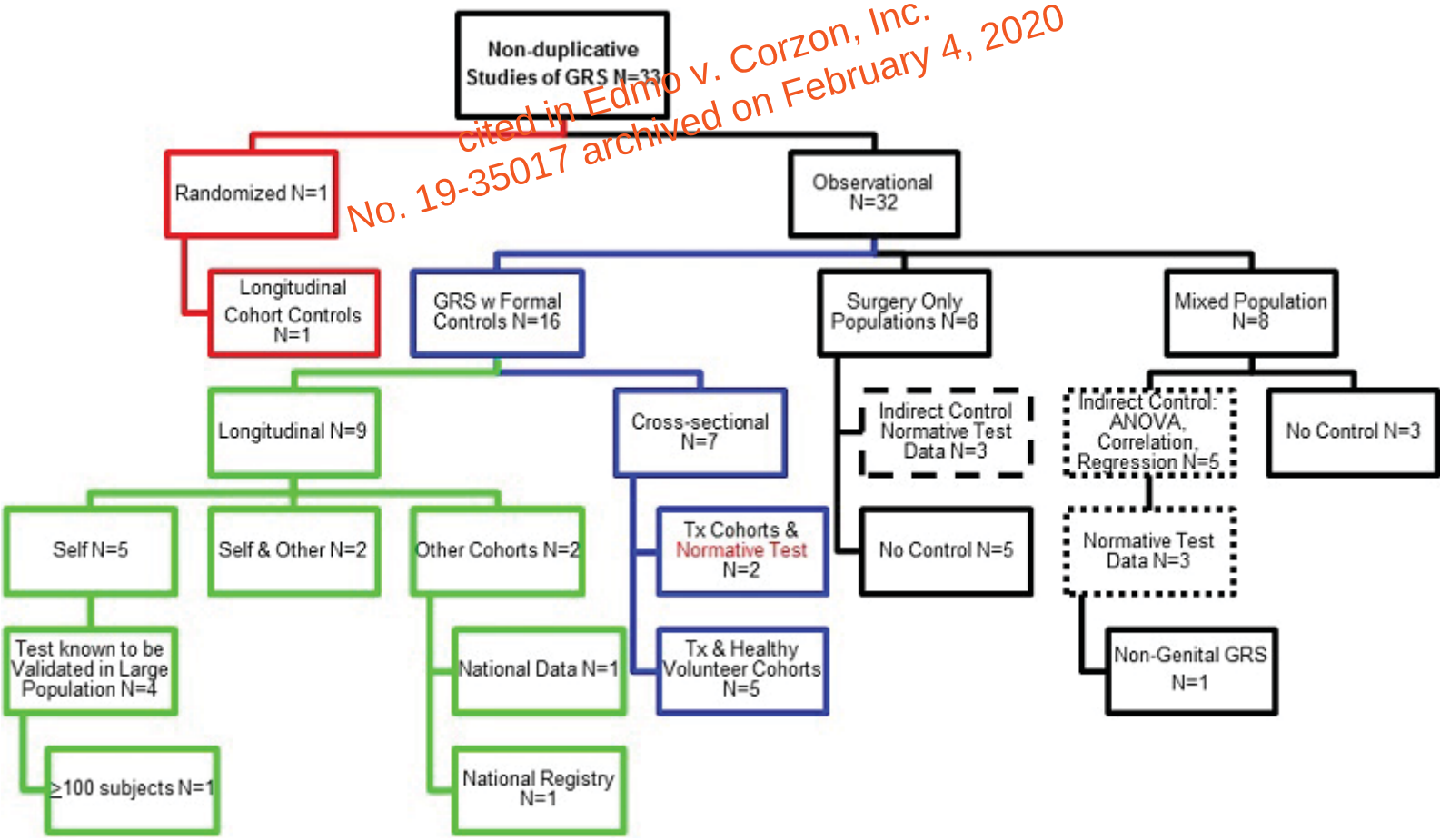
CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

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*	Required A (cross-gender identification) and B (aversion to one's natal	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	Further characterization by sexual orientation Distinguished from Atypical Gender

	Child-hood (302.6)]	gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	disturbance has been continuous (not limited to periods of stress) for at least 2 years.	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^{o} and 2^{o} 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	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	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 • e.g., intersex

	same name)		• 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^{o} and 2^{o} sex characteristics &/or acquiring sexual traits of the other sex • Clinically significant distress or impairment in social, occupational, or other important areas of functioning	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^{o} and 2^{o} 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	• Marked discordance between natal 1^{o} and 2^{o} 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)	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity

		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 desire to be rid of natal 1^{O} and 2^{O} sex characteristics** • Marked desire to acquire 1^{O} and 2^{O} 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 2^{O} sex characteristics ** or in young adolescents, prevent the development of the anticipated 2^{O} 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.	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 1^{O}=primary 2^{O}=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	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper

		15 formal applications for surgical reversal			
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	Cross-sectional	294 clinic patients w GD	79	79(100%)	-

et al.	Control: Normative test data	had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded			
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.	187	79 (42.2%)	See prior box.

		13 declined participation or were excluded for incomplete questionnaires.			
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 29-64).	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,*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)

Cohen-Kettenis	
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 Substantive &/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	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.

			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%.**	
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		MMPI SCL-90	The number in the available adult patient	Most of the MMPI scales were already in the normal range at

2005			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.**	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

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