

A CURRENT MODEL OF SEX INCLUDING ALL BIOLOGICAL COMPONENTS OF SEXUAL REPRODUCTION

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I

INTRODUCTION

Sex and gender are both broad terms that have evolved so that they have overlapping definitions colloquially. Historically, sex was considered the term for biological characteristics related to reproduction. Gender by contrast has referenced social constructs including parts of speech and culturally assigned characteristics attributed to ideas and inanimate objects.

As a term for biological components related to reproduction, sex was once thought to be limited to internal reproductive organs and visible sexual anatomy. With greater scientific advance, chromosomal and genetic associations were identified. Also, variations in development of the reproductive organs and visible anatomy were observed, providing evidence of independent genetic coding for different elements of sexual reproduction. Current scientific observations reveal that gender identity and sexual orientation are specifically encoded in the brain and that they too can vary independent of the other components of sexual reproduction.¹

Thus, if the word sex references biology related to sexual reproduction, it includes gender identity, sexual orientation, sexual interest, internal reproductive organs, visible sexual anatomy, gametes, and sex hormones.

Recognition of the greater biological complexity of sex is part of what has informed attempts to redefine the word sex in law, including the proposed definition in H.R. 5, The Equality Act.²

Because the words sex and gender are used interchangeably by many, better clarity is achieved with more specific terms:

While the word sex can be used to categorize people and other living entities on the basis of biological characteristics associated with reproduction, it can also be used to

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1. Like for many biological processes where the details remain the subject of study, such process might be encoded directly by genes, might be epigenetic processes, or might be some related phenomenon.

2. Equality Act, H.R. 5, 117th Cong. (2021).

describe sexual activity. Greater precision is achieved if the category is called biological sex and the activity is called sexual activity.

The word gender is even more fraught. Many forms in English use the word gender in order to solicit the biological sex of the individual. In addition, gender is commonly used as shorthand for gender identity, gender expression, and gender roles even though the three concepts are entirely different.

Gender identity is the term to describe a person's internal sense of their own biological sex.³ A person's gender identity might be classically male, classically female, a combination, or something else. Gender identity has a substantial biological component that seems encoded at birth and that cannot be altered by external forces.⁴ Importantly, despite the language used, gender identity is not a chosen affiliation like would be anticipated by the use of the word identity. People do not choose gender identities like they might choose political parties. Rather, people know their gender identities and express them when they have the language to do so.

By contrast, gender expression is the term for how individuals can convey their sense of their biological sex to themselves or externally to others. People may use behaviors and signs of sexual identity that include those determined by society and culture. Unlike hard-wired gender identity, people may choose certain forms of dress, certain haircuts, or certain colors as part of their gender expression. People may also accentuate aspects of their biology as part of their gender expression. While gender expression is often used to convey biological sex, people are not limited to their biology and may opt to express themselves in myriad ways. That is, gender expression includes actions that are chosen whether they align with a person's biology or not.

Finally, gender roles are activities that a given society or cultural group attributes to a particular biological sex.

3. See Joshua D. Safer & Vin Tangpricha, *Care of the Transgender Patient*, ANNALS OF INTERNAL MED. 2019 [hereinafter *Care of the Transgender Patient*] (setting out this definition); see also Table 1, *infra* note 5 at 2451.

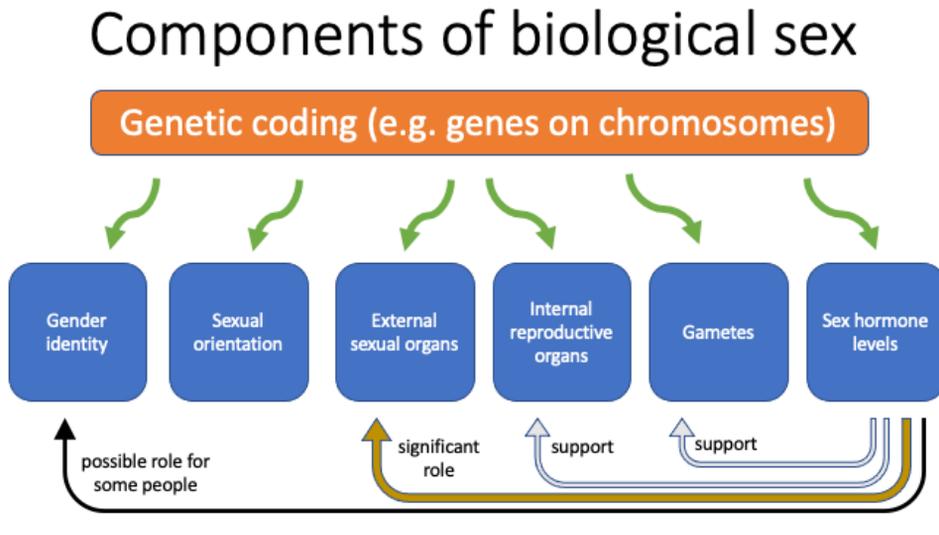
4. See Joshua D. Safer & Vin Tangpricha, *Out of the Shadows: It is Time to Mainstream Treatment for Transgender Patients*, 14 ENDOCRINE PRACT. 248, 248–50 (2008).

Table 1. Definitions.⁵

Gender	Broad term for self-identification, identification of inanimate objects, labeling of language, and stereotypical behaviors that might be considered male, female, or some variation.
Sex	Broad term describing all biological characteristics associated with reproduction.
Gender identity	The internal sense of one's own sex: being male, female, or neither.
Transgender, transsexual, trans, gender nonbinary, gender incongruent, genderqueer	Adjectives used to refer to persons whose gender identity does not align with their sex recorded at birth (the latter primarily based on visible physical anatomy).
Cisgender, non-transgender	Adjectives used to refer to persons whose gender identity aligns with their sex recorded at birth.
Gender expression	How a person communicates gender identity to themselves and others.
Gender roles	Stereotypical behaviors, activities, and positions in society that are designated by society to be male, female, or some variation.

5. Adapted from *Care of the Transgender Patient*, *supra* note 3.

II BIOLOGICAL SEX



There is a growing appreciation for the multiple biological components associated with sexual reproduction. In addition, there is greater recognition that the components must be independently encoded to at least some degree. Fundamentally, sexual reproduction includes individuals knowing their sex, knowing their choice of partners, having the anatomy for reproduction, having the gametes that can combine, and engaging in the necessary activity for reproduction relevant to the specific organism.

If biological sex is the term for the elements in physiology that relate to reproduction, then as depicted in Figure 1, the components of biological sex that can be independently encoded by genes and other related phenomena would include gender identity, sexual orientation, reproductive anatomy, gametes, and hormone levels.

Some of the mechanisms for the genetic coding of anatomical structures and physiology are known.⁶ Specifically, some components of biological sex can be linked to specific genes and some are multifactorial. However, the genetic control for much of biological sex is poorly understood. Many mechanisms have been identified through study of people who have visibly varying anatomy - termed intersex or DSD (differences in sexual differentiation).

6. See generally Emmanuèle C. Délot & Eric Vilain, *Towards Improved Genetic Diagnosis of Human Differences of Sex Development*, 22 NATURE REVIEWS GENET. 588 (2021) (describing these known mechanisms).

In addition, sex hormone levels may exert influence on some components of biological sex. The impact of sex steroids on the development of external sex organs is well established.⁷ Indeed, even the impact of specific timing in life of sex steroids is known to a significant degree. The degree of androgen exposure in utero can determine the appearance of external genitalia from a typically female appearance (vagina, labia, clitoris with urethra below) to a typically male appearance (scrotum, penis with urethra inside). Androgen exposure in puberty has impact on sexual anatomy along with bone structure, fat distribution, muscle mass, and skin texture. Androgen exposure after puberty has impact on the latter three.

Sex steroids play a role with biology of gametes and of internal reproductive organs too. Thus, genes that influence sex hormone levels can have indirect impact on other elements of biological sex in addition to genes specific to the given biological sex component.

By contrast, the biological mechanisms underlying sexual orientation and gender identity are not well understood other than the recognition that underlying biological factors must exist.

III

EVIDENCE OF BIOLOGICAL UNDERPINNINGS FOR GENDER IDENTITY

While gender identity incongruence with visible anatomy had been considered a mental health concern with mental health solutions, observations of both people with intersex/DSD conditions and of transgender people have provided evidence that gender identity must have a biological component. Indeed, in the early 21st century there has been a substantial change in the understanding of the framework for gender identity etiology.⁸ The appreciation that there must be a significant biological component underlying gender identity, something programmed into the brain that is present at birth, is derived from data divided into several broad categories.⁹

The first category with the most rigorous data comes from the experience of historical attempts to manipulate gender identity among intersex individuals.¹⁰ Historically, there has been an interest in surgical correction of variances in genitalia due to a fear that such variances would be traumatic later in life. The logic was that the choice could be determined based on what was felt to be most

7. See generally YEN & JAFFE'S REPRODUCTIVE ENDOCRINOLOGY (Jerome Strauss & Robert Barbieri eds., 8th ed. 2019) (including chapters on development, puberty, reproduction, DSDs).

8. *Care of the Transgender Patient*, *supra* note 3.

9. See Aruna Saraswat, et al., *Evidence Supporting the Biologic Nature of Gender Identity*, 21 ENDOCRINE PRACT. 199, 199–204 (2015).

10. See, e.g., Heino F. L. Meyer-Bahlburg, *Gender Identity Outcome in Female-Raised 46,XY Persons with Penile Agenesis, Cloacal Exstrophy of the Bladder, or Penile Ablation*, 34 ARCHIVES SEXUAL BEHAV. 423, 423–38 (2005); William G. Reiner & John P. Gearhart, *Discordant Sexual Identity in Some Genetic Males with Cloacal Exstrophy Assigned to Female Sex at Birth*, 350 NEW ENG. J. MED. 333, 333–41 (2004).

feasible surgically. The person would be assigned the sex category that matched the surgery chosen. Unambiguous rearing in that sex category would reliably result in the person living as a member of the designated sex. Creation of female genitalia (that is, vaginoplasty), is a more straightforward surgery than creation of male genitalia (that is, phalloplasty) so that such people were more often designated female than male.

The most illustrative study relevant to the recognition of gender identity as an independent biological phenomenon is from Johns Hopkins and was published in the *New England Journal of Medicine* in 2004.¹¹ Surgeons followed established practice and treated cloacal exstrophy (a syndrome with lack of development in both the reproductive and gastrointestinal tracts) by creating female genitalia on all patients including those with XY chromosomes. Despite the then standard aggressive program with both surgery and rearing consistent with the assigned gender identity, a majority of the XY individuals treated subsequently reported male gender identity. Other series have been less intensive with regard to querying the gender identity of similarly treated individuals in varying circumstances, but are consistent that gender identity cannot be routinely manipulated with external forces.¹²

The second category is best represented by one paper.¹³ For transgender individuals with an identical twin a forty percent concordance rate is noted. That is, forty percent of the identical twins are also trans. The relatively high concordance rate contrasts with a negligible concordance rate among fraternal twins, whose difference from identical twins is primarily the degree of similarity in DNA.

The third category includes research in several areas that observe some association of androgen exposure in utero on gender identity. Historic animal studies have suggested that female offspring of mothers treated with high levels of testosterone might exhibit more “male typical” behavior.¹⁴ Among humans, individuals with XX chromosomes would usually be predicted to have female gender identity. However, in virilizing congenital adrenal hyperplasia where individuals are exposed to larger than usual amounts of androgens in utero, studies show that about 5 percent of the individuals have male gender identity,¹⁵ a far higher percentage of male gender identity than seen among individuals with XX chromosomes in general. In contrast, individuals with complete androgen insensitivity syndrome (CAIS) have XY chromosomes but typically

11. Reiner & Gearhart, *supra* note 10.

12. *Id.*

13. Gunter Heylens et al., *Gender Identity Disorder in Twins: A Review of the Case Report Literature*, 9 J. OF SEXUAL MED. 751, 751–57 (2012).

14. See Charles H. Phoenix et al., *Organizing Action of Prenatally Administered Testosterone Propionate on the Tissues Mediating Mating Behavior in the Female Guinea Pig*, 65 ENDOCRINOLOGY 369 (1959).

15. See Arianne B. Dessens et al., *Gender Dysphoria and Gender Change in Chromosomal Females with Congenital Adrenal Hyperplasia*, 34 ARCHIVES SEXUAL BEHAV. 389 (2005).

have female gender identity.¹⁶ Thus, there are at least some individuals who are dependent on some amount of testosterone in order to be able to have male gender identity.

Two variations on the direct androgen exposure data include attempts to associate digit ratios with gender identity along with observations that a disproportionately high number of transgender men may have had a high testosterone entity called polycystic ovarian syndrome (PCOS). The second-to-fourth digit length ratio (2D:4D) may serve as proxy for prenatal androgen activity. Although study results have been variable, the most recent data, reported along with a meta-analysis of prior data, suggest that transgender women may have 2D:4D consistent with gender identity.¹⁷ A corresponding finding among transgender men could not be established.

Among individuals with an entity called 5-alpha-reductase deficiency who have ambiguous genitalia and who are initially reared as female, a majority eventually report male gender identity with a change in gender expression at puberty.¹⁸ Such individuals lack the potent androgen, dihydrotestosterone but they have both testosterone and functioning androgen receptors which may be a key distinction between them and individuals with CAIS.

The fourth category is the association of some elements of brain anatomy with gender identity. The classic study from the 1990s was the observation that staining of a region of the brain called the stria terminalis could correlate with gender identity rather than chromosomes in multiple individuals including some who did not have hormone treatment.¹⁹ Although the tissue specimens from deceased people made for a very visible representation of a brain correlation with gender identity, subsequent attempts to replicate the findings with radiological modalities like magnetic resonance imaging (MRI) in living people have been less clear.

In addition to the data summarized above, attempts have been made to associate genes and other visible biological characteristics with gender identity. Most such attempts have remained rudimentary. Gene associations reported include CYP17 genes and the RYR3 gene.²⁰

16. See Tom Mazur, *Gender Dysphoria and Gender Change in Androgen Insensitivity or Micropenis*, 34 ARCHIVES SEXUAL BEHAV. 411 (2005).

17. Eva-Maria Siegmann et al., *Digit Ratio (2D:4D) and Transgender Identity: New Original Data and a Meta-Analysis*, SCI. REPORTS (2020).

18. See generally J. Imperato-McGinley et al., *Androgens and the Evolution of Male-Gender Identity Among Male Pseudohermaphrodites with 5alpha-reductase Deficiency*, NEW ENG. J. MED. (1979) (describing this developmental phenomenon).

19. J. N. Zhou et al., *A sex difference in the human brain and its relation to transsexuality*, 378 LETTERS TO NATURE (Nov. 1995).

20. See Eva-Katrin Bentz et al., *A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to-female transsexualism*, 90 FERTILITY AND STERILITY 56 (July 2008); Rosa Fernández et al., *The CYP17 MspA1 Polymorphism and the Gender Dysphoria*, 12 J. SEXUAL MEDICINES 6 1329 (June 2015); Fu Yang et al., *Genomic Characteristics of Gender Dysphoria Patients and Identification of Rare Mutations in RYR3 Gene*, 7 SCI. REPORTS (2017).

The data for the specific biology of gender identity remain modest. Other than a suggestion that there may be some influence from androgens on at least some people, the data shed little light on the mechanisms by which such biology would exert its influence.²¹ Still, the data that do exist are sufficiently strong that there is broad medical consensus that gender identity is essentially part of human biology even if so, many details remain to be learned.

IV

IMPLICATIONS OF THE RECOGNITION THAT GENDER IDENTITY HAS A MAJOR BIOLOGICAL COMPONENT ON CATEGORIZATION OF PEOPLE BY SEX

The biological basis concept has influenced a significant change in the approach to care for transgender people. Along with greater social awareness, the acceptance of the biological model has provided a basis for the focus on treatment to align the bodies of transgender people with their gender identities rather than to think that the gender identities can be manipulated.²²

The current medical approach to transgender people who seek medical intervention is to consider strategies to align patients' bodies with their gender identities. The medical model emphasizes the relevant biology independent of the patients' choices of how to identify. Specific medical interventions are influenced by patient choice often relating to external factors in the patients' lives.

Further, if the medical treatment for transgender people is simply assisting people in reconciling their bodies with their hard-wired gender identities, the mental health component to care can shrink. If patients can articulate their gender identity in an unambiguous way, then treatment can proceed.

While there are adults who are confident in their gender identity and who have clear goals for treatment, there are others who are less able to articulate their gender identity and who may benefit from greater support from mental health providers. Also, some individuals may be clear about their gender identities but less clear about their desires for medical intervention to align gender identity and appearance. The latter group may benefit from guidance from both mental health providers and providers who can help set expectations about medical interventions.

The Endocrine Society Guidelines²³ prefer that mental health providers be involved in transgender determination for adults, but the document notes that any sufficiently knowledgeable provider can make this determination. The provider or the provider's designee should be able to identify mental health

21. See Joshua D. Safer, *Research Gaps in Medical Treatment of Transgender/Nonbinary People*, J. CLINICAL INVESTIGATION (2021).

22. *Care of the Transgender Patient*, *supra* note 3.

23. Wylie C. Hembree et al., *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline*, 102 J. CLINICAL ENDOCRINOLOGY & METABOLISM 3869 (2017).

conditions that might confound the assessment. Children may articulate their gender identity in a more heterogeneous fashion. Therefore, the Endocrine Society Guidelines²⁴ recommend that assessment of gender identity and treatment considerations for children and adolescents should involve of a team of clinicians including mental health professionals.

For categorization of people by sex in science and medicine, the knowledge that there are multiple components to biologic sex makes clear the need to reference the specific domain of interest for a specific situation. It has been recognized for decades that sex categorization requires some additional detail so that people can be precisely defined. For example, people can be divided according to chromosomes, reproductive organs, or other features depending on what is being measured. In larger studies, people are often categorized either by visible anatomy or by self-identification. In certain disease situations, people may be best categorized by hormone levels or by presence of specific sex-associated genes (independent of whether those genes are present on the typical chromosomes where they usually reside).

The fact that gender identity is one of the biological elements has implications for how people are or should be categorized by sex. For much categorization, the brain – or one’s self designation as A or B – is prioritized for determining where an individual fits. Race and ethnicity are two common examples. Transplantation of organs does not alter a person’s race/ethnicity category; the person’s brain is not changed. Consistent with the law’s stringent standard for sorting acceptable from unacceptable sex discrimination, unless there is a very good, evidence-based reason to focus on a different trait within the set, for general categorization by sex, “brain sex” or gender identity would be the default characteristic.

The determination of sex using gender identity as the default characteristic (instead of visible anatomy or some specific identified genes) may make good intuitive sense, but it can be confounded by the lack of objective criteria for gender identity and the need for self-report. As noted above, adults can reliably assert gender identity unless they suffer mental health conditions which might confuse such a report. Children are less reliable.

Children demonstrate an ability to articulate a gender identity as early as age two and develop facility with gender labeling including pronouns by school age.²⁵ Depending on ages measured and other definitions used, 0.6 to 2.7 percent of children may report some degree of gender incongruence²⁶ although, not all such children will seek medical intervention later life.²⁷ By adolescence,

24. *Id.*

25. See Kristina M. Zosuls et al., *The acquisition of gender labels in infancy: Implications for gender-typed play*, 45 DEVELOPMENTAL PSYCHOLOGY 688 (May 2009).

26. See G. Nicole Rider et al., *Health and Care Utilization of Transgender and Gender Nonconforming Youth: A Population-Based Study*, 141 PEDIATRICS (2018).

27. See Thomas D. Steensma et al., *Desisting and persisting gender dysphoria after childhood: a qualitative follow-up study*, 16 CLINICAL CHILD PSYCHOLOGY & PSYCHIATRY 499 (2011).

children are increasingly able to articulate gender identity. Puberty can be distressing for gender incongruent children. The desire to avoid the “wrong puberty” may be the prompt for some adolescents to report their gender incongruence to parents, health care providers and others.²⁸

The majority of transgender individuals identify themselves to others in late adolescence or adulthood. Whether the late presentation represents delayed recognition of gender incongruence, inability to articulate gender identity, or simply outside pressure to conform is not known. Despite the late presentation, many transgender individuals report that their awareness of their gender incongruence began well before puberty.

V

CONCLUSION

The word sex references the physiological elements associated with reproduction. The biological components of sex were once thought to include only internal reproductive organs and visible sexual anatomy. With greater scientific advance, chromosomal associations were identified and eventually the actual genes on the chromosomes. Also, variations in development of the reproductive organs and visible anatomy were observed, evidence of independent genetic coding for different elements of sexual reproduction. More recent scientific observations reveal that even gender identity and sexual orientation are specifically coded with the result that they too can vary independent of the other components of sexual reproduction. Thus, if the word sex is limited to the biology related to sexual reproduction (genetically coded or otherwise), it would include gender identity, sexual orientation, sexual interest, internal reproductive organs, visible sexual anatomy, gametes, and sex hormones.

Understanding biological complexity can help to inform attempts to redefine the word sex in law and policy. If the use of the word sex in law is meant to reference biological characteristics associated with reproduction, its meaning must grow to reflect the scientific advances that expand our understanding of that biology.

28. See Stephen M. Rosenthal, *Approach to the patient: transgender youth: endocrine considerations*, 99 J. CLINICAL ENDOCRINOLOGY & METABOLISM 4379 (2014).