Management of 46,XY Differences/Disorders of Sex Development (DSD) Throughout Life

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ABSTRACT Differences/disorders of sex development (DSD) are a heterogeneous group of congenital conditions that result in discordance between an individual's sex chromosomes, gonads, and/or anatomic sex. Advances in the clinical care of patients and families affected by 46,XY DSD have been achieved since publication of the original Consensus meeting in 2006. The aims of this paper are to review what is known about morbidity and mortality, diagnostic tools and timing, sex of rearing, endocrine and surgical treatment, fertility and sexual function, and quality of life in people with 46,XY DSD. The role for interdisciplinary health care teams, importance of establishing a molecular diagnosis, and need for research collaborations using patient registries to better understand long-term outcomes of specific medical and surgical interventions are acknowledged and accepted. Topics that require further study include prevalence and incidence, understanding morbidity and mortality as these relate to specific etiologies underlying 46,XY DSD, appropriate and optimal options for genitoplasty, long-term quality of life, sexual function, involvement with intimate partners, and optimizing fertility potential. ***(Endocrine Reviews 40: 1547 – 1572, 2019)***

Differences/disorders of sex development (DSD) are a heterogeneous group of congenital conditions that result in discordance between an individual's sex chromosomes, gonads, and/or anatomic sex (1). Although the term "disorders of sex development" is widely used in recent medical literature, it is not universally accepted by patients and advocates. Alternatives for describing such conditions include the terms "variations in sex development" or "differences," which is implemented in this review.

Some people with DSD possess a 46,XY chromosome complement, collectively referred to as 46,XY DSD (2, 3). People with 46,XY DSD can present with variable degrees of virilization of their external genitalia, along with variable degrees of development of structures derived from the Wolffian and Müllerian ducts (4–6). Testes are identified in many, but not all, affected individuals regardless of their degree of undervirilization (5, 7). Complete absence of virilization results in female-typical external genitalia, and diagnoses in this group may be delayed until puberty or later when a lack of breast development and/or primary amenorrhea is observed (8). Partial virilization is often noted at birth when atypical external genital anatomy is noted (8–10). Regardless of the extent of undervirilization, the underlying cause of 46,XY DSD can be attributed to (i) decreased production of androgens such as testosterone (T) or DHT during fetal sex differentiation, or (ii) impaired androgen action at target tissues throughout life (5, 11–14) (Table 1).

Owing to both the complexity and heterogeneity of conditions labeled 46,XY DSD, optimal management for patients merits an interdisciplinary team approach with the goal of providing holistic care throughout the lifespan (13, 14). Data pertaining to the long-term outcomes of people with 46,XY DSD are beginning to inform medical teams about optimizing management;

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ESSENTIAL POINTS

- Due to the complexity and heterogeneity of conditions under the 46,XY DSD umbrella, interdisciplinary health care teams are best suited to provide care to patients and their families
- Optimal laboratory measurements followed by the molecular diagnosis are strongly recommended before sex assignment
- Several factors influence decisions regarding sex of rearing for 46,XY DSD newborns, including etiology-specific information related to gender development, genital appearance and surgical options, hormone replacement, fertility potential, family preferences, and cultural considerations
- Looking forward, further research in large worldwide samples is needed to explore the influence of hormone exposure, genetic etiology, type and timing of genital surgery, aspects of romantic life, and sexual function
- Counseling patients on their fertility options, as well as discussing parenthood alternatives, is essential
- Patients and parents should have access to mental health support and receive complete and unbiased education about DSD, including treatment options specific to their particular condition
- Mental health providers and peer support should encourage patients and their families to discuss DSD with others in a way that respects privacy while eliminating shame and secrecy

however, much remains to be learned. The aims of this proposal are to review what is known about prevalence, incidence, morbidity, diagnostic tools and timing, sex of rearing, endocrine and surgical treatment, fertility and sexual function, and behavioral development in affected people.

Prevalence and incidence

Data on the incidence and prevalence of 46,XY DSD are sparse, and estimates vary widely because DSD etiology is heterogeneous. Whereas some types of DSD are monogenic conditions, others result from several gene mutations, making a molecular diagnosis difficult to perform (15, 16). Additionally, some etiologies are observed worldwide [*i.e.*, androgen insensitivity syndrome (AIS)] whereas others occur in geographic clusters [*i.e.*, 5α-reductase type 2 deficiency (5α-RD2)] (Table 1) (17–22). Therefore, accurate estimates of prevalence and incidence of many presentations of 46,XY DSD are unavailable.

AIS is thought to be the most common 46,XY DSD etiology followed by gonadal dysgenesis (23). The incidence of AIS and gonadal dysgenesis is reported to be one to five per 100,000 births and one per 80,000 births, respectively (24–26). For other types of 46,XY DSD, epidemiologic studies are lacking due to their rarity. To estimate the incidence and prevalence of 46,XY DSD, a nationwide cohort was conducted in Denmark and the prevalence was 6.4 per 100,000 live-born females whereas the incidence was 0.6 per million females (26). To compare their results with the literature, the authors pooled data from 11 large cytogenetic survey studies and calculated a prevalence of four cases of 46,XY DSD per 100,000 female births. Why prevalence in the Danish population was higher than the pooled prevalence is not clear, but possible bias from pooled results could be an explanation. Another possibility is that the Danish cohort mainly included patients with AIS (78 out 124 cases of 46,XY DSD) and gonadal dysgenesis (25 of 124 cases). Although the Danish sample may not generalize to other areas of the world, the number of cases of AIS and gonadal dysgenesis allows for estimates of prevalence (4.1 per 100,000 live-born females) and incidence (1.5 per 100,000 live-born females).

Morbidity

To optimize health care for people affected by any medical condition, broader knowledge about morbidity and mortality is essential (27). There are many reasons why people with 46,XY DSD may present high morbidity, including hypogonadism, irregular sex hormone replacement, genital surgery, and gonadectomy. To access epidemiological data relevant to people with 46,XY DSD, morbidity and mortality for females with 46,XY DSD were compared with 12,300 female and 12,300 male controls (28). The overall morbidity of females with 46,XY was increased in comparison with unaffected people. For example, women with complete AIS (CAIS) who received a gonadectomy experienced reduced bone mineral density (BMD), although BMD was less affected in women with this condition who retained their testes (29, 30). Women with 46,XY DSD with partial virilization due to gonadal dysgenesis have a normal BMD (31).

Increased prevalence of obesity, insulin resistance, and lipid abnormalities have been reported in women with CAIS, and these are attributed to the loss of androgen receptor signaling (32). However, the prevalence of metabolic syndrome is not well defined in patients with other types of 46,XY DSD. Overall, females with 46,XY had no increased occurrence of circulatory system diseases, including ischemic heart disease, arteriosclerosis, hypertension, and cerebrovascular disease (28).

Regarding cause-specific morbidity, gonadal cancer was increased in females with 46,XY whereas other cancers were not (28). Gonadal tumors such as germ cell tumors (GCTs) result from fetal germ cells and are divided into two groups, seminoma (seminoma/dysgerminoma) and nonseminoma (embryonal carcinoma, yolk sac tumor, choriocarcinoma, and teratoma) tumors (33). Among GCTs, germ cell neoplasia *in situ* and gonadoblastoma (GB) are the most common noninvasive benign tumors that lead to the development of invasive GCTs. Of note, germ cell neoplasia *in situ* is a precursor of GB, but not every case will progress to GB (33, 34). Identified risk factors for GCT development include the presence of Y chromosome, especially the GBY region (TSPY) in the gonadal karyotype, abnormalities of gonadal development, incomplete differentiation of the gonad in individuals with 46,XY or 45,X/46,XY, and delay or block in maturation of germ cells (35–38). Additionally, gonadal location (abdominal or inguinal area) is another risk factor, and individuals with isolated cryptorchidism have higher risk for GCT development than do controls (39). Importantly, GCT risk in 46,XY DSD is mainly related to etiology. GCT risk is higher (15% to 50%) in conditions associated with gonadal dysgenesis compared with disorders of androgen synthesis or action (<1% to 15%) in which testis differentiation and development are normal (40–42). When calculating GCT risk, a diagnosis of AIS requires special attention because the risk of GCTs also relates to delays in germ cell maturation, and germ cell survival depends on androgen action (40, 43).

Overall mortality is similar between females with 46,XY and controls, despite the higher risk of gonadal tumors in the former group. Although there is a lack of evidence about long-term health outcomes for men with 46,XY DSD, cardiovascular morbidity, impaired glucose tolerance, and osteoporosis have been reported in these men when hypogonadism is present (44, 45). Notably, even mild impairment of Leydig cell function in otherwise healthy men with low-normal androgens and elevated LH levels is associated with increased mortality and morbidity (46). As men with 46,XY DSD may experience hypogonadism due to irregular T replacement or androgen insensitivity, careful monitoring of cardiometabolic health is warranted (47). Multinational collaborations and the establishment of patient registries are beginning to ameliorate the lack of knowledge about long-term health outcomes for people with 46,XY DSD while taking into consideration etiology and sex of rearing and gender identity (48).

Finally, androgens are known to exert organizational effects on brain structure and function (49–51); however, how these hormones influence the development and expression of specific psychiatric conditions is unclear. Impaired androgen production or action is a feature of all types of 46,XY DSD, with the exception of cloacal exstrophy, and people with these conditions may be more susceptible to diseases such as depression, addiction, and eating disorders.

Compared with unaffected women, subjects with 46,XY DSD due to CAIS and complete gonadal dysgenesis are more likely to report major depressive episodes, somatization, antisocial personality, and obsessive-compulsive disorders (52). Women with CAIS report self-harm and suicidal tendencies at rates comparable to traumatized women with a history of physical or sexual abuse (53). In a German study, suicidal thoughts were frequently reported by women with partial AIS (PAIS) or CAIS (54). In addition to potential hormonal influences on psychiatric comorbidities, lack of social support for DSD plays a role (55). Additionally, parents of children with DSD sometimes report anxiety, depression, and posttraumatic stress that may contribute to the mental health of affected individuals (56). Finally, variables associated with DSD beyond androgens, including atypical genital anatomy, infertility, surgical/medical interventions, and gender nonconformity, likely contribute to increased distress reported by patients (57).

An investigation of a large number of men and women affected by 46,XY DSD from Europe identified the presence of several somatic and psychiatric comorbidities (58). Receiving a DSD diagnosis early in life, as well as following a healthy lifestyle, were associated with fewer mental and physical health problems for these adults. Another investigation of women with 46,XY DSD from Denmark revealed no increased morbidity or mortality compared with controls (28). Although these initial results are encouraging, more studies are needed from populations both within and outside of Europe to determine whether, and how, differences in health care delivery impact outcomes for people with 46,XY DSD.

Diagnosing DSD

Signs of DSD can be detected during prenatal ultrasound (US), present as atypical genital development in newborns, bilateral inguinal hernias in children, atypical secondary sex characteristics in adolescents, or infertility in adults (59–61). An extensive examination is needed to determine whether other systems in addition to the reproductive system are involved. Such findings indicate the presence of potential DSD-candidate genes. Complementary studies to the physical examination such as hormonal, imaging, and genetic investigations are often necessary to establish an underlying diagnosis, excluding life-threatening

Table 1. Main Features of the 46,XY DSD Conditions

	Defects of Gonadal Development			Defects of Androgen Production				
		Gonadal Dysgenesis			LHCGR Defects			
DSD Etiology	46,XY OT DSD	Complete Form	Partial Form	Smith–Lemli–Optiz Syndrome	Complete Form	Partial Form	20,22-Desmolase Deficiency	StAR Deficiency
Inheritance	Generally sporadic	Autosomal recessive, X-linked; autosomal dominant, linked to male sex (for both forms)		Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive
Most common sex assignment	Male	Female	Male/female	Male	Female, male—mild form	Male/female	Female, male—mild form	Female, male—mild form
Gender change	Rare	Rare	Rare	Rare	Rare	Rare	Rare	Rare
External genitalia	Atypical	Female	Atypical	Micropenis and/or hypospadias, hypoplasic or bifid scrotum; female	Female micropenis (mild form)	Atypical to male	Female micropenis (mild form)	Female micropenis (mild form)
Müllerian duct derivatives	Present	Present	Present or absent	Rarely present	Absent	Absent	Absent	Absent
Wolffian duct derivatives	Hypoplastic to normal	Absent	Present	Absent to male	Absent to hypoplastic	Male	Absent to hypoplastic	Absent to hypoplastic
Gonads/ usual position	Ovary and testis/ intra-abdominal, inguinal	Streak gonads/ intra-abdominal	Dysgenetic gonads/ intra-abdominal, inguinal, or scrotal region	Testis/ inguinal or scrotal region	Testis/inguinal or intra-abdominal	Testis/scrotal or inguinal region	Testis/ inguinal, intra-abdominal or scrotal region	Testis/ inguinal, intra-abdominal or scrotal region
Associated clinical features	Syndromic features related to genetic cause	Syndromic features related to genetic cause (for both forms)		Mental retardation, syndromic features	None	None	Early adrenal failure	Enlarged adrenal glands, Early adrenal failure
Puberty	Virilization and feminization variable	Absence of spontaneous development	Absent or partial virilization	Normal	Absence of spontaneous development	Partial virilization absence gynecomastia	Absence of spontaneous development	Absence of spontaneous development
Gene location	Autosomal or Y chromosome	Autosomal or X or Y chromosome (for both forms)		11q12-q13	2p21	2p21	15q24.1	8p11.2
Molecular defect	DMRT cluster deletion,	Mutations in different genes (*e.g., SRY, NR5A1/SF1, MAP3K1.*) (for both forms)		Inactivating mutations in *DHCR7*	Inactivating mutations in *LHCGR* (complete inactivation)	Inactivating mutations in *LHCGR* (partial inactivation)	Mutations in *CYP11A1*	Mutations in *STAR*
	mutation in *SRY, SOX9*	Duplication of different genes (*e.g., WNT4, DAX1*) (for both forms)						

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conditions (adrenal or renal failure or Wilms tumors) and inform the medical management plan (Fig. 1) (62, 63).

Hormonal studies

Hormonal analyses using blood and urine samples are important for identifying diagnoses and for monitoring hormone replacement (Fig. 2). Most clinical laboratories use immunoassays that are limited by low specificity due to cross-reactivity with steroids and metabolites. Additionally, immunoassays measure only one steroid at a time. Multiple hormonal analyses are often needed to diagnose 46,XY DSD, requiring specialized laboratories capable of interpreting results within the context of age- and sex-specific reference ranges (64). Mass spectrometry–based steroid hormone assays, liquid chromatography linked with tandem mass spectrometry, and gas chromatography linked with tandem mass spectrometry allow for simultaneous analyses of multiple hormones and their metabolites with high specificity in a small sample of serum (0.1 to 0.2 mL). Biochemical analyses by liquid chromatography linked with tandem mass spectrometry are becoming increasingly common for routine clinical use in some parts of the world; however, assays continue to be unavailable in several countries (64).

Imaging studies

US of pelvic and inguinal/perineal regions, cystourethrography or genitography, and MRI are the imaging

Table 1. *Continued*

Defects of Androgen Production						Defects of Androgen Action		
3β-HSD2 Deficiency	17α-Hydroxylase Deficiency	POR Deficiency	17,20-Lyase Deficiency	17β-HSD3 Deficiency	5α-RD2 Deficiency	Complete Form	Partial Form	Defects in the Synthesis or Action of AMH
Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	X-linked recessive	X-linked recessive	Autosomal recessive
Male	Female in most patients	Male	Female	Female	Female	Female	Female	Male
Rare	Rare	Rare	Rare	Not so rare	Frequent	Rare	Not so rare	None
Atypical	Female- like to atypical	Atypical	Atypical	Atypical, frequently female-like at birth	Atypical, frequently female-like at birth	Atypical	Atypical, frequently female-like at birth	Male
Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Present
Male	Hypoplastic to normal	Hypoplastic to normal	Normal	Normal	Normal	Hypoplastic to normal	Normal	Normal
Testis/ inguinal, intra-abdominal or scrotal region	Testis/intra-abdominal or inguinal	Testis/intra-abdominal, inguinal or scrotal region	Testis/intra-abdominal inguinal or scrotal region	Testis/ inguinal or intra-abdominal region	Testis/inguinal or intra-abdominal region	Testis/inguinal or intra-abdominal region	Testis/inguinal or intra-abdominal region	Testis/ bilateral cryptorchidism, unilateral cryptorchidism, hernia or ectopic testis
Adrenal failure or not	Hypertension (low renin)	Antley–Bixler syndrome	None	None	None	None	None	None
Partial virilization, variable gynecomastia	Absent or slight virilization, variable gynecomastia	Partial virilization	Poor virilization, variable gynecomastia	Virilization, variable gynecomastia	Virilization, absence of gynecomastia	Absence of virilization, gynecomastia	Virilization, gynecomastia	Virilization, absence of gynecomastia
1p13.1	10q24.3	7q11.2	10q24.3	9q22	2p23	Xq12	Xq12	19p13.3 (*AMH*), 12q13 (*AMHRII*)
Mutations in *HSD3B2*	Mutations in *CYP17A1*	Mutations in *POR*	Mutations in the redox partner binding site of CYP17A1	Mutations in *HSD17B3*	Mutations in *5RD5A2*	Mutations in *AR* (complete inactivation)	Mutations in *AR* (partial inactivation)	Mutations in *AMH* or *AMHRII*

Abbreviations: LHCGR, LH/choriogonadotropin receptor; OT, ovotesticular; POR, cytochrome p450 oxidoreductase; StAR, steroidogenic acute regulatory protein.

techniques that aid clinical evaluation of individuals with 46,XY DSD (65–67). Choice of technology is influenced by patient age, indication, and accuracy. For example, diagnostic US is used during pregnancy, as the accuracy of sonographic fetal sex identification during gestation is well established (68). The ability to identify fetal sex correctly improves with increasing gestational age (69), and identification of atypical genital development can be detected early (60). Prenatal diagnosis of 46,XY DSD allows for opportunities to educate families and health care personnel prior to the birth of the affected child.

Goals for imaging after birth include verification of a uterus and vagina/urogenital sinus (UGS), as well as localization of gonads, when such structures are present. Imaging may also be needed to evaluate the kidneys, adrenals, and terminal spine (70, 71). US is recommended as the initial imaging modality for clinical assessment because it is easily accessible and does not require sedation or contrast agents (72). However, the quality of information provided by US is dependent on the evaluator's expertise as well as the device used. Although genitography and MRI are also useful for visualizing internal anatomy, genitoscopy/cystoscopy performed during surgical procedures are considered the gold standard for this purpose. Knowledge of internal anatomy, such as the presence and length of the UGS, relationship of the UGS to the urethra, and position of the external urethral sphincter are necessary for planning surgical strategies (67, 73). Genitography also reveals internal reproductive anatomy of young patients but may require confirmation with cystoscopy. Owing to the invasive nature of cystoscopy, this technique is used concomitantly with surgical procedures when these are desired. Low CT resolution for evaluation of pelvic anatomy restricts the use of this technique for investigating and staging tumors associated with 46,XY DSD such as Wilms tumors and GCTs (67). The evaluation of intrapelvic structures using MRI and US are considered equally sensitive; however, MRI is better suited for visualizing gonads (72). Streak gonads are difficult

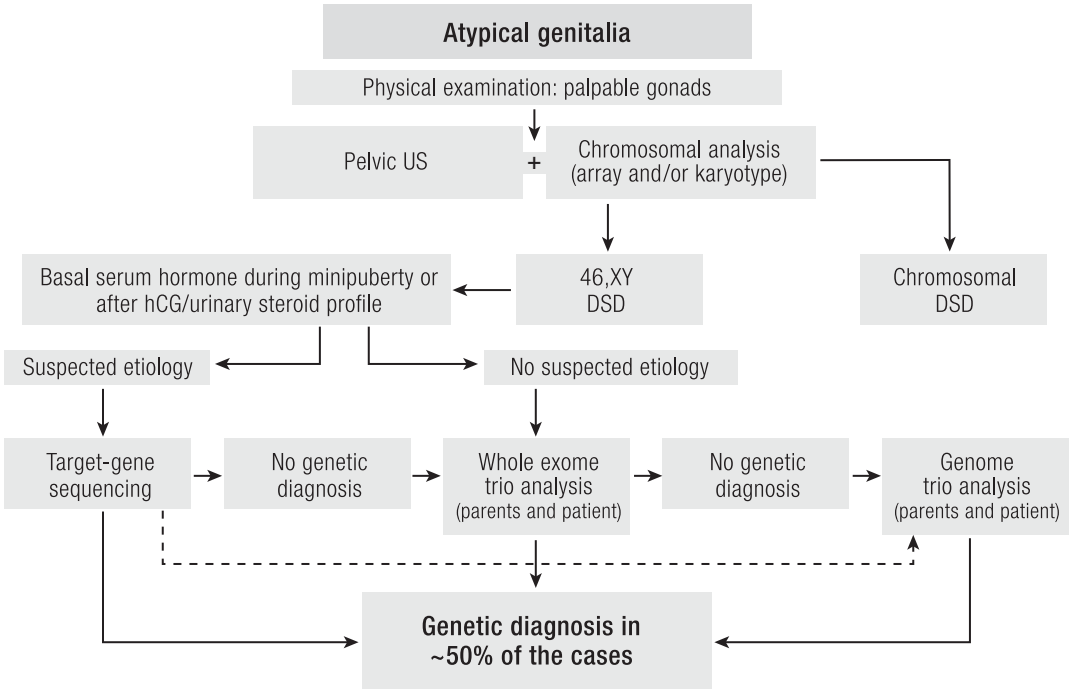


Figure 1. Flowchart for the evaluation of atypical genitalia.

to detect by MRI, and laparoscopy is the gold standard for assessing these intra-abdominal tissues. Laparoscopy may also be used to visualize gonads in patients with 46,XY ovotesticular DSD to retain gonadal tissue that is congruent with sex or rearing as well as to assess tumor risk. Information obtained from laparoscopy can guide biopsy, removal, or mobilization of the streak tissue or gonads (74, 75).

Genetic studies

PCR amplification of the *SRY* gene is the fastest method to disclose the presence of the Y chromosome in a newborn. The karyotype is often the first test ordered when trying to classify DSD (3, 16). Karyotype, quantitative fluorescence PCR, fluorescence *in situ* hybridization analysis, and array techniques [array-comparative genomic hybridization (aCGH) and single-nucleotide polymorphism (SNP) array] are all capable of identifying sex chromosomes (Fig. 3). Although results from array techniques are obtained faster than those from G-banding, arrays are less effective at detecting sex chromosome mosaicism (66).

Several genes related to 46,XY DSD have been shown to exert a dose-dependent effect on sex differentiation and development, including duplications (*DAX1* and *WNT4*) and deletions (*ATRX*, *DMRT1*, *EMX2*, and *WT1*) (Fig. 3). Multiplex ligation-dependent probe amplification, SNP array, and aCGH techniques detect copy number variations (CNVs). Multiplex ligation-dependent probe amplification detects specific target sites whereas the others examine the entire genome. Resulting CNVs range from several genes (contiguous genes syndrome) to small variations. SNP array or aCGH should be used first when investigating causes of 46,XY DSD for patients with malformations or syndromic features, as their effectiveness to detect pathogenic CNVs is ~30% (16, 59, 61, 76–78). However, careful interpretation of results is critical, as small genotype imbalances (10 kb) are commonly detected with uncertain clinical significance (79).

The introduction of next-generation sequencing methods has significantly improved the ability to identify molecular diagnoses underlying 46,XY DSD (16, 79–81). As such, individual gene sequencing has been replaced by panels of DSD candidate genes and whole-exome sequencing (WES)/whole-genome sequencing (WGS) (Fig. 3). WES and WGS allow for the identification of novel genetic causes of 46,XY DSD (82–84) in addition to mutations in genes already known to be associated with these conditions (16, 66, 79, 85, 86). However, potentially inconclusive results such as identification of variants of unknown significance or a combination of pathogenic variants identified in different genes (*i.e.*, oligogenic disease) may prevent a definitive diagnosis. Furthermore, results from high-throughput DNA tests have revealed inconsistent associations between DSD phenotypes and molecular findings, and thus the need for complementary hormonal and imaging tests remains (16, 85). Finally, WES and WGS strategies are expensive, thus limiting their application for first-line diagnostic investigation in many clinical settings. As technical and bioinformatic advances continue, it is anticipated

that costs for these molecular tests will decrease. Despite their limitations, molecular genetic tests play an increasingly important role in the management of DSD, as these allow for prognostic predictions, genetic counseling, and individualized management (Fig. 3) (16, 87). In summary, only half of patients with nonsyndromic forms of 46,XY DSD receive a genetic diagnosis. Although genetic evaluation of patients can include a karyotype, chromosomal microarray, single gene sequencing, gene slice panels, and WES, these options are rarely exhausted owing to costs and unavailability. As next-generation sequencing becomes less expensive and more efficient, perhaps more patients worldwide will receive a genetic diagnosis associated with their DSD (16, 86).

Prenatal diagnostics

Suspicion of 46,XY DSD prior to birth is influenced by family history or atypical/discordant genital appearance visualized by prenatal US (72, 88). Prenatal diagnosis of DSD has increased as a result of the frequent use of noninvasive prenatal testing (NIPT) by cell-free DNA analysis of maternal blood to screen for aneuploidy during the first trimester of pregnancy (61, 88, 89). NIPT identifies Y chromosome sequences such as *SRY* using quantitative fluorescent PCR in maternal blood from as early as 7 weeks of gestation (60, 69). In a large cohort of pregnant women screened for common chromosomal abnormalities by NIPT, a genotype/phenotype discordance was identified in ~1 in 1500 to 2000 pregnancies (61). The DSD diagnosis in cases of incongruent NIPT (*i.e.*, female genitalia in 46,XY fetus) included vanishing twin (small Y chromosome signal), CAIS, mosaic monosomy (X/XY), and 9p deletion syndrome (61).

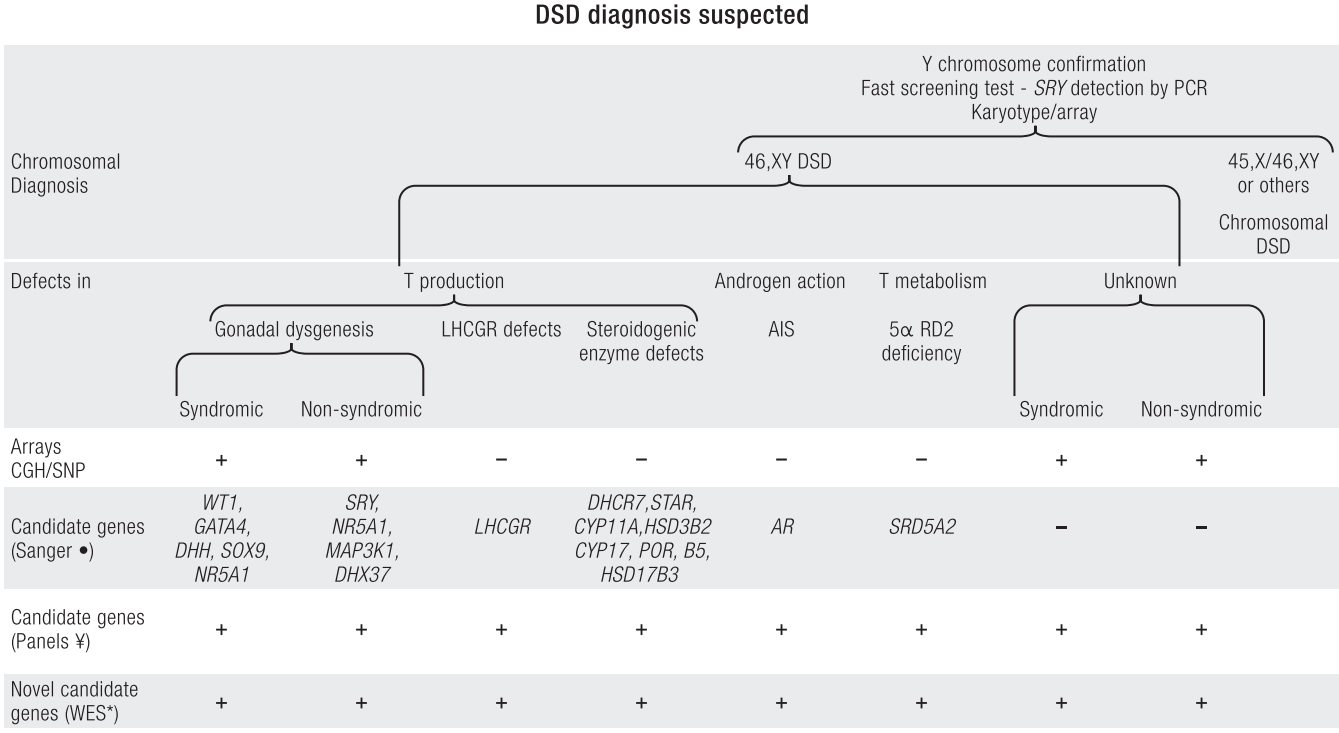
NIPT is a safe procedure with high accuracy (98% to 99%) for identifying sex. Nonetheless, a diagnosis may not be established if a fetal fraction is too small, as may occur with maternal obesity, or if the sample is collected too early in gestation. Moreover, NIPT methodology in many commercial laboratories is not able to distinguish between fetal and maternal cell-free DNA. Another cause of an abnormal NIPT result is the presence of a vanishing twin (90). In cases of genotype/phenotype discordance, NIPT can be repeated or alternative testing can be considered (91). A detailed US to assess fetal genital phenotype is recommended to detect genital abnormalities and exclude potential causes of misdiagnosis such as an empty second gestation sac or demised twin (61). When NIPT is unavailable,

Diagnosis	Gonadal dysgenesis	LHCGR defects	Steroidogenic enzyme defects	AIS	5-α-RD2 deficiency
Defects / Parameters	In T production			In T/DHT action	In T metabolism
Baseline and hCG stimulated T levels*	Low			Normal or elevated	
Levels of T precursors	Low	Low	20,22-desmolase → ↓All steroids 3β-HSD II → ↑17OHPREG 17α-hydroxylase → ↑PROG 17,20 desmolase → [↑17OHPROG ↓A] 17β-HSD III → ↑A/T ratio	Normal	Normal
DHT levels	Low	Low	Low	Normal	Generally low ↑T/DHT ratio
AMH levels	Low	Normal	Normal	Normal	Normal
LH levels	↑	↑↑	↑	↑↑	Normal
FSH levels	↑↑	Normal/↑	Normal	Normal/↑	Normal
Uterus in pelvic imaging	Present or absent	Absent	Absent	Absent	

Note that cloacal exstrophy is not included, as this diagnosis is based on the phenotype. *In newborns (6–36 h after birth), during minipuberty (days 15–90 after birth), and after pubertal age measurement of T baseline levels provides information on the ability of the testes to secrete T. In prepubertal patients, it is necessary to stimulate endogenous T production with human chorionic gonadotropin (hCG). Precursors of T [17-hydroxypregnenolone (17OHPREG), 17-hydroxyprogesterone (17OHPROG), androstenedione (A), progesterone (PROG)] and DHT may also be measured (after exogenous T or hCG stimulation tests).

Figure 2. Diagnostic approach for patients with 46,XY DSD based on hormonal analysis and imaging studies.

Figure 3. Genetic approach to 46,XY DSD diagnosis. AIS includes both complete and partial forms. •Sanger sequencing is recommended when the phenotype (clinical or hormonal patterns) is strongly indicative of diagnosis or to exclude 5α-RD2 in newborns. ¥Panel sequencing is first recommended except in conditions described under Sanger sequencing. *WES: Using family trio–based sequencing (affected person and parents) allows better discrimination of variant pathogenicity. LHCGR, LH/choriogonadotropin receptor.



karyotype or DSD candidate gene analyses can be performed by chorionic villus biopsy or by amniotic fluid cells obtained from the 9th to 11th and 15th to 20th weeks of gestation, respectively. Disadvantages of these tests compared with NIPT is that they are performed later in the pregnancy and are associated with an increased risk of miscarriage (0.5% to 3%) (92, 93).

Finally, DSD is suspected when male- or female-typical genitalia are not visualized by US after 14 weeks of gestation of prenatal life (60, 73, 94). A prenatal diagnosis of Smith–Lemli–Opitz syndrome (94) can be performed in a fetus with atypical genitalia by measuring 7-dehydrocholesterol, in serum or other tissues, including cultured fibroblasts, amniocytes, or chorionic villi, as well as in amniotic fluid (95).

Postnatal diagnostics

Partial virilization of the external genitalia is usually identified during the neonatal period as a result of a medical examination or during routine care by the baby's relatives. Complete absence of virilization may be missed in some newborns presenting with a female phenotype. The identification of a Y chromosome or its fragments is a fundamental step to direct the diagnosis of 46,XY DSD (96) (Figs. 1 and 2). The presence or absence of structures derived from the Müllerian ducts, such as the uterus, can be visualized with pelvic US to aid the diagnosis.

In newborns (6 to 36 hours after birth) measurement of testicular hormone baseline levels provides information about the ability of the testes (if present) to secrete hormones such as T and anti-Müllerian hormone (AMH) (Fig. 2) (97). During the period of spontaneous activation of hypothalamic–pituitary–gonadal axis (*i.e.*, minipuberty, days 15 to 90 after birth), these hormones should be (re)evaluated. Testicular hormone values obtained during minipuberty can help to differentiate 46,XY DSD secondary to (i) insufficient androgen production due to gonadal dysgenesis or defective androgen synthesis, (ii) defects in target tissue responsiveness to androgens (androgen insensitivity), or (iii) defects in T metabolism such as 5α-RD2 deficiency. For example, low or undetectable T and AMH levels indicate complete testicular dysfunction (Leydig and Sertoli cell dysfunction), and 46,XY DSD due to gonadal dysgenesis should be suspected (98–100). This diagnosis is further confirmed by the identification of a uterus by pelvic US (67, 72). For patients with cloacal exstrophy, testicular hormone production during minipuberty should not differ from that observed in healthy boys.

Steroid precursors (progesterone, dehydroepiandrosterone, androstenedione, 17α-hydroxyprogesterone, and 17α-hydroxypregnenolone) and DHT may also be evaluated to search for enzymatic defects in adrenal and/or gonadal steroid synthesis and 5α-RD2

deficiency, respectively (Fig. 2) (66). Identification of the accumulation of steroid precursors or low DHT levels can guide genetic diagnostics, and a molecular defect can be confirmed with individual gene sequencing, panels of DSD-candidate genes, WES, or WGS (Fig. 1) (16, 79, 81).

As just mentioned, a biochemical diagnosis of 5α-RD2 deficiency can be based on an elevated serum T/DHT ratio (35, 36). To analyze this ratio, T levels should be in the postpubertal range. After the first 3 to 5 months of life, basal levels of T and gonadotropins are low and no longer informative, and therefore it is necessary to stimulate endogenous T production with exogenous human chorionic gonadotropin or administer an injection of T ester in prepubertal patients (101, 102). In newborns, a normal T/DHT ratio does not exclude 5α-RD2 deficiency because transcription of the isoenzyme 5α-RD1 frequently occurs (103, 104). To determine the T/DHT ratio correctly, with the additional advantage of using a small serum sample (0.1 to 0.2 mL), DHT should be measured with chromatography or mass spectrometry because commercial immunoassays present high cross-reactivity with T (105). Metabolomics can also diagnose 5α-RD2 deficiency (106, 107). For example, an elevated ratio of 5β/5α reduced steroid urinary metabolites indicates 5α-RD2 deficiency prior to puberty and in orchidectomized adults (107–109). Considering the prevalence of normal T/DHT ratios in affected newborns and the importance of a correct diagnosis to plan for medical management, including male sex rearing, mutational analysis of *SRD5A2* is indicated as the first approach to 5α-RD2 deficiency diagnosis when feasible (107, 110).

Patients with 46,XY DSD due to CAIS and defects in *LHCGR* present similar phenotypes before puberty but dissimilar hormonal profiles after puberty. The hormonal profile for CAIS is characterized by elevated LH and T levels, whereas that for *LHCGR* defects is high LH and low T levels (5). The phenotype of patients with PAIS is quite variable and overlaps with many other conditions categorized as 46,XY DSD. In these cases, a molecular diagnosis is helpful to define etiology (16, 17, 47, 111). That said, a molecular diagnosis occurs in only 10% to 20% of unselected cases of 46,XY DSD (112). However, when subjects are selected by specific AIS characteristics such as normal male basal and stimulated serum T levels and steroid precursors coupled with gynecomastia at puberty, the molecular diagnosis is achieved in 73% of PAIS subjects using *AR* exonic sequencing (113).

Sex of Rearing

Decisions regarding sex of rearing in newborns with DSD are complex and can be especially challenging for those with a 46,XY karyotype and severe undervirilization of the genitalia (14, 114, 115). Such decisions are based on the understanding that gender identity, or the gender a person identifies with, does not always align with a person's genetic, gonadal, or anatomic sex. Sexual attraction toward males, females, or both is likewise difficult to predict according to a person's biological sex. Such discordance between sex, gender identity, and sexual orientation illustrates the complexity physicians and caregivers face when deciding on a sex of rearing for a newborn with 46,XY DSD. As older children recognize and reveal their gender identity over time, decisions regarding sex of rearing do not apply to them (116).

Psychological support is a keystone for interdisciplinary management (54, 63, 117), and every parent caring for an affected child should be offered counseling by an experienced mental health specialist. Ideally, this support should begin once a diagnosis is suspected, and then continue throughout childhood and beyond (118, 119). Unfortunately, no evidence-based model for delivering mental health care to people affected by 46,XY DSD has yet to be developed, and variability in access to mental health providers exists both within countries and cross-culturally (120).

Distress about the general health of their child, coupled with the fear of stigma surrounding their child's diagnosis, is often reported by parents. Thus, a straightforward and comprehensive explanation about what to expect regarding their child's future social development, sexual function, fertility, and need for hormone replacement and/or surgery must be discussed with parents prior to their decisions regarding sex of rearing for their child (70, 115).

"Sex steroid replacement is an important component of management for some types of 46,XY DSD."

A special issue written by senior endocrinologists with a combined experience of >300 years in the treatment of DSD offers guidance on decisions surrounding sex of rearing for children with 46,XY DSD residing in countries and cultures spanning four continents (121). For example, sufficient outcomes data exist to support female sex of rearing for newborns affected by CAIS or complete 46,XY gonadal dysgenesis (122–124). For 46,XY DSD secondary to steroid 5α-RD2 deficiency or 17β-hydroxysteroid dehydrogenase deficiency type 3, data are less clear; however, female rearing is associated with a high likelihood of patient-initiated male reassignment later in life (22, 116, 125, 126). Prior to the late 20th century, decisions about sex of rearing were based on the hypothesis of gender neutrality at birth (127). Since then, more knowledge has been obtained about the impact of prenatal androgens on psychosexual development (116, 128, 129). For instance, patients with 46,XY DSD who are exposed to (and respond to) androgens during early development are more likely to develop a male gender than those with low/absent prenatal androgen exposure, regardless of their degree of virilization at birth (116). Furthermore, prenatal

androgen exposure is a better predictor of male gender development than androgen exposure later in life (116). This increased understanding of endocrine influences on psychosexual development has translated to changes in clinical practice. For example, a retrospective evaluation of 554 patient charts in the DSD European Registry revealed that prior to 1990 only 35% of patients with a 46,XY karyotype and atypical genitalia were raised male. After 1999, most (68%) young children with 46,XY DSD including atypical genitalia were raised male (114).

Despite the association between early androgen exposure and male identification, for most patients with 46,XY DSD, sex of rearing continues to be the best predictor of gender development (130), and patient-initiated reassignment observed in ~20% of patients studies retrospectively is the exception rather than the rule (116). Factors in addition to androgens impact psychosexual development in ways that may be unique to different etiologies underlying 46,XY DSD. This potentially condition-specific sensitivity to influences on gender development underscores the importance of establishing a molecular diagnosis prior to deciding on a sex of rearing for young patients (10, 16, 71).

At the hospital nursery, it is important to discuss what is known about gender development with parents and give them the opportunity to discuss their concerns for their child (131). The incongruence between karyotype and sex of rearing may cause distress, and an explanation that karyotype does not define gender is recommended. Sharing prevalence estimates that 1 out of 25,000 men possesses a 46,XX karyotype and 1 out of 16,000 women has a Y chromosome is helpful to illustrate the independence of the karyotype from psychosexual development (23, 132).

Parents often want guidance about how to explain their child's diagnosis to family and friends. Instruct parents to use simple explanations such as the baby had an alteration in genital development and some tests are necessary to guide sex assignment. Of note, parents' concerns about discussing their child's DSD were noted at the first Disorders of Sex Development (DSD) Consensus meeting in Chicago in 2005 (1). In summary, it is important to inform parents that evidence supports female rearing in newborns with CAIS or complete gonadal dysgenesis (122, 133, 134). The opposite is recommended for individuals with 5α-RD2 and 17β-hydroxysteroid dehydrogenase type III (17β-HSD3) deficiencies (126, 135). For other types of DSD, condition-specific outcomes related to psychosexual development, anatomy, fertility potential, and the need for subsequent medical and surgical treatment must be considered when deciding on sex of rearing (87, 97, 121, 136, 137). Data support male rearing in all patients with 46,XY with micropenis, as this option optimizes fertility potential and requires no surgical treatment of patients (134, 138). Finally, any decision about rearing should respect parents' cultural and religious beliefs about what is best for their child, including postponing or opting out of genital surgery completely (63, 115, 139).

Hormone Treatment Across Development

Sex steroid replacement is an important component of management for some types of 46,XY DSD (73, 140). The goals of replacement include induction and maintenance of secondary sex characteristics as well as other aspects of pubertal development, including growth. Bone mineral optimization and promotion of uterine development may also be helped by treatment with sex steroids for some patients. Hormone replacement can also impact psychosocial and psychosexual development, as well as general well-being, in positive ways for some people (141–143). Induction and maintenance of pubertal development is necessary in most patients affected by 46,XY DSD regardless of male or female rearing; however, specific indications depend on the underlying etiology of the condition.

Androgen replacement

Most individuals affected by 46,XY DSD have a deficiency in either androgen production or action as part of their condition (15, 144). For those raised male, T replacement should strive to mimic masculine pubertal induction between 10 and 12 years of age, provided the child's projected height and growth are normal and he indicates a desire and readiness for puberty (5). Intramuscular, short-acting injections of T esters are the most suitable formulation to induce male puberty, although other options include oral T undecanoate and transdermal preparations (145, 146). The initial dose of short-acting T esters is 25 to 50 mg/mo intramuscularly, with further increments of 50 mg every 6 to 12 months thereafter. After reaching a replacement dose of 100 to 150 mg/mo, the delivery interval can decrease to every 2 weeks.

An adult dose of 200 to 250 mg every 2 weeks (short-acting T esters), 1000 mg every 10 to 14 weeks (long-acting T esters), or 50 to 100 mg for T gel or other transdermal preparations applied topically are effective to maintain male secondary sex characteristics (Table 2) (5, 146). Monitoring of T levels should be performed on the day preceding the next hormone administration, and serum levels should fall just above the lower limit of the normal range for eugonadal men. Transdermal preparations should be started at 50% of an adult replacement dose (146).

For patients with 5α-RD2 deficiency or PAIS, higher doses of intramuscular T preparations or topical DHT can be used to optimize virilization (6, 147–149). For boys and men with PAIS, T esters

Table 2. Doses, Advantages, and Disadvantages of Available Testosterone (T) Formulations for Clinical Use

Formulation	Dose	Advantages	Disadvantages
Short-acting T esters (enanthate, cypionate, or mixed esters); intramuscular	• Initial dose: 25–50 mg/mo	• Low cost	• Does not mimic the circadian rhythm
	• After 6–12 mo: 50–100 mg/mo	• One dose every 2–3 weeks	• Provides supraphysiological levels of T within the first days after injection
	• Adult dose: 250 mg every 2–3 wk	• Suitable for low doses	• Fluctuation in mood or libido
			• Erythrocytosis
Long-acting T (undecanoate); intramuscular	• Adult dose: 1000 mg/12 wk	• Four injections per year	• High cost
		• Does not provide supraphysiological levels of T	• Not suitable for low doses
			• Pain at injection site
			• Risks of pulmonary oil microembolism
Transdermal patch	• Adult dose: 5 mg/d	• Mimics the circadian rhythm	• Daily use
		• Moderate cost	• Often causes skin irritation at the site
		• Leads to physiological levels of T	• High cost
			• No data available for low doses
Transdermal gel	Adult dose: 50-100 mg/d	• Quick and efficient absorption	• Daily use
		• Maintains satisfactory levels of T	• High cost
		• Unusual skin irritation at the site	• No data available for low doses
			• Potential risk for T transfer to partner or another person who is in close contact
Subcutaneous implants	• Adult dose: 600 mg/4–6 mo	• Leads to stable and physiological T levels	• Possibility of extrusion and local infection
		• One implant every 6 mo	• Not suitable for low doses
T undecanoate oral tablets	• Adult dose: 80–160 mg/d	• The only effective and safe oral T ester	• Daily use two to four daily doses
		• Does not cause hepatotoxicity	• Variability of absorption according to meals
			• Unstable T serum levels
			• No data available for low doses
Buccal patch	• Adult dose: 30 mg/12 h	• Mimics the circadian rhythm	• Twice daily
		• Leads to physiological levels of T	• High cost
		• Does not seem to cause mucosal irritation	• Short experience of clinical use
			• Not suitable for low doses
			• Alterations in taste and irritation gum

(250 to 500 mg once or twice a week) can increase DHT levels to promote penile growth in addition to male secondary characteristics (150–152). Similarly, percutaneous administration of DHT results in phallic growth for infants and children with 5α-RD2 deficiency (149). Maximum penile length is obtained in patients 6 months after starting higher androgen replacement doses. Standard replacement regimens should be reinstituted after that period of time (101, 153). Importantly, DHT treatment increases penile length without the unwanted side effects of gynecomastia or influencing bone maturation (147). Although these results from increased androgen replacement are promising, clinical trials

designed to test the effectiveness and safety of high-dose T and/or DHT replacement in the promotion of virilization for undervirilized boys and men are needed.

Estrogen replacement

Estrogen replacement is recommended for girls with 46,XY DSD using low doses of hormone starting around 9 to 11 years of age (Table 3). Low doses (one-sixth to one-fourth of an adult dose) are used to avoid excessive bone maturation. Estrogen replacement should be titrated every 6 months according to the clinical response (*i.e.*, breast Tanner stage, bone age). This strategy ensures gradual feminization with full pubertal maturation reached within 2 to 3 years of starting replacement. For females with unwanted tall stature, the initial replacement dose can be the same as that used for adult women.

There are several options available for estrogen replacement as well as different combinations and doses of progestins (142, 154, 155); however, 17β-estradiol (oral or transdermal) is preferred. Transdermal delivery is thought best to replace with a bioidentical hormone, and transdermal delivery avoids hepatic first-pass metabolism, resulting in less thrombogenicity and more neutral effects on lipids (156–158). It is also easier to administer small doses of estrogen by cutting up a patch or by using a metered-dose gel dispenser. An initial recommended dose of oral 17β-estradiol is 5 μg/kg daily, titrated every 6 to 12 months to an additional 5 μg/kg daily until an adult dose of 1 to 2 mg daily is achieved (146). In case of transdermal replacement, the initial recommended dose for the 17β-estradiol patch is 3.1 to 6.2 mg/24 h overnight (one-eight to one-fourth of the 25 mg/24 h patch). Transdermal doses can increase 3.1 to 6.2 mg/24 h every 6 months until an adult dose of 50 to 100 mg/24 h twice a week is achieved (159). Once breast development is complete, an adult dose can be maintained continuously. For patients who do not possess a uterus, estrogen alone is indicated (63, 156). Progesterone is needed to induce endometrial cycling and menses in patients with a uterus. For the latter group, medroxyprogesterone acetate (5 to 10 mg/d) and micronized progesterone (200 mg/d from the 1st to the 12th day of each month) are appropriate to maintain uterine health.

Some females with CAIS report decreased psychological well-being and sexual dissatisfaction following bilateral gonadectomy and subsequent estrogen replacement (160, 161). T treatment has been proposed as an alternative to estrogen for hormone replacement in these women, and such treatment improves sexual desire (162). Long-term follow-up studies on the impact of T replacement on additional psychological measures, as well as on bone metabolism and cardiovascular outcomes, are needed (163). Summaries of the available preparations of androgen and estrogen replacement for

Table 3. Doses, Advantages, and Disadvantages of Available Estrogen Formulations for Clinical Use

Formulation	Dose	Advantages	Disadvantages
17β-Estradiol oral tablets	• Initial dose: 5 μg/kg/d • Every 6–12 mo: increase to 10 μg/kg/d, then 15 μg/kg and then 20 μg/kg/d • Adult dose: 1–2 mg daily	• Natural estrogen, preferable to synthetic estrogens	• Low doses are not available in all countries
17β-Estradiol transdermal patch	• Initial dose: 3.1–6.2 μg/24 h (one-eighth to one-fourth of 25 μg/24 h patch) • Every 6 mo: increase to 3.1–6.2 μg/24 h • Adult dose: 50–100 μg/24 h twice a week	• Avoid hepatic first-pass metabolism (potentially better for IGF1 synthesis) • Lower thrombogenicity • Neutral effect on lipids • Suitable to administer low doses	• Potential skin irritation at the site
17β-Estradiol transdermal gel	• Adult dose: 1–2 mg daily	• Same advantages as those of transdermal patches	• No dosage-equivalent data between patches • Not suitable for low doses • Potential risk transfer to partner or another person who is in close contact
Estradiol valerate oral tablets	• Adult dose: 1–2 mg daily		• Synthetic estrogen (not physiological) • Increased risk of venous tromboembolism • Not suitable for low doses

patients with 46,XY DSD are displayed in Tables 2 and 3.

Glucocorticoid replacement

It is necessary for 46,XY DSD patients with classical forms of congenital lipoid adrenal hyperplasia, 3β-hydroxysteroid dehydrogenase type II (3β-HSD2), and 17α-hydroxylase/17,20-lyase deficiency to receive glucocorticoid replacement for adrenal insufficiency as well as hypertension management (164, 165). Mineralocorticoid replacement is also required for patients with 46,XY DSD who are salt-losing (166).

Surgical Considerations

Preoperative evaluation and goals for surgical intervention

The physical examination to prepare for genital surgery focuses on length and diameter of the phallus, location of the urethral meatus, and presence of an orifice that reveals a potential vaginal cavity (167, 168). When a single perineal opening is observed, a UGS is suspected. Depending on the degree of undervirilization, patients can present with a normally formed scrotum, hemiscrotum, separated labioscrotal folds, or some degree of penoscrotal transposition. Careful palpation is required to identify gonads in the inguinal region, labioscrotal folds, or scrotum.

Because congenital malformations of the external genitalia associated with 46,XY DSD do not affect micturition, surgical intervention is not typically required during the neonatal period. For some families, the atypical appearance of the patient's genitalia causes distress and may result in subsequent distress for the patient as well. Furthermore, atypical genital anatomy may impact long-term urinary and reproductive function. Thus, the aims of surgical intervention in the context of 46,XY DSD are to alter genital appearance to better correspond with sex of rearing, reconstruct anatomy to allow for future sexual activity and optimize fertility potential, and prevent the development of urinary and genital tract complications such as infections and gonadal malignancy (169–171).

Masculinizing procedures

Surgical procedures for patients with 46,XY DSD raised male can include correction of hypospadias and scrotal abnormalities, relocation of the testes to the scrotum or removal when dysgenetic, and resection of Müllerian remnants (172, 173). Correction of hypospadias includes correction of phallic curvature (orthophalloplasty) and construction of a urethra to the tip of the glans (urethroplasty). For patients with a small penis (174), preoperative administration of T may increase penile length and improve resilience of tissue to surgical handling (175). Despite favorable reports of using T to improve urethroplasty outcomes, there is a lack of guidance on how best to do so.

Orthophallopasty is achieved by degloving the penis either with or without sectioning the urethral plate, depending on the degree of curvature of the phallus. If the curvature is mild ($<30°$), correction can be achieved with one to three nonabsorbable stitches in the midline of the dorsal aspect of the penis without sectioning the urethral plate (176). If the curvature is $>30°$, the urethral plate must be initially sectioned and the ventral chordee is either resected or incised with multiple corporotomies (177).

A number of urethroplasty techniques exist, with no agreement on which is best (178). Urethroplasty can be performed by tubularization of the preserved urethral plate, with or without an onlay preputial flap. If the plate has to be sectioned, then a preputial tubularized flap can act as a substitute for the urethra and this can be achieved with a one-stage procedure. For patients with important curvature, who required sectioning of the original urethral plate with a long gap, urethroplasty can be performed as a planned, two-stage procedure after preparing the urethral bed with preputial flaps or grafts during orthophalloplasty (177, 179). As just alluded to, both one-stage (*i.e.*, simultaneous orthophalloplasty and urethroplasty) and two-stage (*i.e.*, orthophalloplasty first, followed by urethroplasty 6 to 9 months later) procedures are used; however, the two-stage approach typically results in better cosmetic outcomes and fewer postoperative complications for patients with severe hypospadias and significant chordee (173, 174, 179–181).

Depending on the degree of undervirilization, scrotoplasty can consist of simple or complex mobilization and suturing of scrotal flaps to the midline followed by covering the urethra. This procedure can be performed simultaneously with urethroplasty. However, when there are concerns about the vascular supply to the skin pedicles used in the hypospadias repair, scrotoplasty can be performed separately. For patients with undescended testes, simultaneous orchidopexy may be performed (175).

The surgical treatment of gonads of patients with 46,XY DSD aims to preserve testicular function (production of T and sperm) and prevent malignancy (37, 40, 182). For patients with partial gonadal dysgenesis, PAIS, or disorders of T or DHT biosynthesis, orchidopexy can be performed (17, 40, 42, 182, 183).

For patients with ovotesticular DSD, conservative gonadal surgery guided by intraoperative histological analysis in frozen sections of gonadal tissues is indicated to define the margins between ovarian and testicular components, with preservation of gonadal tissue that is concordant with the gender identity (174).

Finally, gonadectomy is recommended for patients at risk for neoplastic transformation of germ cells (GBs and/or invasive GCTs) in dysgenetic gonads (184). The risk for GCTs is also increased in patients with undescended testes, including all other 46,XY DSD syndromes. Although data are limited, in AIS the risk seems to be higher in the partial form than in the complete form, and tumor prevalence in this condition increases after puberty.

Current guidelines of the American Urological Association recommend that orchidopexy be performed between 6 and 18 months of age for patients with undescended testes (172). Both orchidopexy and gonadectomy can be performed with open or laparoscopic approaches (75, 185). Testes relocated to the scrotum in young patients should undergo periodic surveillance by physical examination (168). After puberty, repositioned testes should be evaluated annually with US or eventual biopsy. When gonadectomy is recommended, patients may then choose to have testicular prostheses placed in the scrotum (185, 186).

Müllerian remnants

Müllerian structures are rudimentary in some patients and present as a cystic prostatic utricle. These utricles may be left *in situ* when asymptomatic, but in cases of recurrent urinary tract infection, stones, or significant postvoid urethral dribbling due to urinary pooling, they can be removed either laparoscopically or through a sagittal posterior incision of the perineum (75, 185). With either approach, great care must be taken to prevent injury to the vas deferens, seminal vesicles, and pelvic nerves so as to avoid subsequent infertility, erectile dysfunction, and urinary incontinence (175, 187, 188).

Late evaluation of patients with 46,XY DSD operated in childhood due to proximal hypospadias reveals that many felt that their genitals had an unusual appearance or presented some degree of urinary or sexual dysfunction (173, 189, 190). Objectively, most patients with DSD have a penile length below the −2.0 SD (5.2 ± 2.0 cm) (151, 172, 189).

Dysfunctional voiding and lower urinary tract symptoms are also more frequent in these patients than in controls (173, 191). However, between 55.6% and 91% of these patients were satisfied with their overall sexual function after genitoplasty, when considering sexual contacts, libido, erections, orgasm, as well as size of the penis and volume of ejaculation (137, 151, 173, 190, 192, 193).

Feminizing procedures

The presence of a UGS requires an accurate understanding of the patient's internal anatomy to plan an appropriate surgical approach to achieve feminization (167, 194, 195). The location of vaginal insertion into the UGS, vaginal cavity, and inferior urinary tract can be visualized with intraoperative genitoscopy or MRI when such structures exist. Endoscopic evaluation during surgery confirms the location of vaginal insertion and allows for vaginal catheterization to improve identification and mobilization of the vaginal channel (194). When imaging studies are unable to identify the presence of intra-abdominal gonads, laparoscopy is recommended to identify whether gonadal tissues are present (75). Feminizing genitoplasty includes reduction of phallic size when enlarged, opening the UGS to separate the urethra from the vaginal introitus, and constructing labioscrotal folds.

Similar to masculinizing genitoplasty, a number of procedures have been developed to reconstruct female genitalia in patients affected by 46,XY DSD. Feminizing techniques have evolved over time to achieve better cosmetic outcomes (196, 197); however, functional outcomes and patient satisfaction with surgical care remain to be documented after newer surgical approaches (196). Many techniques have been proposed over the years to separate the urethra from the vaginal introitus and bring both to the surface of the perineum. For example, an inverted U-shaped perineal skin flap was first proposed to expose and enlarge the introitus, and this technique continues to be widely used today (195). An alternative to the skin flap approach to vaginoplasty is the "pull-through" for patients with a high vaginal insertion. However, pull-through vaginoplasty is limited by unsatisfactory cosmetic outcomes associated with this procedure (198, 199). Yet another vaginoplasty technique for patients with high vaginal insertion is known as the Passerini–Glazel procedure. This technique uses UGS tissue to create the anterior wall of the vagina in combination with phallic skin flaps to create the distal vagina and introitus (200). Although the Passerini–Glazel procedure results in good cosmetic outcomes, complications such as vaginal stenosis and a short vagina are common (201). Sexual function and genital sensitivity in women who received Passerini–Glazel genitoplasty revealed reduced clitoral sensitivity (202). As a result of these unsatisfactory outcomes, variations in the Passerini–Glazel procedure have been proposed to maintain satisfactory cosmetic outcomes while optimizing functional results. One such variation is the total urogenital sinus mobilization (TUM) technique initially developed for patients with cloacal anomalies (203). Good results have been reported with TUM (197), although there is a risk of urinary incontinence with this procedure (204, 205).

As feminizing genitoplasty continued to evolve, partial UGS mobilization was proposed. Partial UGS mobilization was thought to be superior to TUM in that it kept the anterior dissection of the UGS distal to the pubourethral ligaments, thus decreasing the risk of incontinence (206). Another surgical access to high vaginal insertion is an anterior sagittal transrectal

approach (ASTRA). With ASTRA, a posterior longitudinal incision is made in the midline of the perineal surface, opening the anterior wall of the rectum to allow for a better surgical approach in cases of high vaginal insertion (207, 208). A promising study of women who received ASTRA reported a low frequency of complications (209). If the UGS persists, complications such as urinary infections, postvoid dribbling, and difficulties with sexual intercourse can occur (170, 194). For this group of women, additional surgical techniques can be used to mobilize a posterior vagina, including buccal mucosa grafts and perineal skin flaps (194). The large number of vaginoplasty techniques developed over time reveals the challenging nature of such procedures. As postoperative complications and the need for additional surgeries to correct these are common with even the most advanced approaches, surgeons continue to strive to improve upon vaginoplasty techniques to optimize outcomes for their patients. Finally, for women with 46,XY DSD who possess a short vagina and wish to engage in vaginal intercourse, dilation with acrylic molds results in adequate vaginal length without surgical intervention. Success is usually achieved with 6 months of dilation (210). Vaginal lubricant may be required for sexual intercourse.

Clitoridectomy, or removal of the entire clitoris, was the first surgical procedure used to reduce phallic size in girls with DSD (211). This technique is no longer used, as it is now understood that clitoral function is important for satisfactory sexual function (206, 212, 213). The resulting technique of resecting the clitoral body while preserving the neurovascular bundle was developed (214). With a better understanding of clitoral anatomy came further advances in clitoroplasty procedures, such as reducing the glans of the clitoris ventrally to avoid damage to the dorsal neurovascular bundle (215). Kogan *et al.* (216) further described preserving the neurovascular bundle attached to the dorsal portion of the tunica albuginea to protect the nerves and blood supply. However, despite attempts to preserve nerves and blood supply during clitoroplasty, atrophy and necrosis of clitoral tissue can occur in severely virilized individuals (166). For some patients, labia minora can be created using redundant clitoral skin obtained during clitoroplasty. This skin is divided longitudinally and then sutured along either side of the vagina. When necessary, the reduction of labioscrotal folds is performed to create the labia majora, often using a Y-V plasty technique (217).

For girls with CAIS the risk for GCTs is low, and therefore the gonads can be retained in these patients until complete pubertal maturation (37, 218, 219). However, data on safety to retained gonads are incomplete in many of the 46,XY DSD conditions. For patients who retain their gonads, careful monitoring including US or MRI is suggested (218).

Timing of surgery

Appropriate surgical management for DSD has been a topic of discussion since the first guidelines were published in the 1950s (220). Historically, a female appearance of the external genitalia in a newborn with palpable gonads resulted in female sex of rearing, because it was thought that learning, or "nurture," had a greater influence in gender identity development than biology or "nature" (221, 222). Additionally, unsatisfactory cosmetic and functional outcomes associated with masculinizing surgeries, coupled with the need for multiple procedures to achieve male appearance and function, supported the idea that female rearing was optimal for these newborns. Feminizing surgical procedures were performed in the past when both knowledge about underlying etiologies and long-term outcome information about patients with 46,XY DSD were unavailable. As the passage of time allowed for molecular diagnoses and behavioral studies to be conducted, several patients with 46,XY DSD reared female exhibited gender dysphoria and presented phenotypes compatible with 5α-RD2 deficiency, the diagnosis most likely associated with gender dysphoria among those affected by 46,XY DSD (116).

Since the publication of the more recent DSD consensus, aspects of care including timing of surgery and decisions about sex of rearing have been questioned. While both the American Academy of Pediatrics and the original Consensus recommended genital surgery in children with DSD to occur early in life (*i.e.*, up to 18 months of age) (1, 223), members of human rights organizations, ethicists, patient advocates, and some health care providers strongly oppose such practices (169, 170, 224). The experiences of late-treated patients from a large Brazilian cohort illustrate the complexities surrounding timing of treatment of atypical genital anatomy (116).

"Fertility potential varies depending on the underlying etiology od 46,XY DSD as well as the severity of the condition."

It has been reported that some parents and surgeons prefer early surgery, as younger patients are thought to heal better from such procedures and escape stigma associated with living with atypical anatomy (175, 185, 194, 225). While studies comparing outcomes of early (before age 12 months) vs late genital surgery exist (169, 218), controversy concerning timing of genitoplasty persists. Results from a multi-institutional study on contemporary genitoplasty procedures performed in young children with moderate to severe atypical genitalia reported good cosmetic outcomes, although minor and major complications occurred (192). Opposition to early surgery is based on retrospective studies that report poor cosmetic and functional outcomes coupled with the irreversibility of these procedures for patients too young to provide informed consent. Thus, more outcome data on current genitoplasty procedures are needed. Until such data are available to parents and physicians, the best time to perform genital surgery in

patients with 46,XY DSD, if ever, remains debatable. Until this controversy concerning surgical timing is resolved, parents and physicians are left to make surgical decisions for affected children on a case-by-case basis with input from other members of the health care delivery team.

Sexual Function, Intimate Partner Involvement, and Fertility

Whereas some adults with 46,XY DSD report dissatisfaction with their sexual lives and intimate relationships, others do not. Stigma, compromised self-esteem, negative body image, social anxieties, and traumatic sexual experiences contribute to dissatisfaction when it exists (54, 55, 151, 190, 226), as do suboptimal mental health, endocrine, and surgical interventions. Owing to both the rarity and heterogeneity of 46,XY DSD, studies of sexual function and involvement with intimate partners frequently enroll patients affected by different etiologies and treatment histories, thus making it difficult to conclude how these variables impact sexual relationships. Furthermore, such studies are conducted in a range of countries, where cultural differences in expectations for romance and sexual function exist (227–230). These challenges likely explain the discrepant results from studies pertaining to these important aspects of life for people with 46,XY DSD (161, 192, 228, 231).

Sexual function

Women sexual function and intimate partner

Some studies reveal that most women with 46,XY DSD are involved in sexual relationships (193, 228), whereas others do not (124). For instance, one-third of affected women from Europe reported having a steady intimate partner (193), whereas a more inclusive review of international patients estimated that two-thirds are involved in such relationships (161). Two factors that influence intimacy and sexual involvement in DSD are atypical genital anatomy and history of genital surgery (57, 186, 193, 232). To better understand these influences, sexual function was assessed in women with 46,XY DSD who were evaluated according to their (i) degree of responsivity to androgens, as inferred by their degree of genital virilization at birth, and (ii) genital surgical history (193). A significant minority (37.5%) of women reported overall dissatisfaction with their sexual function, and all participants reported sexual anxiety. Patients with no virilization reported low sexual desire and arousal, as well as dyspareunia. These problems were more frequently reported by women with CAIS compared with those with complete gonadal dysgenesis (193). Thus, escaping genital virilization does not preclude women with DSD from experiencing difficulties with sexual function.

Women with 46,XY DSD who are virilized at birth are more likely to report dissatisfaction with their vaginal length and overall sexual function compared with women with 46,XY with a female genital phenotype. Regardless of their genital phenotype, most (92%) of the affected women who reported sexual difficulties attributed these to their DSD. Finally, ~70% of affected women with a female phenotype live with an intimate partner, similar to rates reported by unaffected control women. In contrast, only 50% of women with DSD including virilization report having a partner (161, 193). The increased sexual dysfunction reported by the latter group of women most assuredly impacts their decreased likelihood of having an intimate partner. Most women with 46,XY DSD report a female heterosexual orientation regardless of the degree of virilization of their genitalia at birth; however, attraction to females as well as bisexuality are reported by a significant minority (116). Finally, women with DSD who are virilized often received genital surgery as children. Although the number of surgical procedures received was not found to be related to sexual functioning (193), certain types of procedures caused dysfunction. For example, women who received a total clitoridectomy in childhood were less likely to achieve orgasm than were those who received clitoral reduction (210, 211).

Male sexual function and intimate partner

Sparse literature exists regarding sexual function of men with 46,XY DSD. There is a high likelihood of dissatisfaction with penile length (70%) and lack of ejaculation (50%) (193), and men with DSD are also likely to report a fear of sexual contact (44%), problems with erection (22%), and precocious ejaculation (43%). Despite these problems, men with DSD are more satisfied than women with their surgical outcomes and sexual function (173, 193). Men with 46,XY DSD are typically attracted to females; however, both homosexuality and bisexuality are reported in studies of patients raised male (116).

When specific etiologies underlying DSD are examined, men with partial gonadal dysgenesis report both sexual experiences with partners (233) and satisfaction with their sexual function (229). In contrast, men with PAIS are unlikely to do so (234). Although there is a need to understand how men affected by different forms of DSD function sexually, insufficient data exist to inform patients and health care providers about this topic.

For both men and women with 46,XY DSD, quality of sexual life is lower compared with unaffected adults (161). Specifically, those with DSD were less likely to have a sexual partner, more likely to report sexual insecurities and problems, and less satisfied with overall quality of sexual life. People with 46,XY DSD tend to engage in sexual activity at later ages than do controls, and a considerable number of affected

individuals report never engaging in sexual activity with a partner (161, 228, 232). Patients report greater sexual dysfunction than does the general population (161, 234), and an inability to achieve orgasm and low arousal are the most frequently reported problems (193, 210, 235).

Fertility

Individuals with 46,XY DSD often face infertility. This may be due to abnormal gonadal development and progressive gonadal failure, prophylactic gonadectomy for malignancy risk, abnormal hormone production that impairs gamete formation, or anatomic barriers such as lack of a uterine structure (236). For clarity, we use the term "biological fertility" to refer to having a child with one's own genetic material, whereas "fertility" refers to carrying a child who does not share a parent's genetic material. Fertility is important to most affected individuals, and patients and parents desire discussion of this topic with their health care providers (237, 238). Careful counseling about fertility chances and discussing valuable alternatives such as adoption are fundamental (38). When considering fertility potential, it is also important not to assume heterosexual orientation and to be open-minded about the many ways in which fertility can be achieved for individuals or partners.

Fertility potential varies depending on the underlying etiology of 46,XY DSD as well as the severity of the condition. For example, individuals with complete gonadal dysgenesis lack gonadal development and gametes and thus do not have biological fertility potential; however, they may possess a uterus, and women with this condition have successfully carried pregnancies via oocyte donation (239, 240).

In comparison, patients with partial gonadal dysgenesis have varying degrees of testicular and internal reproductive development, an thus some experience azoospermia whereas others are fertile (241). Similar to the variable fertility outcomes observed in patients with gonadal dysgenesis, those with androgen biosynthetic defects also experience a range of outcomes. To illustrate, infertility is common in individuals with 5α-RD2 deficiency due to oligospermia, low semen volume, and increased viscosity, but biological fertility is possible (237, 242–245). Biological fertility has also been documented in those with nonclassical congenital lipoid adrenal hyperplasia, 3β-HSD2 deficiency, and *LHCG* receptor defect (242). There are no reported cases of biological fertility in individuals with classic congenital lipoid adrenal hyperplasia, cytochrome p450 oxidoreductase deficiency, complete CYP17A1 deficiency, or 17β-HSD3 deficiency (246, 247).

There are also no reported cases of biological fertility in CAIS. Biological fertility is reported in patients with PAIS, both spontaneously and with assisted reproductive technology (248). Absence of Müllerian structures currently prevents carrying a pregnancy for people with CAIS or PAIS; however, advances in uterine transplants may change this in the future (249, 250). Finally, biological fertility is possible for men with defects in the synthesis or action of AMH, but infertility is common due to azoospermia or other ductal abnormalities (38).

Quality of life

Quality of life (QoL) is defined as "an individual's perception of their position in life in the context of culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns" (251). In DSD, several factors related to gender and sexuality decrease QoL (117, 118, 252). Similar to sexual function and relationships, too few studies have investigated QoL in people with 46,XY DSD. Among the studies that have been conducted, weaknesses such as small sample sizes, lack of standardized tools for assessment, and inclusion of participants with various 46,XY conditions exist—the same weaknesses associated with studies of sexual function and relationships.

In the 1990s, the QoL group of the World Health Organization (WHOQOL) developed a generic instrument for assessing QoL in both healthy people and those affected by illness and disease (WHOQOL-100) (253). A short version of this questionnaire (WHOQOL-BREF) was developed to measure QoL in people across cultures (254). The WHOQOL-BREF has been used to study people with 46,XY DSD in Brazil, China, and several European nations (255–258). Generally speaking, people with a DSD score lower in the area of social relationships (255) and men with 46,XY DSD report better QoL than do affected women (258). Questions regarding sexual function and relationships are included in the social relationship's domain of the WHOQOL-BREF and likely contribute to the low scores. However, some studies report similar or better QoL in people with DSD compared with unaffected men and women (256). In an investigation including a large number of men and women affected by 46,XY DSD from Europe, most perceived their health to range from fair to very good despite the presence of many somatic and psychiatric comorbidities (58). Perhaps these discrepancies reflect cultural differences in the burden of being affected by these conditions.

"Information sharing in DSD is essential for a comprehensive understanding by parents and patients."

Delivery of Care

Guidelines for delivery of care to patients with DSD have changed a great deal since the mid-20th century and continue to evolve as knowledge about DSD accrues (70, 140). What remains constant since the 2006 Consensus is the recommendation for open, complete communication about DSD with patients

and parents, coupled with access to interdisciplinary care for affected families (1). In this section we describe recommendations for family-centered, interdisciplinary care, including education for physicians, patients, and caregivers.

Information sharing in DSD is essential for a comprehensive understanding by parents and patients. A qualitative analysis of communication skills of fellows undergoing training in pediatric endocrinology showed large variation in completeness, quality of wording, and evidence of empathy. Several relevant aspects of competent clinical communication were not mentioned or were inadequate among these trainees. Training of physicians who care for patients with DSD is necessary to avoid inadequate delivery of information to patients and their families. Guidelines for the assessment of communication between health professionals and individuals with DSD and their parents are starting to be developed (259).

Family-centered, interdisciplinary care

Family-centered care acknowledges that family is the major source of strength and support to children, and that patient and family perspectives should inform clinical decision-making (260). Family-centered care improves knowledge and enhances quality of life for patients, and decreases distress for caregivers (261). Interdisciplinary care is provided by a team of specialists who work together to provide health care for patients and families. In the context of DSD, interdisciplinary care includes nursing, medical specialists, surgical specialists, and mental health, social work, and peer-to-peer support (262). Optimally, the team works with a family as soon as DSD is suspected to provide appropriate information during the medical evaluation (140). A shared decision-making model requires an emphasis on effective communication to normalize the family's experience, understand and address the family's knowledge, background, and concerns, educate the family about sex differentiation and development, and facilitate support networks (263). Discussions conducted with an interdisciplinary team allow team members to provide their expertise while maintaining a cohesive message for the patient and family.

Patients with DSD, particularly those with an atypical genital phenotype, are prone to stigmatization that can be harmful for psychosocial well-being. This is particularly true when the medical condition is not understood by the patient, the parents, and members of the community, as well as when patients cannot make their own decisions regarding clinical management. Accessible, culturally sensitive education about DSD for patients, families, and the community improves social acceptance of DSD (264). Mental health and peer support are thus foundations of care (54, 117, 265). However, delivery of mental health services for those affected by 46,XY DSD is hampered by a lack of evidence-based information about who benefits from, and how best to administer, psychological support (13). Although research is beginning to identify psychosocial screening tools for assessing patients and families within DSD clinics, tested protocols for the delivery of developmentally appropriate mental health care are not yet available. Low satisfaction with overall medical care reported by patients would presumably improve if providers had access to such protocols as part of their interdisciplinary toolkit (266). As mental health support is increasingly viewed as an alternative to early genitoplasty for protection from stigma associated with genital ambiguity (63), and as parents are increasingly called to take part in shared decision-making with health care teams for planning and implementing their child's treatment (267), identifying and ameliorating distress in patients and parents is a research priority. In reality, the receipt of family-centered, interdisciplinary care remains elusive to many people with DSD throughout the world (120, 268, 269). Barriers are geographic, as DSD teams are unavailable in many countries, as well as economic, as it is expensive to provide comprehensive, interdisciplinary care to patients and their families (63).

Educating affected people and their loved ones

Historically, both patients and parents were either totally uninformed or inadequately informed about DSD and related treatment options (270, 271). More recently, patients and parents report increased knowledge in these areas; however, there remains room for improvement. A key principle of family-centered care is the ongoing provision of complete and unbiased information to patients and families (260).

Assisting patients and parents with strategies to discuss DSD with family members and loved ones is needed (272–274). However, such strategies remain difficult, as concerns about stigma (120, 139, 273, 274) and the desire to protect privacy (265, 275) can result in avoidance of information sharing. For example, parents report increased stigma with raising a child whose genetic sex is atypical or incongruent with their sex of rearing, as well as raising a child with a history of a delayed decision about sex of rearing (276). Thus, parents with these experiences would benefit from situation-specific instruction on how to share such information with others.

In addition to the challenge of protecting privacy while providing information about DSD to others, parents also recognize that such communication evolves over time (265). For example, parents' desire to understand for themselves a particular diagnosis following the birth of an infant with DSD is later replaced by the need for language and skills to effectively communicate this information to maturing children and adolescents. Thus, education for parents is both ongoing and dynamic (265).

As mentioned earlier, discordance between genetic sex and sex of rearing is perceived as stigmatizing by some parents (276). Women with 46,XY DSD report less knowledge about their medical history than do affected men (270), and women with 46,XY DSD report dissatisfaction with how they received education about their sex chromosome complement and gonadal sex (272). Additionally, many parents are hesitant to discuss aspects of DSD seen as potentially stigmatizing with family and friends (13). Peer support can provide practical and credible advice on how to discuss such sensitive topics while minimizing stigma and maximizing transparency (275). Many parents and patients desire such support (265, 270), and the most recent update on the diagnosis and care of people with DSD includes a discussion of the importance of peer support for delivering care and providing education (70).

Future Research

Advances of reproductive endocrinology

Advancing technology and innovative thinking may enable future fertility for individuals with DSD currently considered to be infertile. Initial data indicate that germ cells are present in gonads of many individuals with DSD, particularly at younger ages (277). Thus, experimental techniques pioneered in oncofertility, including prepubertal gonadal cryopreservation, may be useful for those with DSD (277). This raises many ethical issues, including those of consent and assent, experimental treatment causing false hope, cost and distributive justice, and potential transmission of DSD to offspring (278). Notably, it should not be assumed that an individual's gametes must match his or her gender to discuss biological fertility potential (38, 238, 278).

Evidence-based care

For patients and parents who opt for genital surgery (masculinizing or feminizing) as part of a DSD treatment plan, there remains a need for objective information regarding optimal timing for, as well as risks and benefits associated with, various surgical approaches currently in use (196). Such studies should include measures of cosmetic outcomes, urethral and sexual function, overall QoL, and patient satisfaction with treatment. Similar research is also needed in people with DSD who do not receive genital surgery to determine the risks and benefits of this choice (273, 279). Studies of current surgical techniques are necessary because most literature available to inform patients, parents, and physicians about surgical treatment choices is based on dated procedures (196). Perhaps this explains reports of adverse (232, 280) as well as satisfactory outcomes (167, 193, 196, 281). Additionally, although providers agree that mental health support is essential for patients and families, there is limited understanding of who would benefit from this support and how to deliver it.

In summary, improvement in clinical and surgical practice for treating patients with 46,XY DSD resulted from the original Consensus meeting. Stemming from that meeting is the recognition of the importance of interdisciplinary teams to provide care to patients and their families, the value of molecular diagnostics, and the need for collaborations to study ways to optimize outcomes for affected people. What remains to be improved is understanding how to talk about DSD, as well as developing evidence-based mental health care, surgical interventions, and fertility optimization.

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Abbreviations

3β-HSD2, 3β-hydroxysteroid dehydrogenase type II; 5α-RD2, 5α-reductase type 2 deficiency; 17β-HSD3, 17β-hydroxysteroid dehydrogenase type III; aCGH, array-comparative genomic hybridization; AIS, androgen insensitivity syndrome; AMH, anti-Müllerian hormone; ASTRA, anterior sagittal transrectal approach; BMD, bone mineral density; CAIS, complete androgen insensitivity syndrome; CNV, copy number variation; DSD, differences/disorders of sex development; GB, gonadoblastoma; GCT, germ cell tumor; NIPT, noninvasive prenatal testing; PAIS, partial androgen insensitivity syndrome; QoL, quality of life; SNP, single-nucleotide polymorphism; T, testosterone; TUM, total urogenital sinus mobilization; UGS, urogenital sinus; US, ultrasound; WES, whole-exome sequencing; WGS, whole-genome sequencing.