Standardised data collection for clinical follow-up and assessment of outcomes in differences of sex development (DSD): recommendations from the COST action DSDnet

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Abstract

The treatment and care of individuals who have a difference of sex development (DSD) have been revised over the past two decades and new guidelines have been published. In order to study the impact of treatments and new forms of management in these rare and heterogeneous conditions, standardised assessment procedures across centres are needed. Diagnostic work-up and detailed genital phenotyping are crucial at first assessment. DSDs may affect general health, have associated features or lead to comorbidities which may only be observed through lifelong follow-up. The impact of medical treatments and surgical (non-) interventions warrants special attention in the context of critical review of current and future care. It is equally important to explore gender development early and refer to specialised services if needed. DSDs and the medical, psychological, cultural and familial ways of dealing with it may affect self-perception, self-esteem, and psychosexual function. Therefore, psychosocial support has become one of the cornerstones in the multidisciplinary management of DSD, but its impact remains to be assessed. Careful clinical evaluation and pooled data reporting in a global DSD registry will allow linking genetic, metabolomic, phenotypic and psychological data. For this purpose, our group of clinical experts and patient and parent representatives designed a template for structured longitudinal follow-up. In this paper, we explain the rationale behind the selection of the dataset. This tool provides guidance to professionals caring for individuals with a DSD and their families. At the same time, it collects the data needed for answering unsolved questions of patients, clinicians, and researchers. Ultimately, outcomes for defined subgroups of rare DSD conditions should be studied through large collaborative endeavours using a common protocol.

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Introduction

The term differences (disorders) of sex development (DSD) refers to a heterogeneous group of conditions that affect the urogenital tract and result in atypical sex development. The prevalence of the individual conditions is mostly very low and only a small fraction of all conditions characterised by variations in sex characteristics pose major clinical challenges and/or require multidisciplinary care (1). Recent outcome studies suggest that having a DSD may impact an individuals' health status and psychological well-being in every stage of life (2, 3, 4), though physical or psychological comorbidities have been rarely studied in detail, especially in adults. Influencing factors include the rarity of the respective conditions, individual drawbacks to participate in medical studies and the dispersion of affected individuals over decentralised health care structures, with frequent loss of patients for follow-up. In addition, the quality of care for individuals with a DSD varies considerably across Europe, between centres and within diagnostic groups. Patient satisfaction with care is lowest amongst individuals with the rarest conditions (5).

The development of a concrete and evidence-based protocol for structured review and clinical data collection in children and adults who have a DSD, at various age intervals, may be pivotal in addressing these difficulties (6) (Fig. 1). It minimises bias in clinical assessments and can provide guidance to clinicians who do not regularly see these patients. In fact, there is a need to support health care professionals in assessing a small amount of data regularly as part of a holistic routine clinical care. Equally important, it enables exchange of data amongst clinical

centres and in research networks such as the international DSD Registry I-DSD ([www.https://i-dsd.org](https://i-dsd.org)), allowing large-scale multicentre studies. For patients, it can increase understanding of their condition, provide clarity about one's future medical needs, enhance compliance and facilitate discussions with caregivers (7). From a healthcare point of view, adherence to an evidence-based assessment protocol can serve as a quality indicator and benchmarking tool (8).

Several aspects of DSD management are surrounded by controversy or uncertainty and have led to a thorough revision of clinical practice in recent years (1). For example, genital surgery in young children is more often avoided nowadays in order to protect childrens' rights of an open future and integrity of the body; and increasing numbers of children grow up with atypical-looking genitalia, of which the psychological impact is not known (9). Many DSD teams provide psychological support to affected families as a standard component of care nowadays, children are informed early about their condition, and gender issues are openly discussed (6). Some teams include peer support in the medical management plan (10). Structured longitudinal assessment of individuals with a DSD across centres may provide future evidence in favour or against these new practices, with specific relevance to (rare) individual diagnoses, provided that all relevant parameters are considered in parallel and by standardised measurement tools.

In accordance with patient aspirations, the promotion of a standardised protocol that uses a non-binary vocabulary and medical approach can be paramount in inducing societal change as well as amongst the medical community, in attitudes towards gender perception

Figure 1

Schema of the longitudinal I-DSD registration tool showing time points, ages for data entry, starting at the age of diagnosis. Neonatal data, including genetic information if available, should always be entered regardless of the age at diagnosis.

and normative paradigms of sex, including genital characteristics (11). This will by itself be instrumental in defining the place, timing and the specific medical need of genital surgery.

Development of consensus on standardised data collection

The development of a meaningful, holistic schedule for clinical assessment that allows for standardised longitudinal data collection over time in individuals who have a DSD has been the primary goal of an expert multidisciplinary working group, including representatives from patient support groups. This group operated in the period 2013–2017 in the framework of the European Cooperation in Science and Technology (COST) Action BM1303 “DSDnet” (www.DSDnet.eu), funded by the European Union Horizon 2020 programme. Collaboratively, the group (1) reviewed the literature on existing instruments for clinical phenotyping at all ages; (2) defined their major strengths and shortcomings as well as hitherto insufficiently covered areas of (para)medical attention; and (3) discussed essential characteristics of a qualitative longitudinal follow-up programme until agreement was reached on a protocol for standardised assessment at various ages that was versatile enough to be used in clinical settings as well as within electronic global platforms such as the I-DSD Registry.

General dataset and ages at which follow-up assessments are recommended

Criteria for referral of a child for expert evaluation are specified in the UK guidelines (12). At first referral, linking the case to original health records and obtaining consent for sharing data (local, national, international) are crucial. Basic DSD-related information, such as diagnosis, karyotype, birth-assigned sex, and social gender should also be included (Table 1). Thereafter, appropriate time intervals for clinical revision of patients depend on the respective conditions, patient age, and individual circumstances. However, for registration and research purposes, it was considered crucial to standardise a minimal set of time points, corresponding to important developmental milestones, at which relevant clinical data should be collected (Fig. 1).

A summary of neonatal data, where available, should be collected in all cases with later presentation (Table 2). Clinical revision at age 4 years (Table 3) allows for comprehensive assessment of psychological developmental milestones, associated symptoms, and growth patterns, including catch-up growth. The process of informing the child about the condition should start as soon as possible after diagnosis, along with the provision of support in acquiring a vocabulary to talk about the DSD (13). Practical advice on this matter can be found at support group resources (e.g. www.dsdfamilies.org or <https://www.iglyo.com/wp-content/uploads/2018/10/Supporting-Your-Intersex-Child.pdf>). At age 8 years (Table 3), relevant information on growth and development shortly before start of puberty can be obtained. At this age the child understands more complex information about how the body functions and about the specific DSD. Gender identity or eventual dysphoria may be ascertained and children experiencing uncertainty can be referred for expert psychological or psychiatric evaluation and support. Pubertal development and progression (Table 4) may be compromised in many children who have a DSD. Some children may need hormonal induction of puberty. Standardised assessment at the start of puberty and the outcome of pubertal development are therefore paramount to document, though most children will need clinical revision more frequently. Transition to adult healthcare should be discussed early on during this period (8, 14).

Much less evidence is available to guide timing of clinical revision in adulthood (Table 5). In favour of standardised assessment of young individuals aged 18–25 years is that they are in the process of gaining independence and have recently transitioned to adult care. Many young people are newly forming intimate relationships, which potentiates new concerns and/or required healthcare intervention. Topics such as sexual function, sexual orientation, and gender identity may become central in their lives. In addition, baseline information on typical health issues in adulthood such as bone mineral density, blood pressure, and obesity should be collected. Issues around fertility and forming a family may dominate between ages 25 and 40 years.

During the age intervals of 40–60 and 60–80 years, long-term effects of treatment or (lack of) hormonal treatment and comorbidities may become apparent (8). Physical and mental health issues of adults living with a DSD are major determinants of overall quality of life (QoL) (4). It is therefore crucial to capture such information

Table 1 Neonatal assessment (within first month of birth).

Parameters	Units/ options	Parameters	Units/ options
General		Surgery	
Date of Assessment	dd/mm/yyyy	Left Gonad Biopsy	Yes/ No/ Not known
Age at Assessment	years	Right Gonad Biopsy	Yes/ No/ Not known
Gestational Age	weeks	Left Gonadectomy	Yes/ No/ Not known
Birth Weight	g	Right Gonadectomy	Yes/ No/ Not known
Birth Length	cm	Genital reconstructive surgery**	None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age
Birth Head Circumference	cm	Reasons for genital reconstructive surgery	Functional / cosmesis / both
Weight	kg	Post Surgical Complications	Yes/ No/ Not known; if yes, describe.
Height	cm	Psychosocial	
BMI	kg/m ²	Change in Legal Sex	Yes/ No/ Not known
Mothers Height	cm	Psychosocial Support Offered to Parents	Yes/ No/ Not known
Fathers Height	cm	Ongoing Psychosocial Support	Yes/ No/ Not known
Mid Parental Height	cm	Medication	
Original Sex Assigned	Male/ Female/ Both/ Not assigned/ Other	Testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known
Current Gender	Male/ Female/ Both/ Not assigned/ Other	Oestrogen	Yes (IM, Oral, Transdermal)/ No/ Not known
Child raised as	Male/ Female/ Both / Other	DHT	Yes (IM, Oral, Transdermal)/ No/ Not known
Associated Conditions*		Aromatase Inhibitor	Yes/ No/ Not known
Known Syndrome	Yes/ No	GnRH analogues	Yes/ No/ Not known
External Phenotype		Glucocorticoids	Yes/ No/ Not known
Meatus	Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	Fludrocortisone	Yes/ No/ Not known
Left Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	Other drugs	Yes/ No/ Not known
Right Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	Lab Tests	
Genital Tubercle Length	<10/ 10-20/ 21-25/ 26-30/ >30 mm	LH	Low/ Normal/ High/ Not known
Phallus Size	Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	FSH	Low/ Normal/ High/ Not known
Labioscrotal Fusion	Yes/ No	AMH	Low/ Normal/ High/ Not known
Anogenital Distance 1# (AGD1)	mm	Inhibin B	Low/ Normal/ High/ Not known
Anogenital Distance 2## (AGD2),	mm	Androstenedione	Low/ Normal/ High/ Not known
External Masculinisation Score (EMS)		Total Testosterone	Low/ Normal/ High/ Not known
External Genitalia Score (EGS)		Free Testosterone	Low/ Normal/ High/ Not known
Internal Phenotype		Dihydrotestosterone	Low/ Normal/ High/ Not known
Imaging Modality- Left Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Oestradiol	Low/ Normal/ High/ Not known
Imaging Modality- Right Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		

(Continued)

Table 1 Continued.

Parameters	Units/ options	Parameters	Units/ options
Left Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	17-OHP	Low/ Normal/ High/ Not known
Right Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	Urine steroids	Normal/ Abnormal
Imaging Modality- Uterus	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	hCG Stimulation Test	Specify protocol
Uterus Morphology	Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known	Adrenal Stimulation Test	Specify protocol
Imaging Modality- Left Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	11-deoxycortisol	Low/ Normal/ High/ Not known
Imaging Modality- Right Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Pregnenolone	Low/ Normal/ High/ Not known
Left Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	17-OH Pregnenolone	Low/ Normal/ High/ Not known
Right Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	DHEA	Low/ Normal/ High/ Not known
Distance- Vaginal Confluence to Bladder Neck	cm		
Distance- Vaginal Confluence to Introitus	cm		
Imaging Modality- Left Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		
Imaging Modality- Right Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		
Left Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known		
Right Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known		

*Associated conditions: CNS, heart, renal, skeletal, skin, ENT, eyes, blood and lymph, craniofacial, adrenal, GI tract, haematological, respiratory, SGA (small for gestational age), short stature, non-defined syndrome, other. **Genital reconstructive surgery field may be repeated.

AGD 1: Distance from the centre of the anus to the posterior base of the labioscrotal folds; ##AGD 2: Distance from the centre of the anus to the anterior base of the phallus.

in order to allow for future research and appropriate management.

Genetic and biochemical data

Most causes of DSD are genetic; however, drugs, environmental toxins, and maternal and placental causes are also relevant and/or may influence outcomes. A clear diagnosis can determine the spectrum of potentially affected organs, current/future health consequences, and treatment options (8).

A comprehensive diagnostic approach consists of an extensive family history over at least three generations, as well as a physical exam of the whole body which includes the genital organs. This will then guide the clinician towards further diagnostic imaging, biochemical and genetic studies. Guidelines for the clinical, biochemical,

and genetic work-up of DSD have been published elsewhere (12, 15, 16).

Collecting genetic information, together with clinical and biochemical data, in a centralised registry allows identification and characterisation of DSD subgroups, including those for which a genetic diagnosis has not been achieved so far. It is possible then to test the diagnostic reliability of specific biochemical and genetic parameters and their usefulness for implementation in clinical diagnostic guidelines. It will also enable studies on the impact of a molecular genetic diagnosis on outcome. Indeed, almost 50% of individuals who have a 46,XY DSD have no genetic diagnosis, and it remains debatable whether and how this impacts management and overall QoL (17).

Although DSDs are congenital conditions, the function of affected organs may decline over time, e.g. testicular function in 45,X/46,XY boys (18). Therefore, any

Table 2 Clinical assessment (at any age if first assessment after 1 month of age).

Parameters	Units/ options	Parameters	Units/ options
General		Surgery	
Date of Assessment	dd/mm/yyyy	Left Gonad Biopsy	Yes/ No/ Not known
Age at Assessment	years	Right Gonad Biopsy	Yes/ No/ Not known
Gestational Age	weeks	Left Gonadectomy	Yes/ No/ Not known
Birth Weight	g	Right Gonadectomy	Yes/ No/ Not known
Birth Length	cm	Genital reconstructive surgery**	None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age
Birth Head Circumference	cm	Reasons for genital reconstructive surgery	Functional / cosmesis / both
Weight	kg	Post Surgical Complications	Yes/ No/ Not known; if yes, describe.
Height	cm	Psychosocial	
BMI	kg/m ²	Change in Legal Sex	Yes/ No/ Not known
Mothers Height	cm	Psychosocial Support Offered to Parents	Yes/ No/ Not known
Fathers Height	cm	Ongoing Psychosocial Support	Yes/ No/ Not known
Mid parental height	cm	Medication	
Original Sex Assigned	Male/ Female/ Both/ Not assigned/ Other	Testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known
Current Gender	Male/ Female/ Both/ Not assigned/ Other	Oestrogen	Yes (IM, Oral, Transdermal)/ No/ Not known
Child raised as	Male/ Female/ Both / Other	DHT	Yes (IM, Oral, Transdermal)/ No/ Not known
Associated Conditions*		Aromatase Inhibitor	Yes/ No/ Not known
Known Syndrome	Yes/ No	GnRH analogues	Yes/ No/ Not known
External Phenotype		Glucocorticoids	Yes/ No/ Not known
Meatus	Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	Fludrocortisone	Yes/ No/ Not known
Left Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	Other drugs	Yes/ No/ Not known
Right Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	Lab Tests	
Genital Tubercle Length	<10/ 10-20/ 21-25/ 26-30/ >30 mm	LH	Low/ Normal/ High/ Not known
Phallus Size	Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	FSH	Low/ Normal/ High/ Not known
Labioscrotal Fusion	Yes/ No	AMH	Low/ Normal/ High/ Not known
Anogenital Distance 1# (AGD1)	mm	Inhibin B	Low/ Normal/ High/ Not known
Anogenital Distance 2## (AGD2),	mm	Androstenedione	Low/ Normal/ High/ Not known
External Masculinisation Score (EMS)		Total Testosterone	Low/ Normal/ High/ Not known
External Genitalia Score (EGS)		Free Testosterone	Low/ Normal/ High/ Not known
Internal Phenotype		Dihydrotestosterone	Low/ Normal/ High/ Not known
Imaging Modality- Left Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Oestradiol	Low/ Normal/ High/ Not known
Imaging Modality- Right Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		

(Continued)

Table 2 Continued.

Parameters	Units/ options	Parameters	Units/ options
Left Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	17-OHP	Low/ Normal/ High/ Not known
Right Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	Urine steroids	Normal/ Abnormal
Imaging Modality- Uterus	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	hCG Stimulation Test	Specify protocol
Uterus Morphology	Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known	Adrenal Stimulation Test	Specify protocol
Imaging Modality- Left Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	11-deoxycortisol	Low/ Normal/ High/ Not known
Imaging Modality- Right Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Pregnenolone	Low/ Normal/ High/ Not known
Left Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	17-OH Pregnenolone	Low/ Normal/ High/ Not known
Right Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	DHEA	Low/ Normal/ High/ Not known
Distance- Vaginal Confluence to Bladder Neck	cm		
Distance- Vaginal Confluence to Introitus	cm		
Imaging Modality- Left Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		
Imaging Modality- Right Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy		
Left Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known		
Right Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known		

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymph, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. **Genital reconstructive surgery field may be repeated.

#AGD 1: Distance from the centre of the anus to the posterior base of the labioscrotal folds; ##AGD 2: Distance from the centre of the anus to the anterior base of the phallus

initially performed diagnostic laboratory investigation may need to be repeated, if in doubt and of therapeutic consequence. Hormonal and other drug treatments need to be controlled with regular intervals for correct dosing, effectiveness and side effects. Biochemical parameters that qualify best for treatment monitoring need to be identified based on prospectively collected data.

In some individuals who have an unknown cause of their condition, genetic work-up has been performed years ago with methods that are currently outdated. In others, whole exome or whole genome sequencing may reveal variants of unknown significance or monogenetic variants in established DSD genes that do not clearly explain the observed phenotype (e.g. heterozygous MAMLD1 mutations) (19). Finally, DSD genetics may be more complex than initially thought, as demonstrated recently (20). Therefore, genetic results may also require re-evaluation as new knowledge is gained over time.

Medical fields

Family data

A detailed family history, including fertility, is essential to explore possible inheritance mechanisms and to lend support for molecular genetic investigations in individuals with milder phenotypes. Phenotypic variability within families may be broad and may comprise subfertility/infertility as the only sign, depending on the severity of the mutation (21, 22).

Associated conditions

Several comorbidities and non-gonadal organ dysfunctions are associated with specific DSDs (23). Further exploration of these associations is important for targeted follow-up of affected individuals and for understanding the

Clinical Study	C Flück, A Nordenström and others	Longitudinal follow-up of DSD	181:5	552
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Table 3 Childhood assessment (at age 4 years and 8 years)

Parameters	Units/options	Parameters	Units/options
General		Surgery	
Date of Assessment	dd/mm/yyyy	Left Gonad Biopsy	Yes/ No/ Not known
Age at Assessment	years	Right Gonad Biopsy	Yes/ No/ Not known
Weight	kg	Left Gonadectomy	Yes/ No/ Not known
Height	cm	Right Gonadectomy	Yes/ No/ Not known
BMI	kg/m ²	Genital reconstructive surgery**	None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias; age
Mothers Height	cm	Reasons for genital reconstructive surgery	Functional / cosmesis / both
Fathers Height	cm	Post Surgical Complications	Yes/ No/ Not known; if yes, describe.
Mid parental height	cm		
Original Sex Assigned	Male/ Female/ Both/ Not assigned/ Other	Psychosocial, Gender Identity	
Current Gender	Male/ Female/ Both/ Not assigned/ Other	Any Change in Legal Sex	Yes/ No/ Not known
Child raised as	Male/ Female/ Both / Other	Psychosocial Support Offered to Parents	Yes/ No/ Not known
Associated Conditions*		Ongoing Psychosocial Support for parents	Yes/ No/ Not known
Known Syndrome	Yes/ No	Psychosocial Support Offered to Child	Yes/ No/ Not known
Bone age		Ongoing Psychosocial Support for Child	Yes/ No/ Not known
Bone Age date	dd/mm/yyyy	Age-appropriate Information to Child	Yes/ No/ Not known
Bone age result	years	Has Child Questioned Their Gender	Yes/ No/ Not known
Bone age method	TW20/ Radius-ulna-short bone/ Greulich & Pyle	Is Child Distressed About Gender Identity or Assignment	Yes/ No/ Not known
External Phenotype		Medication	
Meatus	Typical female/ Perineal/ Scrotal/ Penoscrotal/ Penile/ Coronal/ Typical male	Testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known
Left Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	Oestrogen	Yes (IM, Oral, Transdermal)/ No/ Not known
Right Gonad Location	Impalpable/ Inguinal/ Inguinoscrotal/ Labioscrotal	DHT	Yes (IM, Oral, Transdermal)/ No/ Not known
Genital Tubercle Length, Phallus Size	<10/ 10-20/ 21-25/ 26-30/ >30 mm	Aromatase Inhibitor	Yes/ No/ Not known
	Within/ Below/ Above the reference range for male; Within/ Below/ Above the reference range for female	GnRH analogues	Yes/ No/ Not known
Labioscrotal Fusion	Yes/ No	Glucocorticoids	Yes/ No/ Not known
External Masculinisation Score (EMS)		Fludrocortisone	Yes/ No/ Not known
External Genitalia Score (EGS)		Other drugs	Yes/ No/ Not known
Internal Phenotype		Lab Tests	
Imaging Modality- Left Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	LH	Low/ Normal/ High/ Not known
Imaging Modality- Right Gonad	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	FSH	Low/ Normal/ High/ Not known

(Continued)

Table 3 Continued.

Parameters	Units/options	Parameters	Units/options
Left Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	AMH	Low/ Normal/ High/ Not known
Right Gonad Morphology	Absent/ Streak/ Testis/ Ovary/ Ovotestis/ Other	Inhibin B	Low/ Normal/ High/ Not known
Imaging Modality- Uterus	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Androstenedione	Low/ Normal/ High/ Not known
Uterus Morphology	Absent/ Müllerian remnants/ rudimentary/ Normal/ Not known	Total Testosterone	Low/ Normal/ High/ Not known
Imaging Modality- Left Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Free Testosterone	Low/ Normal/ High/ Not known
Imaging Modality- Right Fallopian Tube	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Dihydrotestosterone	Low/ Normal/ High/ Not known
Left Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	Oestradiol	Low/ Normal/ High/ Not known
Right Fallopian Tube Morphology	Absent/ Rudimentary/ Normal/ Not known	17-OHP	Low/ Normal/ High/ Not known
Distance- Vaginal Confluence to Bladder Neck	cm	Urine steroids	Normal/ Abnormal
Distance- Vaginal Confluence to Introitus	cm	hCG Stimulation Test	Specify protocol
Imaging Modality- Left Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Adrenal Stimulation Test	Specify protocol
Imaging Modality- Right Vas Deferens	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	11-deoxycortisol	Low/ Normal/ High/ Not known
Left Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known	Pregnenolone	Low/ Normal/ High/ Not known
Right Vas Deferens Morphology	Absent/ Rudimentary/ Normal/ Not known	17-OH Pregnenolone	Low/ Normal/ High/ Not known
		DHEA	Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymph, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** Genital reconstructive surgery field may be repeated.

mechanisms of disease. As many DSD conditions are caused by mutations in transcription factors that regulate the development of several organ systems, this may result in combined functional defects, as for example in WT1 (kidney involvement), NR5A1 (adrenal involvement, spleen hypoplasia) or GATA4 (cardiac defects) mutations (24, 25, 26, 27). Associated conditions are mostly found in chromosomal DSD such as 45,X/46,XY and may only develop over time, requiring medical attention at each follow-up visit, for example cardiac surveillance in all individuals who have 45,X/46,XY mosaicism (18, 28).

External and internal genital phenotype

As genital photography and storage faces ethical and legal challenges, standardised tools are needed to objectively describe the genital aspect in detail. Qualitative visual scales such as the Prader (29) or Quigley (30) scales

are highly observer dependent and do not consider internal and external genital status separately. The anogenital distance correlates with prenatal androgen exposure but lacks standardisation and is difficult to perform in children above 1 year (31). The External Masculinization Score (EMS) is a practical and objective tool, has good inter-observer reliability and correlates with relevant clinical outcomes (12, 32, 33). Limitations include its restricted applicability – only male neonates – and dichotomous nature (e.g. micropenis yes/no). To overcome these problems, a modified EMS, termed “external genitalia score” (EGS), has been developed. The EGS assesses the same anatomical landmarks as EMS while using a gender-neutral vocabulary applicable in all infants up to 2 years of age, and a more gradual scale, reflecting the naturally occurring phenotypic variability of external genitalia. Reference ranges for a mixed European population have been determined

Clinical Study	C Flück, A Nordenström and others	Longitudinal follow-up of DSD	181:5	554
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Table 4 Adolescent assessment (at start of puberty and end of puberty)

Parameters	Units/ options	Parameters	Units/ options
General		Surgery	
Date of Assessment	dd/mm/yyyy	Left Gonad Biopsy	Yes/ No/ Not known
Age at Assessment	years	Right Gonad Biopsy	Yes/ No/ Not known
Weight	kg	Left Gonadectomy	Yes/ No/ Not known
Height	cm	Right Gonadectomy	Yes/ No/ Not known
BMI	kg/m ²	Genital reconstructive surgery**	None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias/ phalloplasty; age
Mothers Height	cm	Vaginal Hypoplasia	Yes / No/ Not known
Fathers Height	cm	Medical management of vaginal hypoplasia	Dilation / Surgery / None
Mid parental height	cm	Type of Vaginoplasty	Intestinal / Peritoneal / Davydov / Vecchiotti / Baloon / Other
Original Sex Assigned	Male/ Female/ Both/ Not assigned/ Other	Post Surgical Complications	Yes/ No/ Not known; if yes, describe.
Current Gender	Male/ Female/ Both/ Not assigned/ Other	Gonadal Germ Cell Cancer	Yes/ No/ Not known
Adolescent raised as	Male/ Female/ Both / Other	Left Gonad	None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other
Associated Conditions*		Right Gonad	None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other
Known Syndrome	Yes/ No	Psychosocial, Gender Identity	
Bone age, bone mineral density	Yes/ No	Change in Legal Sex	Yes/ No/ Not known
Bone Age date	dd/mm/yyyy	Psychosocial Support Offered for Parents	Yes/ No/ Not known
Bone age result	years	Ongoing Psychosocial Support for parents	Yes/ No/ Not known
Bone age method	TW20/ Radius-ulna-short bone/ Greulich & Pyle	Psychosocial Support Offered to Child	Yes/ No/ Not known
Bone mineral density	Yes/ No/ Not known	Ongoing Psychosocial Support for Child	Yes/ No/ Not known
Bone Mineral Density Date	dd/mm/yyyy	Age-appropriate Information to Child	Yes/ No/ Not known
Bone Mineral Density Result	Osteopenia/ Osteoporosis/ Normal	Has Child Questioned Their Gender	Yes/ No/ Not known
Puberty		Is Child Distressed About Gender Identity or Assignment	Yes/ No/ Not known
Breast stage	1/ 2/ 3/ 4/ 5/ Not Known	Physical or Mental Health Status Interferes with Daily Life Activities (education, work)	Yes / Partially / No
Genital stage	1/ 2/ 3/ 4/ 5/ Not Known	Physical or Mental Health Status Interferes with Social Activities (hobbies, friends, relations)	Yes / Partially / No
Axillary hair stage	1/ 2/ 3/ 4/ 5/ Not Known	Medication	
Pubic hair stage	1/ 2/ 3/ 4/ 5/ Not Known	Testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known
Left testicular volume	ml	Oestrogen	Yes (IM, Oral, Transdermal)/ No/ Not known
Right testicular volume	ml	DHT	Yes (IM, Oral, Transdermal)/ No/ Not known
Stretched penile length	cm	Aromatase Inhibitor	Yes/ No/ Not known
Spontaneous puberty	Yes/ No/ Not known	GnRH analogues	Yes/ No/ Not known
Pubertal induction	Yes/ No/ Not known	Glucocorticoids	Yes/ No/ Not known

(Continued)

Table 4 Continued.

Parameters	Units/ options	Parameters	Units/ options
Induction with oestrogen	Yes (Oral, Transdermal)/ No/ Not known	Fludrocortisone	Yes/ No/ Not known
Induction with testosterone	Yes (Oral, Transdermal)/ No/ Not known	Other drugs	Yes/ No/ Not known
Menarche	Spontaneous/ Induced/ Not known	Lab Tests	
Hirsutism	Yes/ No/ Not known	LH	Low/ Normal/ High/ Not known
Gynaecomastia	Yes/ No/ Not known	FSH	Low/ Normal/ High/ Not known
Internal Phenotype		AMH	Low/ Normal/ High/ Not known
Imaging Modality- Left testis	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Inhibin B	Low/ Normal/ High/ Not known
Imaging Modality- Right testis	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Androstenedione	Low/ Normal/ High/ Not known
Left testis Morphology	Absent/ Normal/ Small/ Abnormal	Total Testosterone	Low/ Normal/ High/ Not known
Right testis Morphology	Absent/ Normal/ Small/ Abnormal	Free Testosterone	Low/ Normal/ High/ Not known
Imaging Modality- Uterus	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Dihydrotestosterone	Low/ Normal/ High/ Not known
Uterus Morphology	Absent/ Normal/ Hypoplastic/ Abnormal	Oestradiol	Low/ Normal/ High/ Not known
Imaging Modality- Left ovary	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	17-OHP	Low/ Normal/ High/ Not known
Imaging Modality- Right ovary	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Urine steroids	Normal/ Abnormal
Left ovary Morphology	Absent/ Streak/ Normal/ Polycystic	hCG Stimulation Test	Specify protocol
Right ovary Morphology	Absent/ Streak/ Normal/ Polycystic	Adrenal Stimulation Test	Specify protocol
Sexual Health		11-deoxycortisol	Low/ Normal/ High/ Not known
Menses	Yes/ Primary amenorrhoea/ Secondary amenorrhoea	Pregnenolone	Low/ Normal/ High/ Not known
Age at Menopause		17-OH Pregnenolone	Low/ Normal/ High/ Not known
Fertility Desired	Yes/ No/ Not known	DHEA	Low/ Normal/ High/ Not known
Tissue Storage	Yes/ No/ Not known		
Sperm Assessment	Yes/ No/ Not known		
Sperm count, per million/ml	x million per ml/ Normal/ Abnormal/ Not Reported		
Number of Offspring			
Assisted Conception	Yes/ No/ Not known		

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymp, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other. ** Genital reconstructive surgery field may be repeated.

(S van der Straaten, A Springer, A Zecic, D Hebenstreit, U Tonnhofer, A Gawlik, M Baumert, K Szeliga, S Debulpaep, A Desloovere et al. The external genitalia score (EGS): A European multicenter validation study 2019; personal communication). Additional parameters such as penile curvature and tissue quality are likely related to (surgical) outcome, but these are currently ill-defined and require

further study. Reliable assessment of internal genitalia requires imaging and sometimes surgical procedures such as laparoscopy. Knowledge on the internal anatomy can be helpful in cases where the initial sex/gender of rearing is unclear and to foresee possible complications. Imaging techniques have significant differences in sensitivity, sensibility, and invasiveness. In the longer term,

Table 5 Adult assessment (once per interval: 18-25; 25-40; 40-60; 60-75 years)

Parameters	Units/ options	Parameters	Units/ options
General		Surgery	
Date of Assessment	dd/mm/yyyy	Left Gonad Biopsy	Yes/ No/ Not known
Age at Assessment	years	Right Gonad Biopsy	Yes/ No/ Not known
Weight	kg	Left Gonadectomy	Yes/ No/ Not known
Height	cm	Right Gonadectomy	Yes/ No/ Not known
BMI	kg/m ²	Genital reconstructive surgery**	None/ clitoral surgery / vaginal surgery / labioscrotal surgery / hypospadias surgery / urethral surgery other than hypospadias/ phalloplasty; age
Mothers Height	cm	Vaginal Hypoplasia	Yes / No/ Not known
Fathers Height	cm	Medical management of vaginal hypoplasia	Dilation / Surgery / None
Mid parental height	cm	Type of Vaginoplasty	Intestinal / Peritoneal / Davydov / Vecchietti / Baloon / Other
Original Sex Assigned	Male/ Female/ Both/ Not assigned/ Other	Post Surgical Complications of genital surgery	Yes/ No/ Not known; if yes, describe.
Current Gender	Male/ Female/ Both/ Not assigned/ Other	Gonadal Germ Cell Cancer	Yes/ No/ Not known
Adult raised as	Male/ Female/ Both / Other	Left Gonad	None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other
Associated Conditions*		Right Gonad	None/ GCNIS/ Gonadoblastoma/ Seminoma/ Non-seminoma/ Dysgerminoma/ Other
Known Syndrome	Yes/ No	Breast surgery	None / breast reconstruction/ augmentation/ reduction/ mastectomy
Bone age, bone mineral density		Post Surgical Complications of Breast Surgery	Yes/ No/ Not known; if yes, describe
Bone age date	dd/mm/yyyy	Psychosocial, Gender Identity	
Bone age result	years	Change in Legal Sex	Yes/ No/ Not known
Bone age method	TW20/ Radius-ulna-short bone/ Greulich & Pyle	Psychosocial Support	Yes/ No/ Not known
Bone mineral density	Yes/ No/ Not known	Ongoing Psychosocial Support	Yes/ No/ Not known
Bone Mineral Density Date	dd/mm/yyyy	Full information about condition	Yes/ No/ Not known
Bone Mineral Density Result	Osteopenia/ Osteoporosis/ Normal	Gender role	Female/ Male/ Both/ Neither/ Not known
Puberty		Physical or Mental Health Status Interferes with Daily Life Activities (education, work)	Yes / Partially / No
Breast stage	1/ 2/ 3/ 4/ 5/ Not Known	Physical or Mental Health Status Interferes with Social Activities (hobbies, friends, relations)	Yes / Partially / No
Genital stage	1/ 2/ 3/ 4/ 5/ Not Known	Sexual Health	
Axillary hair stage	Yes/No/ Not Known	Menses	Yes/ Primary amenorrhoea/ Secondary amenorrhoea
Pubic hair stage	1/ 2/ 3/ 4/ 5/ 6/Not Known	Age at Menopause	years
Left testicular volume	ml	Fertility Desired	Yes/ No/ Not known
Right testicular volume	ml	Tissue Storage	Yes/ No/ Not known
Spontaneous puberty	Yes/ No/ Not known	Sperm Assessment	Yes/ No/ Not known
Pubertal induction	Yes/ No/ Not known	Sperm count, per million/ml	x million per ml/ Normal/ Abnormal/ Not Reported
Induction with oestrogen	Yes (Oral, Transdermal)/ No/ Not known	Number of Offspring	

(Continued)

Table 5 Continued.

Parameters	Units/ options	Parameters	Units/ options
Induction with testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known	Assisted Conception	Yes/ No/ Not known
Menarche	Spontaneous/ Induced/ Not known	Medication	
Hirsutism	Yes/ No/ Not known	Testosterone	Yes (IM, Oral, Transdermal)/ No/ Not known
Gynaecomastia	Yes/ No/ Not known	Oestrogen (E)	Yes (IM, Oral, Transdermal)/ No/ Not known
Co-morbidities		DHT	Yes (IM, Oral, Transdermal)/ No/ Not known
Osteoporosis	Yes/ No/ Not known	Aromatase Inhibitor	Yes/ No/ Not known
Type II Diabetes	Yes/ No/ Not known	GnRH analogues	Yes/ No/ Not known
Chronic Kidney Disease	Yes/ No/ Not known	Glucocorticoids	Yes/ No/ Not known
Chronic Liver Disease	Yes/ No/ Not known	Fludrocortisone	Yes/ No/ Not known
Central Nervous System	Yes/ No/ Not known	Progestin (P)	Yes (Oral, Subcutaneous, IM, IUD) / No/ Unknown
Hypertension	Yes/ No/ Not known	Combined E/P (HRT/OC***)	Yes (Oral, Transdermal, Vaginal)/ No/ Not known
Other	Yes/ No/ Not known; if yes, describe	Other drugs	Yes/ No/ Not known
Internal Phenotype		Lab Tests	
Imaging Modality- Left testis	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	LH	Low/ Normal/ High/ Not known
Imaging Modality- Right testis	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	FSH	Low/ Normal/ High/ Not known
Left testis Morphology	Absent/ Normal/ Small/ Abnormal	AMH	Low/ Normal/ High/ Not known
Right testis Morphology	Absent/ Normal/ Small/ Abnormal	Inhibin B	Low/ Normal/ High/ Not known
Imaging Modality- Uterus	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Androstenedione	Low/ Normal/ High/ Not known
Uterus Morphology	Absent/ Normal/ Hypoplastic/ Abnormal	Total Testosterone	Low/ Normal/ High/ Not known
Imaging Modality- Left ovary	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Free Testosterone	Low/ Normal/ High/ Not known
Imaging Modality- Right ovary	US/ MRI/ Genitogram/ Laparoscopy/ Genitoscopy	Dihydrotestosterone	Low/ Normal/ High/ Not known
Left ovary Morphology	Absent/ Streak/ Normal/ Polycystic	Oestradiol	Low/ Normal/ High/ Not known
Right ovary Morphology	Absent/ Streak/ Normal/ Polycystic	17-OHP	Low/ Normal/ High/ Not known
		Urine steroids	Normal/ Abnormal
		hCG Stimulation Test	Specify protocol
		Adrenal Stimulation Test	Specify protocol
		11-deoxycortisol	Low/ Normal/ High/ Not known
		Pregnenolone	Low/ Normal/ High/ Not known
		17-OH Pregnenolone	Low/ Normal/ High/ Not known
		DHEA	Low/ Normal/ High/ Not known

*Associated conditions: CNS, Heart, Renal, Skeletal, Skin, ENT, Eyes, Blood and Lymph, Craniofacial, Adrenal, GI Tract, Haematological, Respiratory, SGA (Small for Gestational Age), Short stature, Non-defined syndrome, Other; ** Genital reconstructive surgery field may be repeated; ***Hormonal replacement treatment/Oral contraceptives

meta-analysis of data will provide further insights on the procedure of choice in specific situations.

The genital phenotype and other sex characteristics change as the individual grows or as a result of hormonal treatment or surgery. Frequent genital inspection is not recommended, but may be helpful in specific situations, especially as it can help parents and children / adolescents to understand that there is a natural variation in clitoral sizes and genital aspect or to discuss eventual parental or patient worries. For example, in 46,XX individuals who have CAH, clitoral size may decrease in response to glucocorticoid treatment after the newborn period. This finding is often very reassuring for parents and may actually convince them that the genital aspect has indeed become unremarkable for a lay person taking care of their baby. On the other hand, clitoral size may increase in periods of undertreatment or non-compliance (34, 35) and/or adolescent girls may feel insecure about its aspect. Thoughtful genital inspection in an adolescent girl, after having obtained her consent, may sometimes help her discussing eventual worries about the genital aspect and/or reassure her that clitoral sensitivity is most important and that the clitoral aspect falls within the natural variation. Gonadal failure may result in the lack or arrest of pubertal development. In such cases, it is important to document genital pubertal progression at the suggested time intervals. Suspicion of complications, e.g. fistulae after hypospadias surgery will also require a genital exam.

In adult life, psychosexual function is an even more important outcome parameter and should be discussed as suggested in Table 5; sometimes, depending on the specific question (eg worries about penile length), this will need to be done in parallel with a genital examination (1, S van der Straaten, A Springer, A Zecic, D Hebenstreit, U Tonnhofer, A Gawlik, M Baumert, K Szeliga, S Debulpaep, A Desloovere et al. The external genitalia score (EGS): A European multicenter validation study 2019; personal communication).

Anthropometric data, body composition and bone health

Documentation of birth weight and length, growth, body composition and bone health parameters is crucial as it may reveal the long-term outcomes of childhood processes such as the postnatal hypothalamic-pituitary-gonadal activation (the 'mini-puberty') and growth patterns in DSD other than Turner syndrome (TS) and Klinefelter syndrome (KS), where evidence is currently scarce. For example, no data are available on the

prevalence and extent of catch-up growth in children with atypical genitalia who were born small for gestational age. In individuals with 45X/46XY karyotypes, growth hormone treatment has variable effects and may need to be optimised (36, 37). Age at start of puberty induction and dosing of sex steroids may affect the growth pattern and body proportions (38). Glucocorticoid overtreatment compromises growth and leads to increased weight and BMI in the longer term (39). Both androgens and oestrogens are important for bone mass accrual and maintenance. Overtreatment with glucocorticoids, vitamin D deficiency, physical activity, and hereditary factors may influence bone health (40).

Medical treatments

Some treatments are offered early in life, but evidence of their long-term efficacy may be lacking, for example, testosterone or dihydrotestosterone (DHT) for micropenis (41). The use of some medications is experimental (e.g. aromatase inhibitors to block the effect of sex hormones (42, 43) or metformin to avoid metabolic consequences (44)), but others, such as growth hormone, gluco- and mineralocorticoids, L-thyroxin, insulin and sex hormone replacement therapy are frequently used in DSD and need constant surveillance and adjustments (45, 46, 47). Standardised guidelines are lacking for most DSD conditions, with the exception of TS and KS (45, 48).

Lifelong steroid and sex hormone replacement therapy may induce side effects that negatively (or positively) impact QoL (4) and optimal dosing may vary with age (49, 50). Very few studies address medical needs to optimise sexual function and to avoid secondary health consequences, especially at older ages. In addition, treatment regimens differ widely across centres and comparison of these protocols may further improve patient management and health-related QoL in the future (2, 51). Large-scale registration and in-depth analysis of comorbidities and of chronic use of certain medications aim to improve care and to positively alter outcomes.

Particular attention has been given to the prenatal treatment of a foetus possibly affected by 21-hydroxylase deficiency with dexamethasone administered to the mother. Benefit-risk ratio is still unclear, and it is currently regarded as experimental (35). From another perspective, drugs such as pain killers given to pregnant women and (environmental) toxins may affect foetal sexual development and fertility (52). This important domain is largely unexplored, and collecting detailed information related to this topic is essential for future exploration.

Fertility and documentation of gonadal cancers

Fertility is strongly reduced in all forms of DSD, for biological and/or psychosocial reasons. Contemporary assisted reproductive techniques (ART) can increase chances to have biological children for some azoospermic individuals with 46,XY DSD and for some who have viable eggs (53, 54). Uterus transplantations have resulted in live births (55). It is anticipated that improvement of hormonal therapies and new technologies (e.g. *in vitro* generation of induced primordial germ cell-like cells) (56) may further increase fertility rates in the future. Assessment and documentation of reproductive capacity of the gonads independent of the patients' social gender has the aim of understanding condition-specific fertility chances (57). It can also facilitate access to international research protocols in this field through recruitment of registered patients.

The mechanisms underlying germ cell cancer development in DSD are increasingly understood. Routine prophylactic gonadectomy to prevent germ cell cancer development is no longer recommended in all individuals at risk; guidelines for selective gonadectomy and surveillance of retained gonads have been published (58, 59). Given the recent practice changes, no long-term outcome data on tumour risk in adulthood are available today, and with the possible exception of complete androgen insensitivity (59, 60), individualised management is hampered by a paucity of condition-specific data (58, 61). Therefore, current recommendations may need to be adjusted based on future insights. With a molecular genetic diagnosis more often reached today, and with systematic registration of pathology results and centralised review of challenging cases, further progress in this matter can be achieved (62).

Surgical fields

Childhood surgery

There are few evidence-based indications for gonadal or genital surgery in early childhood. Gonadal biopsy may, in exceptional cases, support important decisions, for example in relation to sex of rearing in the context of suspected (ovo)testicular DSD (63). Following international criticism of early genital surgery, many centres have restricted such procedures (9). Although debated, early surgery is still offered by some centres for 46,XX CAH patients with severe genital virilisation

and for 46,XY patients with hypospadias. Other centres have restricted such procedures and consider alternative options such as raising severely virilised 46,XX CAH children as males and offer extensive parental support to enhance the information and decision-making process. The developmental, familial, and societal impact of growing up with atypical-looking genitalia is currently not well understood. Psychosocial support appears crucial, and detailed documentation of such decisions in a multicentre registry is essential to allow urgent studies on their appropriateness and long-term consequences (64). Systematic registration can also demonstrate the time and pace needed to definitively implement the proposed practice changes.

There is no scientific evidence nor expert consensus on how surgery or refraining from surgery impacts the individual, family, society, or risk of stigmatisation (1). Standardised and detailed documentation of performed procedures, complications and reasons for and outcome of (non-) intervention are therefore crucial (9). As the focus of many performed genital surgeries nowadays is more on function than in relation to gender assignment, a specific description should be used for the intervention or the reasons to intervene rather than referring to 'feminising / masculinising' genital surgery.

Genital examinations

Genital examinations should be limited and should have a clear and transparent purpose. Living with atypical-looking genitals and/or having had genital surgery may pose psychological and psychosexual challenges that require timely referral to a psychologist or sexologist. This person can then further perform a psychological evaluation, using standardised diagnostic measures and propose appropriate support if needed. The applied methodology depends on the specific goal of such an assessment. No DSD-specific questionnaires to assess psychological and/or psychosexual functioning currently exist, and interpretation of results is seriously hampered by methodological limitations, highlighting the need for psychologists with good knowledge of and experience with the various conditions and for further professional training in this field (65).

Follow-up of adults

Follow-up of adults who had genital surgery in infancy is rarely organised in the routine clinical setting.

High-quality outcome and longitudinal studies are scarce. Difficulties include differences in technical terms, modifications of surgical techniques over the years, heterogeneity of DSD conditions and reporting bias of surgeons towards the techniques they are most experienced with (66). Comprehensive assessment ideally includes recording complications and redo surgery (also in adulthood), cosmetic appearance, functional outcome (micturition, sexuality), and quality of psychosexual life as a minimum, all in relation to preoperative findings and assessed both by a professional and by self-assessment (67, 68, 69, 70).

The hypospadias objective penile evaluation score (HOPE) has been designed for standardised cosmetic evaluation by a professional of hypospadias surgery (71). Although practical and objective, HOPE has important shortcomings, such as the use of genital pictures, lack of evaluation of the scrotum and of possibilities for self-assessment, most notably of penile size, which is considered crucial by many patients (72). A subjective cosmetic evaluation of hypospadias surgery can be obtained with the penile perception score (PPS) and its paediatric variant (PPPS) (73, 74). All the above lack functional parameters such as micturition pattern and erection and ejaculation capacity. A suggestion for a non-photography-based modified HOPE score, with addition of relevant functional and self-perceived assessments is provided in Supplementary Table 1 (see section on [supplementary data](#) given at the end of this article).

Different measures have been used for gynaecological and sexual function assessments of the female genitalia (e.g. (66, 70, 75)). Standardised tools for assessing long-term functional and cosmetic outcome of female genital surgery are in development. Items that are important to assess are listed in Supplementary Table 2.

Psychosocial fields

Trends in sex assignment have changed over the years (33). Sex and gender are fundamental in the development of a person's identity, as well as the individual's integrity, self-esteem, and social relations. Inappropriate focus or a normative perspective on genital, sexual, and psychological issues may cause annoyance or stigmatisation. Therefore, questions about a person's gender experience and gender well-being should be posed with respect for the individual's integrity and in an open-ended way that does not presume a particular gender or increase shame and stigma (65). Both children and adolescents should be

given the possibility to talk about these issues without a parent being present (13).

Assessment of an individual's mental well-being and need for psychosocial support should be part of standard care throughout life. Physical or mental health problems are highly prevalent in individuals who have a DSD (2, 8). Importantly, not the specific diagnosis but the personal health status predicts QoL (4). Overall, individuals with a DSD report good QoL but studies are often contradictory, possibly due to differences in local treatment and care, age and cultural context and differences in methodology. Appropriate QoL questionnaires should focus on social and psychological domains that are relevant for individuals who have a DSD (76). In addition, patient-reported outcome measures related to QoL at all life stages are considered most crucial by patients, and it is clear that they have a central place in holistic care (77). Formal QoL assessment in the context of routine clinical practice is unusual, but as a minimum, it is suggested to record the impact of the condition on the patients' daily life by including a relevant proxy for this. While awaiting more specific key questions, preferably developed by support groups and other stakeholders, a generic set of simple questions is proposed here, which can be adjusted to all ages.

Considering all conditions together, the prevalence of gender dysphoria is only slightly increased in DSD. However, assessing gender identity and gender-related behaviour according to a strict binary or pathologising model will insufficiently capture the broad spectrum of gender-related outcomes (78). Currently, hardly any instrument is available that allows gender assessment according to a spectral rather than a bimodal paradigm. Therefore, new measures and instruments, using a non-binary vocabulary and taking all possible gender outcomes into account need to be developed. In addition, gender role behaviour rather than gender well-being has been given (too) much attention in the past. Indeed, it is crucial not to misinterpret behaviour or sexual orientation as signs of gender dysphoria (11).

From the beginning, psychosocial support for parents, aiming at an enhanced understanding of the medical context and the diagnostic investigations are crucial factors for coping with psychological distress (79). Parent-child bonding, coping abilities and symptoms of stress are important indicators of parental needs on this matter (12). In the presence of a genital difference, parents need guidance on how to raise resilient children and how to communicate early with their child about the condition, including consequences for gender development and

past and future treatment options (80). To what extent psychosocial support and early information may contribute to optimisation of outcomes has never been documented in the context of DSD. Providing further evidence in favour of such support may convince policy makers to invest in psychological counselling, as an important part of preventive care and as a valuable alternative to genital surgery, among others (81, 82).

Many registries such as I-DSD are developing sections that include possibilities for self-reporting of relevant outcome measures, such as reasons for genital surgery or not having such surgery, and self-reported QoL. Altogether, considering the voices of people with DSD and their parents, research and care of DSD can move from a researcher-driven to a participant-driven approach.

Conclusions and perspectives

Consensus was reached on standardised assessments of individuals who have a DSD and on the ages at which clinical revision should be performed in order to capture crucial developmental milestones and/or long-term consequences of the various conditions. In the clinical setting, the tool will ensure and support a high quality of clinical care. Long-term and wide use of this instrument, for example, through the I-DSD Registry, will allow answering critical research questions in the future specifically in relation to outcome, treatment options, comorbidities in adult age and fertility. In addition, patient-reported outcome measures, obtained through patient portals, are expected to become increasingly important and may also be implemented in the I-DSD Registry in the near future.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-19-0363>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Lee PA, Nordenstrom A, Houk CP, Ahmed SF, Auchus R, Baratz A, Baratz Dalke K, Liao LM, Lin-Su K, Looijenga LH, *et al.* Global disorders of sex development update since 2006: perceptions, approach and care. *Hormone Research in Paediatrics* 2016 **85** 158–180. (<https://doi.org/10.1159/000442975>)
- 2 Falhammar H, Claahsen-van der Grinten H, Reisch N, Slowikowska-Hilczer J, Nordenström A, Roehle R, Bouvattier C, Kreukels BPC, Köhler B & dsd-LIFE Group. Health status in 1040 adults with disorders of sex development (DSD): a European multicenter study. *Endocrine Connections* 2018 **7** 466–478. (<https://doi.org/10.1530/EC-18-0031>)
- 3 van de Grift TC, Cohen-Kettenis PT, de Vries ALC, & Kreukels BPC on behalf of dsd-LIFE. Body image and self-esteem in disorders of sex development: a European multicenter study. *Health Psychology* 2018 **37** 334–343. (<https://doi.org/10.1037/hea0000600>)
- 4 Rapp M, Mueller-Godeffroy E, Lee P, Roehle R, Kreukels BPC, Köhler B, Nordenström A, Bouvattier C, Thyen U & dsd-LIFE group. Multicentre cross-sectional clinical evaluation study about quality of life in adults with disorders/differences of sex development (DSD) compared to country specific reference populations (dsd-LIFE). *Health and Quality of Life Outcomes* 2018 **16** 54. (<https://doi.org/10.1186/s12955-018-0881-3>)
- 5 Thyen U, Ittermann T, Flessa S, Muehlan H, Birnbaum W, Rapp M, Marshall L, Szarras-Capnik M, Bouvattier C, Kreukels BPC, *et al.* Quality of health care in adolescents and adults with disorders/differences of sex development (DSD) in six European countries (dsd-LIFE). *BMC Health Services Research* 2018 **18** 527. (<https://doi.org/10.1186/s12913-018-3342-0>)
- 6 Hiort O, Birnbaum W, Marshall L, Wunsch L, Werner R, Schroder T, Dohnert U & Holterhus PM. Management of disorders of sex development. *Nature Reviews. Endocrinology* 2014 **10** 520–529. (<https://doi.org/10.1038/nrendo.2014.108>)
- 7 Thyen U, Lux A, Jurgensen M, Hiort O & Kohler B. Utilization of health care services and satisfaction with care in adults affected by disorders of sex development (DSD). *Journal of General Internal Medicine* 2014 **29**(Supplement 3) S752–S759. (<https://doi.org/10.1007/s11606-014-2917-7>)
- 8 Cools M, Nordenstrom A, Robeva R, Hall J, Westerveld P, Fluck C, Kohler B, Berra M, Springer A, Schweizer K, *et al.* Caring for individuals with a difference of sex development (DSD): a consensus statement. *Nature Reviews. Endocrinology* 2018 **14** 415–429. (<https://doi.org/10.1038/s41574-018-0010-8>)
- 9 Gorduza DB, Quigley CA, Caldamone AA & Mouriquand PDE. Surgery of anomalies of gonadal and genital development in the "post-truth era". *Urologic Clinics of North America* 2018 **45** 659–669. (<https://doi.org/10.1016/j.ucl.2018.06.012>)
- 10 Baratz AB, Sharp MK & Sandberg DE. Disorders of sex development peer support. *Endocrine Development* 2014 **27** 99–112. (<https://doi.org/10.1159/000363634>)
- 11 Kreukels BPC, Köhler B, Nordenström A, Roehle R, Thyen U, Bouvattier C, de Vries ALC, Cohen-Kettenis PT & dsd-LIFE group. Gender dysphoria and gender change in disorders of sex development/intersex conditions: results from the dsd-LIFE study. *Journal of Sexual Medicine* 2018 **15** 777–785. (<https://doi.org/10.1016/j.jsxm.2018.02.021>)
- 12 Ahmed SF, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, Elford S, Hughes IA, Izatt L, Krone N, *et al.* Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (revised 2015). *Clinical Endocrinology* 2016 **84** 771–788. (<https://doi.org/10.1111/cen.12857>)
- 13 Nordenstrom A & Thyen U. Improving the communication of healthcare professionals with affected children and adolescents. *Endocrine Development* 2014 **27** 113–127. (<https://doi.org/10.1159/000363636>)

- 14 Crouch NS & Creighton SM. Transition of care for adolescents with disorders of sex development. *Nature Reviews. Endocrinology* 2014 **10** 436–442. (<https://doi.org/10.1038/nrendo.2014.62>)
- 15 Kulle A, Krone N, Holterhus PM, Schuler G, Greaves RF, Juul A, de Rijke YB, Hartmann MF, Saba A, Hiort O, *et al.* Steroid hormone analysis in diagnosis and treatment of DSD: position paper of EU COST Action BM 1303 'DSDnet'. *European Journal of Endocrinology* 2017 **176** P1–P9. (<https://doi.org/10.1530/EJE-16-0953>)
- 16 Audi L, Ahmed SF, Krone N, Cools M, McElreavey K, Holterhus PM, Greenfield A, Bashamboo A, Hiort O, Wudy SA, *et al.* GENETICS IN ENDOCRINOLOGY: approaches to molecular genetic diagnosis in the management of differences/disorders of sex development (DSD): position paper of EU COST Action BM 1303 'DSDnet'. *European Journal of Endocrinology* 2018 **179** R197–R206. (<https://doi.org/10.1530/EJE-18-0256>)
- 17 Alhomaideh D, McGowan R & Ahmed SF. The current state of diagnostic genetics for conditions affecting sex development. *Clinical Genetics* 2017 **91** 157–162. (<https://doi.org/10.1111/cge.12912>)
- 18 Lindhardt Johansen M, Hagen CP, Rajpert-De Meyts E, Kjaergaard S, Petersen BL, Skakkebaek NE, Main KM & Juul A. 45,X/46,XY mosaicism: phenotypic characteristics, growth, and reproductive function—a retrospective longitudinal study. *The Journal of Clinical Endocrinology and Metabolism* 2012 **97** E1540–E1549. (<https://doi.org/10.1210/jc.2012-1388>)
- 19 Camats N, Fernandez-Cancio M, Audi L, Mullis PE, Moreno F, Gonzalez Casado I, Lopez-Siguero JP, Corripio R, Bermudez de la Vega JA, Blanco JA, *et al.* Human MAMLD1 gene variations seem not sufficient to explain a 46,XY DSD phenotype. *PLOS ONE* 2015 **10** e0142831. (<https://doi.org/10.1371/journal.pone.0142831>)
- 20 Camats N, Fernandez-Cancio M, Audi L, Schaller A & Fluck CE. Broad phenotypes in heterozygous NR5A1 46,XY patients with a disorder of sex development: an oligogenic origin? *European Journal of Human Genetics* 2018 **26** 1329–1338. (<https://doi.org/10.1038/s41431-018-0202-7>)
- 21 Ollivier M, Paris F, Philibert P, Garnier S, Coffy A, Fauconnet-Servant N, Haddad M, Guys JM, Reynaud R, Faure A, *et al.* Family history is underestimated in children with isolated hypospadias: a French multicenter report of 88 families. *Journal of Urology* 2018 **200** 890–894. (<https://doi.org/10.1016/j.juro.2018.04.072>)
- 22 Portnoi MF, Dumargne MC, Rojo S, Witchel SF, Duncan AJ, Eozenou C, Bignon-Topalovic J, Yatsenko SA, Rajkovic A, Reyes-Mugica M, *et al.* Mutations involving the SRY-related gene SOX8 are associated with a spectrum of human reproductive anomalies. *Human Molecular Genetics* 2018 **27** 1228–1240. (<https://doi.org/10.1093/hmg/ddy037>)
- 23 Cox K, Bryce J, Jiang J, Rodie M, Sinnott R, Alkhawari M, Arlt W, Audi L, Balsamo A, Bertelloni S, *et al.* Novel associations in disorders of sex development: findings from the I-DSD Registry. *The Journal of Clinical Endocrinology and Metabolism* 2014 **99** E348–E355. (<https://doi.org/10.1210/jc.2013-2918>)
- 24 Lourenco D, Brauner R, Rybczynska M, Nihoul-Fekete C, McElreavey K & Bashamboo A. Loss-of-function mutation in GATA4 causes anomalies of human testicular development. *Proceedings of the National Academy of Sciences of the United States of America* 2011 **108** 1597–1602. (<https://doi.org/10.1073/pnas.1010257108>)
- 25 Lipska BS, Ranchin B, Iatropoulos P, Gellermann J, Melk A, Ozaltin F, Caridi G, Seeman T, Tory K, Jankauskiene A, *et al.* Genotype-phenotype associations in WT1 glomerulopathy. *Kidney International* 2014 **85** 1169–1178. (<https://doi.org/10.1038/ki.2013.519>)
- 26 Achermann JC, Ozisik G, Ito M, Orun UA, Harmanci K, Gurakan B & Jameson JL. Gonadal determination and adrenal development are regulated by the orphan nuclear receptor steroidogenic factor-1, in a dose-dependent manner. *The Journal of Clinical Endocrinology and Metabolism* 2002 **87** 1829–1833. (<https://doi.org/10.1210/jcem.87.4.8376>)
- 27 Colson C, Aubry E, Cartigny M, Remy AA, Franquet H, Leroy X, Kechid G, Lefevre C, Besson R, Cools M, *et al.* SF1 and spleen development: new heterozygous mutation, literature review and consequences for NR5A1-mutated patient's management. *Clinical Genetics* 2017 **92** 99–103. (<https://doi.org/10.1111/cge.12957>)
- 28 De Groote K, Cools M, De Schepper J, Craen M, Francois I, Devos D, Carbonez K, Eyskens B & De Wolf D. Cardiovascular pathology in males and females with 45,X/46,XY mosaicism. *PLOS ONE* 2013 **8** e54977. (<https://doi.org/10.1371/journal.pone.0054977>)
- 29 Prader A. Male pseudohermaphroditism. *Helvetica Paediatrica Acta. Supplementum* 1974 **34** 79–86.
- 30 Quigley CA, De Bellis A, Marschke KB, el-Awady MK, Wilson EM & French FS. Androgen receptor defects: historical, clinical, and molecular perspectives. *Endocrine Reviews* 1995 **16** 271–321. (<https://doi.org/10.1210/edrv-16-3-271>)
- 31 Thankamony A, Pasterski V, Ong KK, Acerini CL & Hughes IA. Anogenital distance as a marker of androgen exposure in humans. *Andrology* 2016 **4** 616–625. (<https://doi.org/10.1111/andr.12156>)
- 32 Ahmed SF, Khwaja O & Hughes IA. The role of a clinical score in the assessment of ambiguous genitalia. *BJU International* 2000 **85** 120–124. (<https://doi.org/10.1046/j.1464-410x.2000.00354.x>)
- 33 Kolesinska Z, Ahmed SF, Niedziela M, Bryce J, Molinska-Glura M, Rodie M, Jiang J, Sinnott RO, Hughes IA, Darendeliler F, *et al.* Changes over time in sex assignment for disorders of sex development. *Pediatrics* 2014 **134** e710–e715. (<https://doi.org/10.1542/peds.2014-1088>)
- 34 Bougneres P, Bouvattier C, Cartigny M & Michala L. Deferring surgical treatment of ambiguous genitalia into adolescence in girls with 21-hydroxylase deficiency: a feasibility study. *International Journal of Pediatric Endocrinology* 2017 **2017** 3. (<https://doi.org/10.1186/s13633-016-0040-8>)
- 35 Speiser PW, Arlt W, Auchus RJ, Baskin LS, Conway GS, Merke DP, Meyer-Bahlburg HFL, Miller WL, Murad MH, Oberfield SE, *et al.* Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism* 2018 **103** 4043–4088. (<https://doi.org/10.1210/jc.2018-01865>)
- 36 Bertelloni S, Baroncelli GI, Massart F & Toschi B. Growth in boys with 45,X/46,XY mosaicism: effect of growth hormone treatment on statural growth. *Sexual Development: Genetics, Molecular Biology, Evolution, Endocrinology, Embryology, and Pathology of Sex Determination and Differentiation* 2015 **9** 183–189. (<https://doi.org/10.1159/000441342>)
- 37 Martinierie L, Morel Y, Gay CL, Pienkowski C, de Kerdanet M, Cabrol S, Lecointre C, Coutant R, Baron S, Colle M, *et al.* Impaired puberty, fertility, and final stature in 45,X/46,XY mixed gonadal dysgenetic patients raised as boys. *European Journal of Endocrinology* 2012 **166** 687–694. (<https://doi.org/10.1530/EJE-11-0756>)
- 38 Onland-Moret NC, Peeters PH, van Gils CH, Clavel-Chapelon F, Key T, Tjonneland A, Trichopoulou A, Kaaks R, Manjer J, Panico S, *et al.* Age at menarche in relation to adult height: the EPIC study. *American Journal of Epidemiology* 2005 **162** 623–632. (<https://doi.org/10.1093/aje/kwi260>)
- 39 Hagenfeldt K, Martin Ritzen E, Ringertz H, Helleday J & Carlstrom K. Bone mass and body composition of adult women with congenital virilizing 21-hydroxylase deficiency after glucocorticoid treatment since infancy. *European Journal of Endocrinology* 2000 **143** 667–671. (<https://doi.org/10.1530/eje.0.1430667>)
- 40 Vanderschueren D, Laurent MR, Claessens F, Gielen E, Lagerquist MK, Vandenput L, Borjesson AE & Ohlsson C. Sex steroid actions in male bone. *Endocrine Reviews* 2014 **35** 906–960. (<https://doi.org/10.1210/er.2014-1024>)
- 41 Callens N, De Cuypere G, Van Hoecke E, T'Sjoen G, Monstrey S, Cools M & Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis:

- a review. *Journal of Sexual Medicine* 2013 **10** 2890–2903. (<https://doi.org/10.1111/jsm.12298>)
- 42 Hawton K, Walton-Betancourth S, Rumsby G, Raine J & Dattani M. Growth hormone with aromatase inhibitor may improve height in CYP11B1 congenital adrenal hyperplasia. *Pediatrics* 2017 **139**. (<https://doi.org/10.1542/peds.2016-0730>)
 - 43 Merke DP & Cutler GB, Jr. New ideas for medical treatment of congenital adrenal hyperplasia. *Endocrinology & Metabolism Clinics of North America* 2001 **30** 121–135. ([https://doi.org/10.1016/S0889-8529\(08\)70022-7](https://doi.org/10.1016/S0889-8529(08)70022-7))
 - 44 Mapas-Dimaya AC, Agdere L, Bahtiyar G, Mejia JO & Sacerdote AS. Metformin-responsive classic salt-losing congenital adrenal hyperplasia due to 21-hydroxylase deficiency: a case report. *Endocrine Practice* 2008 **14** 889–891. (<https://doi.org/10.4158/EP.14.7.889>)
 - 45 Gravholt CH, Andersen NH, Conway GS, Dekkers OM, Geffner ME, Klein KO, Lin AE, Mauras N, Quigley CA, Rubin K, *et al.* Clinical practice guidelines for the care of girls and women with Turner syndrome: proceedings from the 2016 Cincinnati International Turner Syndrome Meeting. *European Journal of Endocrinology* 2017 **177** G1–G70. (<https://doi.org/10.1530/EJE-17-0430>)
 - 46 Bojesen A, Kristensen K, Birkebaek NH, Fedder J, Mosekilde L, Bennett P, Laurberg P, Frystyk J, Flyvbjerg A, Christiansen JS, *et al.* The metabolic syndrome is frequent in Klinefelter's syndrome and is associated with abdominal obesity and hypogonadism. *Diabetes Care* 2006 **29** 1591–1598. (<https://doi.org/10.2337/dc06-0145>)
 - 47 Poyrazoglu S, Darendeliler F, Ahmed SF, Hughes I, Bryce J, Jiang J, Rodie M, Hiort O, Hannema SE, Bertelloni S, *et al.* Birth weight in different etiologies of disorders of sex development. *The Journal of Clinical Endocrinology and Metabolism* 2017 **102** 1044–1050. (<https://doi.org/10.1210/jc.2016-3460>)
 - 48 Chang S, Skakkebaek A & Gravholt CH. Klinefelter syndrome and medical treatment: hypogonadism and beyond. *Hormones (Athens)* 2015 **14** 531–548. (<https://doi.org/10.14310/horm.2002.1622>)
 - 49 Arlt W, Willis DS, Wild SH, Krone N, Doherty EJ, Hahner S, Han TS, Carroll PV, Conway GS, Rees DA, *et al.* Health status of adults with congenital adrenal hyperplasia: a cohort study of 203 patients. *The Journal of Clinical Endocrinology and Metabolism* 2010 **95** 5110–5121. (<https://doi.org/10.1210/jc.2010-0917>)
 - 50 Nordenstrom A, Rohle R, Thyen U, Bouvattier C, Slowikowska-Hilcz J, Reisch N, Claahsen van der Grinten H, Brac de la Perriere A, Cohen-Kettenis PT, Kohler B, *et al.* Hormone therapy and patient satisfaction with treatment, in a large cohort of diverse disorders of sex development. *Clinical Endocrinology* 2018 **88** 397–408. (<https://doi.org/10.1111/cen.13518>)
 - 51 Liivak K & Tillmann V. 24-hour blood pressure profiles in children with congenital adrenal hyperplasia on two different hydrocortisone treatment regimens. *Journal of Pediatric Endocrinology & Metabolism* 2009 **22** 511–517. (<https://doi.org/10.1515/jpem.2009.22.6.511>)
 - 52 Hurtado-Gonzalez P & Mitchell RT. Analgesic use in pregnancy and male reproductive development. *Current Opinion in Endocrinology, Diabetes, and Obesity* 2017 **24** 225–232. (<https://doi.org/10.1097/MED.0000000000000338>)
 - 53 Casteras A, De Silva P, Rumsby G & Conway GS. Reassessing fecundity in women with classical congenital adrenal hyperplasia (CAH): normal pregnancy rate but reduced fertility rate. *Clinical Endocrinology* 2009 **70** 833–837. (<https://doi.org/10.1111/j.1365-2265.2009.03563.x>)
 - 54 Slowikowska-Hilcz J, Hirschberg AL, Claahsen-van der Grinten H, Reisch N, Bouvattier C, Thyen U, Cohen Kettenis P, Roehle R, Kohler B, Nordenstrom A, *et al.* Fertility outcome and information on fertility issues in individuals with different forms of disorders of sex development: findings from the dsd-LIFE study. *Fertility & Sterility* 2017 **108** 822–831. (<https://doi.org/10.1016/j.fertnstert.2017.08.013>)
 - 55 Brannstrom M. Uterus transplantation. *Current Opinion in Organ Transplantation* 2015 **20** 621–628. (<https://doi.org/10.1097/MOT.0000000000000246>)
 - 56 Hayashi K, Ogushi S, Kurimoto K, Shimamoto S, Ohta H & Saitou M. Offspring from oocytes derived from in vitro primordial germ cell-like cells in mice. *Science* 2012 **338** 971–975. (<https://doi.org/10.1126/science.1226889>)
 - 57 Islam R, Lane S, Williams SA, Becker CM, Conway GS & Creighton SM. Establishing reproductive potential and advances in fertility preservation techniques for XY individuals with differences in sex development. *Clinical Endocrinology* 2019 **91** 237–244. (<https://doi.org/10.1111/cen.13994>)
 - 58 van der Zwan YG, Biermann K, Wolffenbuttel KP, Cools M & Looijenga LH. Gonadal maldevelopment as risk factor for germ cell cancer: towards a clinical decision model. *European Urology* 2015 **67** 692–701. (<https://doi.org/10.1016/j.eururo.2014.07.011>)
 - 59 Tack LW, Maris E, Looijenga LJ, Hannema SE, Audi L, Kohler B, Holterhus PM, Riedl S, Wisniewski A, Fluck CE, *et al.* Management of gonads in adults with androgen insensitivity: an international survey. *Hormone Research in Paediatrics* 2018 **90** 236–246. (<https://doi.org/10.1159/000493645>)
 - 60 Cools M, Wolffenbuttel KP, Hersmus R, Mendonca BB, Kaprova J, Drop SLS, Stoop H, Gillis AJM, Oosterhuis JW, Costa EMF, *et al.* Malignant testicular germ cell tumors in postpubertal individuals with androgen insensitivity: prevalence, pathology and relevance of single nucleotide polymorphism-based susceptibility profiling. *Human Reproduction* 2017 **32** 2561–2573. (<https://doi.org/10.1093/humrep/dex300>)
 - 61 Cools M, Drop SL, Wolffenbuttel KP, Oosterhuis JW & Looijenga LH. Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers. *Endocrine Reviews* 2006 **27** 468–484. (<https://doi.org/10.1210/er.2006-0005>)
 - 62 Spoor JA, Oosterhuis JW, Hersmus R, Biermann K, Wolffenbuttel KP, Cools M, Kazmi Z, Ahmed SF & Looijenga LHJ. Histological assessment of gonads in DSD: relevance for clinical management. *Sexual Development: Genetics, Molecular Biology, Evolution, Endocrinology, Embryology, and Pathology of Sex Determination and Differentiation* 2018 **12** 106–122. (<https://doi.org/10.1159/000481757>)
 - 63 Mouriquand PD, Gorduz DB, Gay CL, Meyer-Bahlburg HF, Baker L, Baskin LS, Bouvattier C, Braga LH, Caldamone AC, Duranteau L, *et al.* Surgery in disorders of sex development (DSD) with a gender issue: if (why), when, and how? *Journal of Pediatric Urology* 2016 **12** 139–149. (<https://doi.org/10.1016/j.jpuro.2016.04.001>)
 - 64 Schweizer K, Brunner F, Gedrose B, Handford C & Richter-Appelt H. Coping with diverse sex development: treatment experiences and psychosocial support during childhood and adolescence and adult well-being. *Journal of Pediatric Psychology* 2017 **42** 504–519. (<https://doi.org/10.1093/jpepsy/jsw058>)
 - 65 D'Alborton F, Vissani S, Ferracuti C & Pasterski V. Methodological issues for psychological evaluation across the lifespan of individuals with a difference/disorder of sex development. *Sexual Development: Genetics, Molecular Biology, Evolution, Endocrinology, Embryology, and Pathology of Sex Determination and Differentiation* 2018 **12** 123–134. (<https://doi.org/10.1159/000484189>)
 - 66 Jesus LE. Feminizing genitoplasties: where are we now? *Journal of Pediatric Urology* 2018 **14** 407–415. (<https://doi.org/10.1016/j.jpuro.2018.03.020>)
 - 67 Springer A, Tekgul S & Subramaniam R. An update of current practice in hypospadias surgery. *European Urology Supplements* 2017 **16** 8–15. (<https://doi.org/10.1016/j.eursup.2016.09.006>)
 - 68 Szymanski KM, Whittam B, Monahan PO, Kaefel M, Frady H, Cain MP & Rink RC. Validation and preliminary results of the parental assessment of children's external genitalia scale for females (PACE-F) for girls with CAH. *Urology* 2019 **130** 132–137. (<https://doi.org/10.1016/j.urology.2019.04.034>)
 - 69 Lee P, Schober J, Nordenstrom A, Hoebeke P, Houk C, Looijenga L, Manzoni G, Reiner W & Woodhouse C. Review of recent outcome data of disorders of sex development (DSD): emphasis on surgical and sexual outcomes. *Journal of Pediatric Urology* 2012 **8** 611–615. (<https://doi.org/10.1016/j.jpuro.2012.10.017>)

- 70 Kreukels BPC, Cohen-Kettenis PT, Roehle R, van de Grift TC, Slowikowska-Hilcz J, Claahsen-van der Grinten H, Linden Hirschberg A, de Vries ALC, Reisch N, Bouvattier C, *et al.* Sexuality in adults with differences/disorders of sex development (DSD): findings from the dsd-LIFE study. *Journal of Sex & Marital Therapy* 2019 1–18. (<https://doi.org/10.1080/0092623X.2019.1610123>)
- 71 van der Toorn F, de Jong TP, de Gier RP, Callewaert PR, van der Horst EH, Steffens MG, Hoebeke P, Nijman RJ, Bush NC, Wolffenbuttel KP, *et al.* Introducing the HOPE (hypospadias objective penile evaluation)-score: a validation study of an objective scoring system for evaluating cosmetic appearance in hypospadias patients. *Journal of Pediatric Urology* 2013 **9** 1006–1016. (<https://doi.org/10.1016/j.jpuro.2013.01.015>)
- 72 Aho MO, Tammela OK, Somppi EM & Tammela TL. Sexual and social life of men operated in childhood for hypospadias and phimosis. A comparative study. *European Urology* 2000 **37** 95–100; discussion 101. (<https://doi.org/10.1159/000020107>)
- 73 Weber DM, Landolt MA, Gobet R, Kalisch M & Greeff NK. The Penile Perception Score: an instrument enabling evaluation by surgeons and patient self-assessment after hypospadias repair. *Journal of Urology* 2013 **189** 189–193. (<https://doi.org/10.1016/j.juro.2012.08.178>)
- 74 Weber DM, Schonbuecher VB, Landolt MA & Gobet R. The Pediatric Penile Perception Score: an instrument for patient self-assessment and surgeon evaluation after hypospadias repair. *Journal of Urology* 2008 **180** 1080–1084; discussion 1084. (<https://doi.org/10.1016/j.juro.2008.05.060>)
- 75 Crouch NS, Liao LM, Woodhouse CR, Conway GS & Creighton SM. Sexual function and genital sensitivity following feminizing genitoplasty for congenital adrenal hyperplasia. *The Journal of Urology* 2008 **179** 634–638. (<https://doi.org/10.1016/j.juro.2007.09.079>)
- 76 Bennecke E, Thyen U, Gruters A, Lux A & Kohler B. Health-related quality of life and psychological well-being in adults with differences/disorders of sex development. *Clinical Endocrinology* 2017 **86** 634–643. (<https://doi.org/10.1111/cen.13296>)
- 77 Sanders C, Hall J, Sanders C, Dessens A, Bryce J, Callens N, Cools M, Kourime M, Kyriakou A, Springer A, *et al.* Involving individuals with disorders of sex development and their parents in exploring new models of shared learning: Proceedings from a DSDnet COST Action Workshop. *Sexual Development* 2018 **12** 225–231. (<https://doi.org/10.1159/000490081>)
- 78 Hyde JS, Bigler RS, Joel D, Tate CC & van Anders SM. The future of sex and gender in psychology: five challenges to the gender binary. *American Psychologist* 2019 **74** 171–193. (<https://doi.org/10.1037/amp0000307>)
- 79 Pasterski V, Mastroyannopoulou K, Wright D, Zucker KJ & Hughes IA. Predictors of posttraumatic stress in parents of children diagnosed with a disorder of sex development. *Archives of Sexual Behavior* 2014 **43** 369–375. (<https://doi.org/10.1007/s10508-013-0196-8>)
- 80 Magritte E. Working together in placing the long term interests of the child at the heart of the DSD evaluation. *Journal of Pediatric Urology* 2012 **8** 571–575. (<https://doi.org/10.1016/j.jpuro.2012.07.011>)
- 81 Liao LM, Wood D & Creighton SM. Parental choice on normalising cosmetic genital surgery. *BMJ* 2015 **351** h5124. (<https://doi.org/10.1136/bmj.h5124>)
- 82 Cools M, Simmonds M, Elford S, Gorter J, Ahmed SF, D'Alberton F, Springer A, Hiort O & Management Committee of the European Cooperation. Response to the Council of Europe Human Rights Commissioner's issue paper on human rights and intersex people. *European Urology* 2016 **70** 407–409. (<https://doi.org/10.1016/j.eururo.2016.05.015>)

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