Management of disorders of sex development

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Abstract | The medical term disorders of sex development (DSDs) is used to describe individuals with an atypical composition of chromosomal, gonadal and phenotypic sex, which leads to differences in the development of the urogenital tract and reproductive system. A variety of genetic factors have been identified that affect sex development during gonadal differentiation or in specific disorders associated with altered androgen biosynthesis or action. The diagnosis of DSDs in individuals and the subsequent management of patients and their families requires a targeted and structured approach, involving a multidisciplinary team with effective communication between the disciplines. This approach includes distinct clinical, imaging, laboratory and genetic evaluations of patients with DSDs. Although treatment of patients with DSDs can include endocrine and surgical options, many patients have concerns that arise from past incorrect treatments that were founded on the traditional binary concept of the sexes. To dispel these concerns, it is necessary to create centres of expertise for DSDs that include physicians, surgeons, psychologists and specialists in diagnostic procedures to manage patients and their families. Additionally, the inclusion of trained peer support in the multidisciplinary DSD team seems to be integral to the supportive management of patients with DSDs. Most importantly, dealing with DSDs requires acceptance of the fact that deviation from the traditional definitions of gender is not necessarily pathologic.


Introduction

Disorders of sex development (DSDs) constitute a group of congenital conditions that affect urogenital differentiation and are associated with chromosomal, gonadal and phenotypic sex abnormalities (Box 1). This nomenclature and the subsequent classification of distinct DSDs was introduced in 2005, following a consensus conference of the major paediatric endocrine societies (referred to as the Chicago conference). On the basis of biological principles and current understanding of genetic pathways, DSD classification enables a better understanding of the underlying pathogenetic mechanisms. Prior to 2005, elusive and sometimes pejorative expressions such as hermaphroditism, pseudohermaphroditism, sex reversal and intersex were used to describe patients with DSDs.

Increasing demand from patients, healthcare professionals and the general public to change established clinical practices for the management of patients with DSDs led to the Chicago conference being organised. Synchronous with the introduction of the new classification system, a new terminology and scientific basis for biological understanding was established that would eventually assist in the management of patients with DSDs and their families. The new terminology has rapidly diffused, finding its way into general medical textbooks and is today generally accepted.

Inclusion of the term ‘disorder’ reflects the fact that most parents and medical professionals have a traditional binary concept of sex development. Understanding that not every deviation from binary sex development is pathologic is a basic requirement for medical professionals caring for individuals with DSDs. Accordingly, the terms ‘differences of sex development’ and ‘variations of sex development’ are more appropriate in many circumstances, especially when referring to the social and cultural aspects of DSDs in individuals with minor medical problems. Nonetheless, many individuals with DSDs have severe medical problems related to their condition or the treatment they received; many DSDs are chronic incurable disorders that place a considerable burden on patients and their families.

The Chicago conference occurred at a time when enormous advances had been and were being made in elucidating the molecular pathways involved in sexual development. Currently, in excess of 50 genes have been shown to be involved in either gonadal development or sexual differentiation (on the basis of sex steroid biosynthesis and action), adding substantial complexity to the original classification. New techniques, such as comparative genomic hybridisation and next-generation sequencing, are increasingly being used to unravel genetic aberrations in many complex rare diseases and will potentially revolutionize diagnostics in the near future. These techniques have provided novel insights into the diversity of DSDs and the time-controlled processes that lead to the respective phenotypes of individuals with DSDs, which result mainly from androgen-related effects.

Furthermore, epigenetic modifications are seen as a consequence of DSDs and might also be the basis of atypical pathways involved in sex development. Diagnostic DNA analysis has largely been responsible for translating
Key points

- Disorders of sex development (DSDs) include at least 50 different congenital abnormalities of urogenital differentiation
- The terms ‘variations of sex development’ and ‘differences of sex development’ can also be used to describe individuals with DSDs
- Diagnosis of DSDs requires clinical assessment, morphological determination, endocrine evaluation and genetic studies; however, the pathogenetic mechanisms have only been elucidated in a subset of individuals with DSDs
- Management of patients with DSDs should involve a group of specialists working in an interdisciplinary team in a dedicated Centre of Expertise
- Important areas of DSD research include personalized approaches to patient management and the development of diagnostic strategies that combine modern genetic techniques with endocrine evaluations

Box 1 | Biological classification of DSDs

46,XX
- Disorders of gonadal development
  - Ovotesticular DSD
  - Testicular DSD
  - Syndromic forms
- Disorders of androgen excess
  - Congenital adrenal hyperplasia (mostly steroid 21-hydroxylase deficiency)
  - Aromatase deficiency
- Luteoma
- Intrigeneric
- Unclassified disorders
- Mayer–Rokitansky–Küster–Hauser syndrome
- Complex syndromic disorders

46,XY
- Disorders of gonadal development
  - Ovotesticular DSD
  - Complete or partial gonadal dysgenesis, monogenic forms (caused by mutations in SRY, SF1, WT1 and others)
  - Syndromic forms
- Disorders of androgen synthesis
  - Syndromic (for example, Smith–Lemli–Opitz syndrome)
  - Associated with congenital adrenal hyperplasia and early androgen biosynthesis defects (for example, mutations and/or deficiencies in STAR, P450ccc, 3β-HSD II, P450OR and CYP17A1)
  - Associated with androgen biosynthesis defects (for example, mutations and/or deficiencies in SRD5A2 and HSD17B3)
- Associated with androgen disruption
  - Disorders of androgen action
    - Complete and partial androgen insensitivity
  - Unclassified disorders
- Hypospadias of unknown genetic origin
- Epispadias
- Complex syndromic disorders

Chromosomal DSDs

- 45,X (Turner syndrome and variants)
- 45X/46,XY (mixed gonadal dysgenesis)
- 47,XXY (Klinefelter syndrome and variants)
- Other complex chromosomal rearrangements

Abbreviations: CYP17A1, steroid 17α-hydroxylase/17,20 lyase; DSDs, disorders of sex development; HSD17B3, testosterone 17β-dehydrogenase 3; 3β-HSD II, 3β-hydroxysteroid dehydrogenase/δ-5-4-isomerase type 2; P450OR, NADPH:cytochrome P450 reductase; P450ccc, cholesterol side-chain cleavage enzyme, mitochondrial; SF1, steroidogenic factor 1; SRD5A2, steroid 5α-reductase 2; SRY, sex-determining region Y protein; STAR, steroidogenic acute regulatory protein, mitochondrial; WT1, Wilms tumor protein. Permission obtained from BMJ Publishing Group Ltd © Hughes, I. A. et al. Arch. Dis. Child. 91, 554–563 (2006).

Historically, the sex of an individual was assigned according to the phenotypic appearance of the genitals. At the end of the 19th century, increasing knowledge of the embryology of sex development led to the recognition of gonadal differentiation as the key event in sex development. This advance led to the concept that individuals with an external female phenotype but proven testicular development, such as those with complete androgen insensitivity syndrome (CAIS), should be considered male. This concept was challenged by John Money and colleagues in the middle of the 20th century who proposed a more detailed hypothesis,1 including the notion that future determination of chromosomal sex should only be a minor criterion in sex assignment and emphasizing the role of gender development over time. Furthermore, although not a practical issue at that time, the role of potential fertility was suggested as a basis for sex assignment. Accordingly, Money classified seven groups of conditions and provided detailed advice on the developmental aspects of each condition. At this time, it was believed that gender was not established at birth, but that it was learned throughout childhood. Children were recommended to be reared in a clear gender role and for that role to be maintained throughout adult life. In the seminal article of the time, the authors stated: “truth is seldom as distressing as the mystery of the unknown,” and advocated full disclosure to parents and patients in an understandable and age-appropriate manner. Surgical correction to the expected gender role was favoured on the basis of the notion that it would stabilize the individual in an ‘optimal’ gender and diminish their embarrassment about the situation.

By the 1990s, there was increasing awareness of the mismanagement of individuals with intersex conditions. The famous ‘John–Joan’ case of a boy who lost his penis through surgery, was subsequently raised as a girl and then later changed gender again to live as a man14 led to the perception that prenatal androgens might influence gender development. Furthermore, management guidelines from

this time recognized the hazards of irreversible procedures, especially in young infants and children, in view of the unpredictable outcomes. To develop a more comprehensive approach to classify affected individuals, reproductive function, sexual function and overall phenotypic appearance of the genitals (following appropriate surgical and hormonal therapies) were taken into account to achieve an overall gender-appropriate appearance with appropriate gender role behaviour.15 As a consequence of the increased understanding of the biological aspects of gender, a number of studies have focused on gender role behaviour.16 The early effects of androgen action on the developing brain were found to
have a substantial effect on gender-related behaviour and development in early childhood. In 2003, a clinical evaluation study was initiated by the German Ministry for Research and Education, leading to a survey on management issues and health-related quality of life (HRQOL) in children, adolescents and adults with DSDs. Participants included 439 probands who underwent a psychosocial evaluation with standardized instruments and who agreed to a review of their previous DSD-specific medical data. In children, an overall reduction of HRQOL was reported, particularly in the areas of self-esteem and physical well-being; however, atypical gender role behaviour and genital surgery were not associated with HRQOL. Interestingly, in adolescents, no increased gender dysphoria was found, but difficulties in partnerships and sexual relationships were noted. In adults, dissatisfaction with previous genital surgery and their overall sex life, as well as sexual anxieties, were prevalent.

Currently, diagnosis, decision-making processes, prognosis with possible interventions and overall management of patients with DSDs is not optimal and needs to be improved. This situation has led to joint national recommendations that advocate the collaboration of several medical disciplines in the management of patients and their parents. However, the comprehension that individuals with DSDs challenge the binary understanding of male and female sex, together with new approaches and alternative ways of management, have neither been included in current guidelines nor implemented into clinical practice.

**Diagnosis**

Caring for patients with DSDs is now generally accepted to require a professional approach that involves a multidisciplinary team. This acceptance reflects the many facets of sex and gender development and the recognized need for a well-coordinated approach to diagnosis, disclosure and therapy. However, the age at presentation of a patient with a DSD can range from birth to late adolescence or even early adulthood, and referral pathways to the DSDs multidisciplinary team are not yet clearly defined. The lack of these pathways to effective management is a common problem for many complex rare diseases and this predicament has been actively discussed within the European Union and its member states via a European Committee of Experts on Rare Diseases (EUCERD). So far, EUCERD recommendations have resulted in the implementation of national plans for the creation of Centres of Expertise (CoEs) for many, if not all, rare diseases that occur within the member states of the European Union. CoEs are expert structures that provide specific levels of organization and collaboration for the management and care of patients with rare diseases in a defined vicinity, mostly on a national level, but also on an international level.

Of key importance is the ability to provide a multidisciplinary approach that integrates medical and other professional and social science disciplines (Figure 1). As patients who have DSDs should ideally be followed up throughout life, CoEs have to ensure the effective transition of care from childhood through adolescence to adulthood, and should be capable of providing care to all age groups and conditions. Specifically for DSDs, a protocol has been developed for the implementation of multidisciplinary teams with the correct set of tools to meet operational needs. The protocol includes recommendations for the formation and development of the team, the assessment of team capabilities and limitations, the visions and goals of the team and the overall functioning of the team. However, a shortfall exists between the need for comprehensive multidisciplinary DSDs teams and the tools and resources provided by health-care authorities to plan and implement the creation of these teams.

The availability of a multidisciplinary team is a prerequisite for the structured assessment of any patient with a DSD and the overall planning of diagnostic and therapeutic procedures (Figure 1). This model should facilitate the development of new standards of care in patients with DSDs and establish the basis for long-term surveillance and hopefully improved patient outcomes. Independent of whether DSDs are considered a disease or a variation, high quality diagnostic procedures are the foundation of improved care.

**Structured clinical investigation**

Currently, the clinical assessment of individuals with DSDs often focuses on the appearance of the genitals and uses the historic Prader classification or adaptations thereof. From the description of clinical features involving localization of the meatus urethrae, the size of the phallus and the localization of the gonads, an external masculinization

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Figure 1 | Composition of a team managing patients with disorders of sex development. The multidisciplinary team (blue circles) and its interactions are coordinated by a patient navigator (blue box) who contacts external specialists and institutions (yellow box) and manages communication between the disciplines and the patient. Peer counselling (green box) of the patient is an important component of the team.
Figure 2 | Evaluation of disorders of sex development by clinical, laboratory and genetic investigations. Diagnostic procedures should be done in a step-wise fashion. After a thorough clinical and imaging assessment, determination of the karyotype is mandatory. The verification of Müllerian structures leads to a clinical diagnosis and subsequently to laboratory analysis of defined analytes or biochemical profiles. For final verification, either targeted gene analysis or targeted next-generation sequencing approaches should be done before an untargeted analysis is performed. Abbreviations: CAH, congenital adrenal hyperplasia; CGH, comparative genomic hybridization; DHT, dihydrotestosterone; DSD, disorder of sex development; FISH, fluorescent in situ hybridization; FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; 17-OHP, 17-hydroxyprogesterone; SRY, sex-determining region Y protein.

score can be calculated. A new aspect that has been included in the clinical description of patients with DSDs is measurement of the anogenital distance as a manifestation of the effects of androgens during embryogenesis.

However, these assessments do not take into account overall and localized differentiation or changes that occur over time. In some patients, for instance, a hemiuterus, androgen-mediated development of the epididymis and external genital structures can develop asymmetrically as a consequence of disparate development of the testes (with unequal secretion of anti-Müllerian hormone in the testes).

With regard to the internal structures, the exact localization of the convergence of the vagina and urethra (not included in the Prader classification) is necessary for morphological evaluation and surgical prognosis. As a consequence, improved structured descriptions of genital variance are required and time-dependent postnatal changes need to be documented. In older children, adolescents and adults, a competent urological or gynaecological examination has to focus attention on accompanying dysmorphic features. The appearance of labio-scrotal folds and phallic structures should be assessed as well as the shape of pubic hair growth and its distribution according to Tanner stages as great variability exists even among healthy individuals. If present, the vaginal introitus should be inspected and both the vaginal and urethral length measured. The presence of prostatic tissue and a qualitative assessment of gonadal tissues needs to be documented, which requires the use of imaging techniques (predominantly ultrasonography and MRI) and possibly also endoscopic or laparoscopic assessments. Documentation of the phenotype is mandatory, but is often lost as no consensus on structured standardized documentation has yet been agreed upon. With knowledge of this variability, only preliminary advice about suitable diagnostic procedures for DSDs is available (Figure 2). Furthermore, the sex-dependent development of extra-genital structures, including the brain, has to be taken into account.

Endocrine evaluation

Laboratory investigations are still a hallmark for identification of the pathogenetic mechanisms underlying DSDs and the assessment of gonadal and adrenal function. Screening of newborn babies for the most common form of congenital adrenal hyperplasia (steroid 21-hydroxylase deficiency) by measuring levels of 17-hydroxyprogesterone has been introduced in many Western countries. This investigation enables early diagnosis (particularly in boys) and also provides a rapid diagnosis in 46,XX children who have androgenised
genitalia; however, every abnormal screening analysis needs to be independently confirmed. Currently, any determination of steroid levels in blood samples obtained from neonates and young children should be performed by liquid chromatography–tandem mass spectrometry (LC–MS/MS), as the commonly used antibody-based assays do not precisely discriminate between the many disorders of steroid metabolism.41 In the past 4 years, age-related reference intervals for LC–MS/MS-determined levels of sex steroids in healthy children have been published, thus facilitating further discrimination between abnormal hormone profiles.42-49 However, the laboratory determination of levels of sex steroids still poses problems in infants and children, as these measurements frequently require stimulation of the gonads with either human chorionic gonadotrophin or human menopausal gonadotrophin in order to obtain discriminatory values.50-53 Consequently, hormonal assessment of children who have DSDs should be performed in specialized laboratories that collaborate closely with a DSDs CoE.

In addition to serum or plasma analysis, urinary steroid analysis performed by use of gas chromatography–mass spectrometry has proved useful in the identification of several defects in sex steroid biosynthesis that are associated with DSDs.54 This technique can readily be used to diagnose 3-oxo-5α-steroid 4-dehydrogenase 2 (also known as steroid 5α-reductase 2) deficiency, even after gonadectomy, and further enables discrimination between several subtypes of congenital adrenal hyperplasia in a single urine sample without prior stimulation.55-56 Unfortunately, only a few laboratories can apply this methodology and have the necessary experience of diagnosing DSDs. The identification of alternative (so-called ‘backdoor’) pathways of dihydrotestosterone biosynthesis that bypass the classic route via androstenedione and testosterone is expected to increase complexity of the androgen metabolome of DSDs and to present new challenges for diagnostic laboratories.

In patients with a 46,XY DSD, determination of the levels of anti-Müllerian hormone has proved useful for diagnostic differentiation between gonadal dysgenesis and specific disorders of androgen synthesis or action.57-60 Similarly, analysis of another Sertoli cell marker, inhibin B, can be used to assess gonadal function in patients with DSDs.54,61

Over time, diagnostic tests have been developed that assess androgen function in individuals. This advance is considered important as the response to, or ineffectiveness of, androgens is perceived to be pivotal for gender assignment in children who have ambiguous genitalia. Furthermore, these tests were assumed to be the best option for detecting androgen insensitivity before the availability of diagnostic sequencing of the androgen receptor gene. The quantitative and qualitative assessment of androgen binding, however, requires the use of skin fibroblasts obtained from the genitals, which is currently deemed inappropriate. To alleviate this problem, biomarkers that can be measured in blood products are necessary. An in vivo androgen sensitivity test has been developed that can measure changes in the levels of sex hormone-binding globulin in response to the effects of anabolic steroids, correlating with the phenotype of androgen insensitivity syndrome.61-64 However, this test has limitations in certain genetic settings (such as mosaicism due to defined somatic mutations)65 and cannot be used during the first 6–8 months of life (the crucial time for diagnosis). Alternatively, determination of the levels of sex hormone-binding globulin can be used after stimulation with human chorionic gonadotrophin to detect androgen insensitivity, but this test has also not, as yet, been incorporated into general practice.66 Another protein, apolipoprotein D, has demonstrated diagnostic potential as a biomarker of androgen receptor-mediated transcription, but its possible usefulness is limited to the assessment of genital skin fibroblasts.67

Genetic diagnosis

Modern genetic techniques have transformed our understanding of the basis of many common and rare diseases, including DSDs.68 Genetic techniques that scan the whole genome (such as whole-genome sequencing) or at least the coding regions of the genome (whole-exome sequencing) can be used to study DSDs and have enabled the identification of both ‘new genes’ and novel mutations in previously known genes that are associated with an unpredictable phenotype.69-71 However, chromosomal rearrangements that are associated predominantly with syndromic DSDs might require a different approach. As these genetic techniques detect only a fraction of the causes of DSDs, several sensitive techniques (for example, high-resolution comparative genomic hybridisation72 and whole-exome sequencing with very high coverage) are required, as well as an experienced bioinformatician to evaluate the results. The current dilemma is the high variability of genetic causes, especially in 46,XY DSDs and, so far, the usefulness of genetic diagnosis for predicting outcomes is still unknown.

Even though modern genetic techniques are emerging as the most comprehensive diagnostic tools available, they have several limitations. Firstly, genetic techniques are not available in many developing countries for diagnostic purposes as of yet. Secondly, the overall sensitivity and specificity of the techniques is often unclear. Thirdly, the time frame to obtain robust results is measured in weeks rather than days.70 Furthermore, the underlying genetic basis of many 46,XY DSDs is unknown and it is possible that these disorders are primarily caused by epigenetic rather than genetic effects.71

At this time, genetic methods for the diagnosis of DSDs still include determination of the karyotype first, followed (on the basis of clinical and endocrine findings) by targeted genetic analysis of defined genes or, in the case of syndromic forms of DSDs, diagnostic array comparative genomic hybridization.25-77 Targeted parallel sequencing of a set of genes is expected to be used diagnostically in the very near future,74 although many technical and bioinformatic issues have to be solved first.

Management

Managing patients who have DSDs and their families is enormously challenging, owing to the diagnostic and ethical challenges presented by many patients (especially those with a 46,XY DSD) and the difficulty in
offering a precise prognosis for any individual patient. These issues have to be taken into account in any decision-making process and also in communication with the families. Modern concepts of the management of DSDs include the delineation of different choices to empower patients with DSDs and their families to consider their own fate and to evaluate their personal requirements, an approach that includes both biological and social aspects. At present, we have advanced only marginally from the original recommendations for the management of patients with DSDs.

The ethical dilemma in managing patients who have a DSD is a consequence of the conflict between the fundamental right of any child for physical integrity and self-determination, and the right of parents to care for their child in a way they perceive is in its best interest. Parental acceptance that DSDs are not a minor genital anomaly and that the life of a child will eventually differ considerably from the parents' expectations requires time, information and understanding.

Sex assignment

For some specific disorders, recommendations for sex assignment are made on the basis of the genetic diagnosis. This advice is founded mainly on the understanding of how an individual will develop at the time of puberty, but also includes aspects of future fertility. Accordingly, children with a 46,XY karyotype and steroid 21-hydroxylase deficiency are usually raised as female, even if severe virilization has occurred. Conversely, children with a 46,XX karyotype who have androgen deficiency (resulting from a deficiency of either testosterone 17β-hydroxysteroid dehydrogenase 3 or 5α-reductase 2) are usually raised as male, even if severe underandrogenization is evident. These decisions reflect the high potential for androgen synthesis via alternative pathways and the possibility that fertility might be preserved.

Uncertainty in this decision-making process is evident in case reports that describe siblings with identical mutations in testosterone 17β-hydroxysteroid dehydrogenase 3 who were assigned to opposite sexes. Children with a female phenotype and underlying 46,XY complete gonadal dysgenesis or complete androgen insensitivity are usually raised as female; however, a male gender identity has been reported in rare cases in these individuals.

At this time, no straightforward recommendations exist for sex assignment in neonates who have a DSD. To reflect this uncertainty, the German personal status law was changed in 2013 to enable sex assignment to be left open for any child with a DSD who has genital ambiguity. However, current advice still favours a 'social' assignment of sex in all children to protect and maintain the integrity of the family, even though this advice is being challenged by support groups and might be changed in future guidelines.

Surgical

The role of surgery in the management of patients with DSDs is changing, with the advocacy that any surgical intervention in neonates and infants that leads to irreversible changes should be done with the utmost caution. The right to physical integrity and self-determination requires informed consent and the value of these rights has been strengthened in the latest recommendations; parents also have the right to act in the best interest of their child. A moratorium on genital surgery has been proposed by advocacy groups; however, legal procedures have not commenced in most Western countries, where the issue is still being debated. A proposal to include feminizing surgery in the latest United Nations resolution to ban female genital mutilation has been intensely supported and existing practices are currently being debated in professional societies.

Ideally, surgical interventions should construct cosmetically appealing and well-functioning genitalia and preserve fertility in the best possible way. Although great progress has been made in this direction, this goal is still difficult to achieve and patients and parents can have unrealistic expectations. The surgeon has a particular responsibility to provide realistic and honest information about the possible outcomes of the surgery and many discussions with the parents and within the DSDs team might be necessary. Adolescents and adults with a DSD need qualified surgical advice to understand the risk-benefit ratio of their condition and the available surgical options for several reasons. Firstly, these individuals might intend to have sexual intercourse, which might or might not be possible after surgery. Secondly, the preservation or the removal of the gonads has to be discussed. Thirdly, the development of malignant germ cell tumours varies considerably between different DSDs and seems to depend not only on the genetic background of the disorder, but also on environmental factors.

In general, only individuals with a 46,XY DSD have an increased risk of tumour development. The risk of malignancy was previously assumed to be increased in all forms of 46,XY gonadal dysgenesis. However, the finding of a possible decreased risk of malignancy in patients carrying mutations in steroidogenic factor 1 (also known as nuclear receptor subfamily 5 group A member 1) that lead to steroidogenic factor 1 deficiency indicates that the risk of malignancy in gonadal dysgenesis might be dependent on the underlying genetic abnormality. In patients with CAIS, the gonads are frequently retained during and even after puberty, thereby enabling in vivo testosterone synthesis and thus avoiding the necessity of hormonal supplementation. However, estimates indicate an increased risk of gonadal tumours in women with CAIS throughout their lifetime and, therefore, a structured prevention programme needs to be established.

Beyond any doubt, surgical efforts to 'cure' patients with DSDs have been detrimental to many individuals in the past. Surgeons have always tried to offer the best possible care but, in retrospect, this care has not been satisfactory for many individuals with a DSD who have complained forcefully about the surgical procedures used. While surgery offers many valuable options, ranging from vaginoplasty to phalloplasty, and more long-term data is now available, informed consent and realistic expectations are of the utmost importance for patients with
DSDs who are contemplating or undergoing surgery. With growing awareness on both sides, a reconciliation between medical professionals and the many individuals with DSDs who feel damaged by the treatments they received is underway.

**Endocrine**

Although most patients who have DSDs will require hormone therapy at some point during their lifetime, treatment during infancy and childhood must be deemed to be critical, as hormone therapy induces irreversible effects similar to those of any surgical intervention. At the time of expected puberty, children need to be informed about their options for hormone therapy, as delayed pubertal development is associated with reduced acceptance of the DSD. Any medical intervention requires patients to be fully informed about the diagnosis and possible outcomes of endocrine interventions. Refusal of hormone substitution by a patient needs to be discussed, as the procedure is regarded as critical in preventing adverse events, including those that affect bone health. In adolescents who first come to medical attention with their DSD as a result of abnormal pubertal development, the use of gonadotropin-releasing hormone analogues to delay puberty might be necessary for a limited time to permit complete diagnosis and optimal decision making, before any further intervention is justified.

Hormonal induction of puberty is usually performed according to the current practices used for adolescents with pituitary or gonadal failure. Clinical studies of hormonal induction of puberty in patients with DSDs have not been conducted, with the exception of an ongoing clinical trial comparing estrogen treatment with testosterone treatment in gynecomastia women who have CAAIS. A German study of patients with DSDs has shown that although hormone therapy is initiated at a variable age, its overall outcome has not been evaluated in detail. Currently, a European-wide study is addressing the overall effect of medical treatments and simultaneously assessing HRQOL in patients with DSDs.

**Conclusions and recommendations**

Much progress has been made in improving the accuracy of DSD diagnoses and increasing awareness of the unique situation of individuals with DSDs and their families. These advances are of enormous importance, as previously most individuals with DSDs did not receive a diagnosis and many of the current controversies surrounding the management of patients with DSDs are a consequence of this failure. Solving these past problems requires the implementation of evidence-based care.

Improvements in the care of patients with DSDs can be expected from multidisciplinary teams working in qualified centres and adopting the best diagnostic and management processes. The need for multidisciplinary teams to care for patients with DSDs and their families seems to be widely accepted; however, their implementation, qualitative assessment and fundamental financial structure have yet to be defined. National laws and policies are needed to allocate the necessary resources to manage patients who have DSDs. Ideally, these multidisciplinary teams should be part of CoEs for rare diseases and together they would form an international network, which would implement guidelines, conduct clinical research studies and participate in a benchmarking process (as described in the EUERD recommendations). Additionally, all patients should be registered and tracked in the international I-DSD database, thereby enabling follow-up of individuals to be documented and facilitating clinical studies.

Further diagnostic progress might be made with the clinical application of modern genetic techniques, which will probably involve massive parallel sequencing of a variety of known genes in any individual with a DSD (Figure 2). However, true advances can only be made if the obtained genomics data are comparable and interchangeable on shared bioinformatic platforms, ideally associated with the I-DSD database. Furthermore, genetic findings have to be combined with metabolic data to enable an overall integration of approaches to be used as the basis of personalized care. Whether or not identified gene expression profiles can serve as individual biomarkers of sex development both prenatally and over a lifetime needs to be investigated. These studies might provide a better understanding of genotype–phenotype correlations and the estimated risk of germ cell malignancy in individuals with DSDs, thereby reducing the number of unnecessary gonadectomies. If genital surgery is postponed, techniques to obtain reliable results in adolescents have to be refined.

However, even with advances in medical care, the social challenges of dealing with DSDs need to be strongly emphasized. General societal acceptance of variations of sex development must be promoted by DSDs teams with the assistance of qualified peer groups in order to advance medical progress where needed and to reduce discrimination against individuals with DSDs. Integrating additional peer support into the model of care is of the utmost importance (Figure 1). This inclusion will strengthen the acceptance of DSDs and facilitate the sharing of experiences, thereby reducing the stress and isolation felt by patients and their families. Although support of patients is provided via modern media (such as online support), it should also be provided in person, ideally involving trained semi-professional therapists. Only if all these issues are resolved will real improvements in the management of patients with DSDs be achieved.

**Review criteria**

The authors searched PubMed for full-text English-language articles using the following search terms: “DSD and genetics”, “management of DSD”, as well as specific disorder groups such as “gonadal dysgenesis”. The cited articles were mostly publications after 2010. Further articles were identified from the reference lists of selected review articles. Web-based information was selected after general searches using the following keywords: “disorder of sex development”, “centre of excellence” and “rare diseases”.
34. Krone, N. et al. Gas chromatography/mass spectrometry (GC/MS) remains a pre-eminent discovery tool in clinical steroid investigations even in the era of fast liquid chromatography.


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