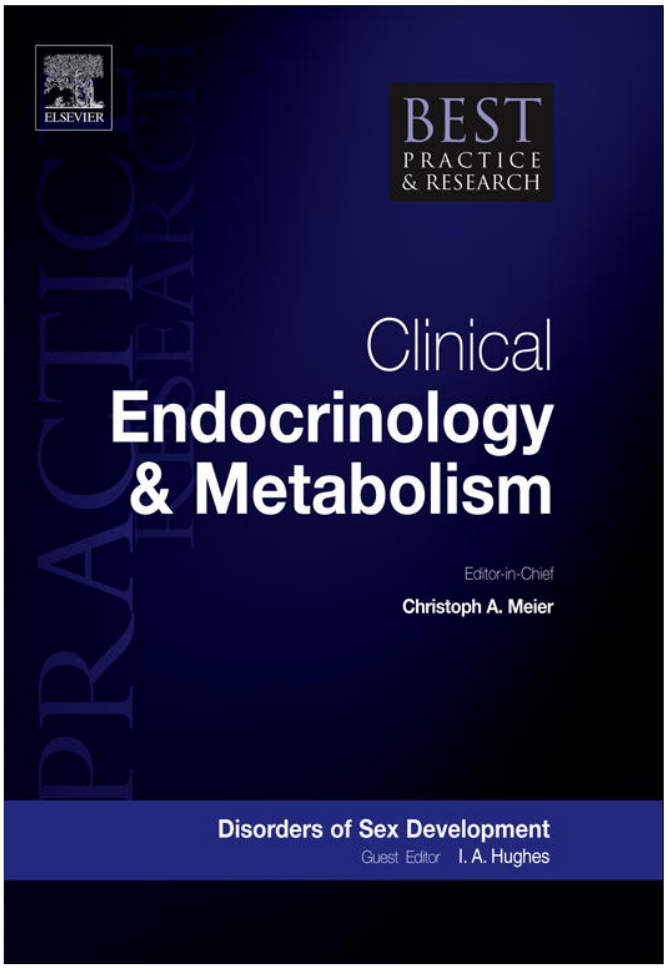

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3

Impact of the consensus statement and the new DSD classification system

V. Pasterski, PhD, Research Psychologist [a,*], P. Prentice, BA, MBChir, ST2 Paediatrics [b], I.A. Hughes, MD, FRCP, FRCPCH, F. Med. Sci., Professor of Paediatrics, Head of Department [a]

[a] *Department of Paediatrics, Addenbrooke's Hospital, University of Cambridge, Level 8, Box 116, Hills Road, Cambridge, CB2 0QQ, UK*
[b] *Whittington Hospital, University College London, London, UK*

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In 2006, a task force of 50 specialists sponsored by the European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES) devised a Consensus Statement outlining the recommendations for the management of disorders of sex development (DSDs; then referred to as 'intersex' disorders) as well as proposing a new nomenclature and DSD classification system. In the 2 years subsequent to its publication, the Statement has been widely cited and endorsed in the literature as a model for patient care. In addition, much of the scientific literature incorporates the newly proposed nomenclature and classification system as part of its own discourse. However, without a systematic analysis of the uptake of recommendations of the Statement, it is not possible to make valid conclusions regarding the uptake of the recommendations within clinical practice. Here we discuss the Consensus Statement and its impact with respect to the newly proposed nomenclature and psychosocial management according to a new study following 60 DSD centres throughout Europe. Finally, we discuss future directions for research in the management of DSD, beginning at the moment of disclosure.

One in 4500 infants is born with abnormalities of the external genitalia.[1] Detection of the abnormality is usually immediate and sets in motion a cascade of event s beginning with diagnostic evaluations and disclosure of intersexual status to the expectant parents. Such episodes are often

* Corresponding author. Tel.: +44 1223 767 183; Fax: +44 (0) 1223 336996.
E-mail address: vp265@medschl.cam.ac.uk (V. Pasterski).

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experienced as distressing for affected families and the burden of lessening the distress falls to the multidisciplinary management team. Advancements in treatment protocols in recent decades, as in the case of congenital adrenal hyperplasia (CAH)[2], have led to improved patient outcomes; however, dissatisfaction has remained with case management, including questions regarding decisions of gender assignment, the need for and timing of surgical interventions as well as issues concerning disclosure/consent. Further discontent has been expressed with respect to what many consider an insensitive and antiquated nomenclature. The call for improvements has come largely from patient advocacy groups together with affected families and has resulted thus far in a *Clinical Guidelines and Handbook for Parents,* produced in conjunction by health professionals and support groups (available online at http://www.dsdguidelines.org). A further response comes from professional societies representing paediatric endocrinology. The European Society for Paediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES) jointly organised a meeting to address overall management concerns. The result was the Chicago Consensus on the management of intersex disorders, and has been published as guidelines encompassing management from birth to adulthood.[3–5]

The Consensus and its impact

Consensus statement

The purpose of a consensus statement, in general, is to offer clearly defined guidelines representing the 'best fit' of ideas from leaders in a particular field. In the case of the Consensus on Management of Intersex Disorders[3,4], the drive was to provide current and comprehensive structure for the treatment of disorders which have historically been controversial, and to overhaul an outdated and insensitive nomenclature. Endocrinologists, surgeons, geneticists, psychologists and patient advocacy group members representing a world community drafted a statement in which they outlined ideals for patient care. Such concepts as diagnostic evaluation, gender assignment, surgical management, sex steroid replacement and psychosocial management received due attention. Briefly, the recommendations of the statement were:

- Use of nomenclature specific to DSD should be revised to reflect careful consideration of the concerns of patients (a new nomenclature has been proposed, Hughes et al., 2006).
- Evaluation and long-term management must be carried out at a centre with an experienced multidisciplinary team.
- Gender assignment must be avoided before expert evaluation in newborns.
- All individuals should receive a gender assignment once appropriate expert evaluations have been carried out.
- Only surgeons with expertise in the care of children and specific training in the surgery of DSD should undertake surgical procedures.
- In cases of virilised females, surgery should only be considered in cases of severe virilisation and should be carried out in conjunction, when appropriate, with repair of the common urogenital sinus.
- Emphasis of surgical intervention in all cases should be on functional outcome rather than strictly on cosmetic appearance.
- Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management to promote positive adaptation for the patient.
- Open communication with patients and families is essential and participation in decision making is encouraged.
- Patient and family concerns should be respected and addressed in strict confidence.

Clearly, the task force charged with developing the guidelines have mostly agreed with the recommendations put forward in the statement, though we should note that the consensus, as with most others, was a majority rather than 100%. Furthermore, numerous subsequent reports in the

literature not only have cited the Consensus Statement as a guide for management, but have also embraced the proposed nomenclature. While this is evidence, on a basic level, of the recognition of the statement, without systematic evaluation, the impact of any consensus statement is unclear and the usefulness of its recommendations undetermined. In this particular case, however, a follow-up study[6] has been conducted assessing current practice in 60 DSD centres spanning 23 European countries. Here we review the Consensus Statement and its impact on clinical practice.

Nomenclature and classification

Owing to the recognition that the then-current nomenclature and labels surrounding intersex conditions were found to be confusing and stigmatising, participants of the consensus meeting set out to adopt a new nomenclature and classification system. 'Intersex' was replaced by a more general and descriptive term, 'disorders of sex development' (DSDs), which refers to congenital conditions in which chromosomal, gonadal or anatomical sex development is atypical. Terms such as 'hermaphrodite' and gender-based diagnostic labels have been replaced with clinically descriptive terms, for example, androgen-insensitivity syndrome or terms derived from the aetiology, for example, 5-alpha-reductase deficiency.

The historical term 'intersex' has been used as a classification primarily to describe the clinical case of an infant whose external genitalia are ambiguous to the degree where clear sex assignment is not possible. However, this classification system introduces a degree of confusion with variance in phenotypic expression of the conditions. For example, the commonest cause of ambiguous genitalia in female (46, XX) infants is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. The result is an over-production of androgen and subsequent virilisation. However, not all cases of CAH result in ambiguous genitalia. Furthermore, total under-virilisation in a male (46, XY) infant, as with complete androgen insensitivity syndrome (CAIS), results in a normal female-appearing phenotype. Both cases of unambiguous genitalia are within the range of presentation, but not clearly subsumed, by the category of 'intersex' conditions. Consequently, the term 'disorder of sex development' (DSD) was proposed to replace the umbrella term in the existing nomenclature. This term is not, in itself, specifically descriptive; rather, it is a global term which broadly encompasses a proposed classification system.

The new nomenclature and the new classification system were largely developed in parallel, though the motivations for the two derive from differing sources. The impetus for revising the terminology itself emanated from affected families and patient advocacy groups; while specialists in the field recognised that a new classification system was overdue and that changes needed to reflect scientific advancements in diagnostic procedures. New techniques such as microarray, comparative genomic hybridisation (CGH) and tissue-selective disruption of candidate genes have been employed to uncover genetic mutations leading to DSD. This allows for a clearer and more accurate classification system. The umbrella term DSD comprises three further classifications, 46,XY DSD; 46,XX DSD and chromosomal DSD, which replace previous classifications such as 'hermaphrodite' and 'pseudo-hermaphrodite'. These terms were considered by many to be pejorative to patients and scientifically meaningless to practitioners. Furthermore, the new classification reflects the role of karyotype in diagnostic evaluations and analyses and the role of sex chromosomes as a starting point for investigations. Table 1 summarises the replacement nomenclature and Table 2 applies the nomenclature in the context of diagnostic categories.

Though it appears that most have been in favour of removing the term 'intersex' from the medical lexicon, some have expressed concern over the use of the word 'disorder' in the DSD title.[7,8] As an example, 'variations of reproductive development' was suggested as an alternative to DSD since some affected individuals are normal in appearance, for example, the female phenotype of an individual with CAIS. However, many of these conditions can be traced to gene mutations causing pathophysiological consequences. For example, the mutation in CYP21 causes 21-hydroxylase deficiency and CAH. This is not dissimilar to other commonly recognised diseases such as sickle cell disease or cystic fibrosis. These are therefore not variations in normal function but abnormally affect physiology, whether by disrupting steroidogenesis or blocking receptor function. As with all of medicine, it is of vital importance to remember that patients are individual people who happen to have a disease or disorder, rather than a person intertwined with or defined by the disorder. Nevertheless, from a medical perspective these conditions represent an abnormal pathophysiology, rather than simple variations within the normal

Table 1
Nomenclature relating to disorders of sex development (DSD).

Previous	Proposed
Intersex	Disorders of sex development (DSDs)
Male pseudohermaphrodite Undervirilization of an XY male Undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite Overvirilization of an XX female Masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

range and should be considered as such. Clinical management depends in large part on an accurate and comprehensive diagnostic terminology.

Criticisms withstanding, the new nomenclature and classification appear to be gaining ground in the scientific literature, whether the focus is psychosocial, genetic or gonadal[9–11], in standard endocrine textbooks[1,12] and in discourse among specialists.[6] Perhaps most telling with respect to the impact of the new classification is the result from the recent follow-up.[6] As part of the survey, respondents were asked to indicate which diagnostic terms were used with regularity in their centre. Results indicated almost universal usage and satisfaction with the revised medical lexicon. As supporting evidence, the same report[6] presented an audit of the scientific literature starting from 2 years prior to the Consensus Statement through 2 years after. There appears to have been a significant reduction in the use of historical terminology and a significant increase in the use of the new nomenclature. In addition, while the use of terms such as 'undervirilisation' and 'sex reversal' was still common in the literature, the terms were used as course descriptors and not as diagnoses. These two sources, the survey of practitioners and review of the literature, present evidence that health professionals involved in the management of families with DSD are moving towards a universal language of communication.

One final note on classification bears consideration. While the uptake of the new nomenclature appears to be almost universal, the taxonomic classification system has met with some dispute. The Consensus Statement specifies 46,XY DSD; 46,XX DSD; and chromosomal DSD as subcategories, with the latter subcategory set aside for disorders of chromosomal sex.[3–5] The recently published coding system produced by ESPE assigns Turner Syndrome (TS) to *Disorders of gonadal differentiation classified elsewhere*.[13] The reason for this is unclear given that ESPE were present at the Chicago Consensus meetings. Clearly, this disconnect will need resolution. TS represents one of the largest cohorts of patients treated in DSD settings. Practically, this suggests that inclusion within the umbrella of DSD is useful at least in terms of application of guidelines recommended in the Consensus Statement.

Psychosocial management

The Consensus clearly designates the need for psychosocial support as crucial to team management for DSD, recognising that diagnosis and medical intervention is not the sole focus of treatment. The Consensus recognises further that the depth of the support will be variable across cases. In the early neonatal period, critical decisions will be made including judgements about gender assignment and the timing and extent of surgical intervention. Parents are extremely vulnerable at this stage with heightened anxieties and desperation for solutions. Compounding the problem, in some cases, is the diagnosis of a DSD within the context of unstable familial relations. In this case, psychological support services should go beyond advising on psychosocial outcome in DSD and focus on immediate coping strategies and improved communications between medical staff and families. Further to the recommendations of the Consensus Statement, a system for identifying families at risk of added distress has been suggested.[14]

Table 2
Proposed classification of causes of disorders of sex development (DSDs).

Sex chromosome DSD	46,XY DSD	46,XX DSD
A: 47,XXY (Klinefelter syndrome and variants) B: 45,X (Turner syndrome and variants) C: 45,X/46,XY (mixed gonadal dysgenesis) D: 46,XX/46,XY (chimerism)	A: Disorders of gonadal (testicular) development 1. Complete or partial gonadal dysgenesis (e.g. SRY, SOX9, SFI, WT1, DHH etc) 2. Ovotesticular DSD 3. Testis regression	A: Disorders of gonadal (ovarian) development 1. Gonadal dysgenesis 2. Ovotesticular DSD 3. Testicular DSD (e.g. SRY+, dup SOX9, RSP01)
	B: Disorders in androgen synthesis or action 1. Disorders of androgen synthesis a. LH receptor mutations b. Smith-Lemli-Opitz syndrome c. Steroidogenic acute regulatory protein mutations d. Cholesterol side-chain cleavage (CYP11A1) e. 3 β-hydroxysteroid dehydrogenase 2 (HSD3B2) f. 17 β-hydroxysteroid dehydrogenase (HSD17B3) g. 5 α-reductase 2 (SRD5A2) 2. Disorders of androgen action a. Androgen insensitivity syndrome b. Drugs and environmental modulators	B: Androgen excess 1. Fetal a. 3 β-hydroxysteroid dehydrogenase 2 (HSD3B2) b. 21-hydroxylase (CYP21A2) c. P450 oxidoreductase (POR) d. 11 β-hydroxylase (CYP11B1) e. Glucocorticoid receptor mutations 2. Fetoplacental a. Aromatase deficiency (CYP19) b. Oxidoreductase deficiency (POR) 3. Maternal a. Maternal virilizing tumours (e.g. luteomas) b. androgenic drugs
	C: Other 1. Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog, Hand-Foot-Genital, popliteal pterygium) 2. Persistent Müllerian duct syndrome 3. Vanishing testis syndrome 4. Isolated hypospadias (CXorf6) 5. Congenital hypogonadotropic hypogonadism 6. Cryptorchidism (INSL3, GREAT) 7. Environmental influences	C: Other 1. Syndromic associations (e.g. cloacal anomalies) 2. Müllerian agenesis/hypoplasia (e.g. MURCS) 3. Uterine abnormalities (e.g. MODY5) 4. Vaginal atresis (e.g. KcKusick-Kaufman) 5. Labial adhesions

According the follow-up study of practices in Europe[6], the call for increased psychological support for DSD patients and their families has largely been answered. Only three centres out of the 60 surveyed reported that this service was currently not available. That is, approximately 95% of centres reported to offer support from a child psychiatrist or paediatric psychologist for newly diagnosed cases. This clearly is a remarkable advancement in the psychosocial management of DSD.

With respect to gender assignment and psychosocial outcome, the apperception of gender as a fundamental component of one's integrity and identity necessitates the most comprehensive evaluation of the outcome literature, which should then be incorporated within the context of individual families. It is clear that conclusive outcome data are sparse, but the literature is growing at a pace that is starting to allow for greater accuracy in identifying future concerns. Of paramount

importance is the consideration of pre- and neo-natal events influencing the development of gender-related constituents of behaviour, that is, gender role behaviour and gender identity. The optimal outcome in cases of gender assignment is a child whose behaviour and identity are in line with the assigned sex. The authors of the Consensus Statement were careful in acknowledging that cross-gender behaviour in a child with DSD does not constitute gender dissatisfaction. To be sure, the extant literature suggests that gender role behaviour and gender identity are likely affected by differing underlying mechanisms and/or critical periods of neural development.[15] With respect to gender-related psychological distress, gender identity appears to the most critical component. That is, cross-gender role behaviour, and later, sexual orientation, enjoy much greater within-sex variance than gender identity. Ultimately, as the developmental mechanisms are not fully understood, the outcome literature is the clearest guide in making decisions about gender assignment in the newborn infant.

In clinical practice, compared with widely agreed upon recommendations, we may glimpse the truth, again, referring to the European follow-up study which also reports on psychological support specialised for DSD.[6] The authors asked centres about the inclusion of psychological services historically and particularly in cases of gender assignment and reassignment. Of the 60 centres surveyed, approximately two-thirds reported the inclusion of a psychologist specialising in DSD in the critical gender-assignment decision-making process. Interestingly, the report also suggests that, while 100% of the parents who were charged with the daunting process of gender assignment were offered psychological support, only about 80% took advantage of the proposed service. While the reasons for this discrepancy are not entirely clear, it is possible that the emotionally charged nature of the process may make it difficult for parents to integrate fully various components of their circumstances. Further, the prospect of involving additional specialists in the process may be overwhelming.

Disclosure

In the context of a DSD diagnosis, the information conveyed to parents and families in the first hours after the birth of the infant will be imprinted on their minds for years to come. It is of utmost importance for health-care specialists to bear this in mind. Clinical impression suggests that not only do parents look to the management team as the primary source of information and advice, but also for support and coping strategies. An alarmed or confused response by the health-care staff may be extremely unsettling to families of newly diagnosed DSD infants and can change entirely the family's experience of the disorder. Likewise, clear, calm and consistent communication may instil a sense of calmness to the parents. Disclosure conditions must also be considered separately. Parent or health-care staff disclosure to the child requires considerations apart from those of disclosure to the parents of the child. With respect to the child, the Consensus recommends disclosure of karyotype, gonadal status and infertility with the view that information, together with psychosocial support, allows the child to integrate the information into his/her sense of self.

Few studies to date have addressed the issue of disclosure in DSD and those which have been published have been retrospective patient reports of satisfaction with the process. While this is a useful starting point, it is difficult, using patient reports, to point to specific features of the process which may have beneficial or detrimental effects. An obvious confound in this approach is memory bias and inaccuracy. In these studies, patients and parents of patients have often reported on events that took place years earlier and within the context high emotional arousal. Furthermore, it is not possible to corroborate reports on the details of the process of disclosure that took place.

Historically, the debate regarding disclosure of medical information has been concerned with whether or not disclosure should take place. From a paternalistic view, the goal has been for the patient to remain insulated from shock and despair subsequent to learning his/her circumstance. In recent years, however, this approach has largely been abandoned in favour of partial or full disclosure, likely due to widespread availability of information in the media and on the Internet. Initially, the question was whether or not to disclose. More relevant in the current climate is the consideration of specific conditions of disclosure, that is, how and when to disclose.

The three existing studies of disclosure in DSD briefly address both conditions. The question of whether or not to disclose a diagnosis to a child/adolescent/adult patient has been the topic of two studies of parents and their daughters who have TS[16,17], and the topic of many papers.[18–20] One further

study reports on parents' and patients' reactions to learning about a diagnosis of Androgen Insensitivity Syndrome (AIS).[21] The authors of all three studies conclude, and most participants agreed, that full disclosure, conducted appropriately, is the optimal approach. Furthermore, negative effects of non-disclosure or secret-keeping behaviours by parents, have been linked to their own negative experiences with health-care providers.[16] Parents who kept all or part of their daughter's diagnosis secret were more likely to be dissatisfied with disclosure they themselves received. In this case, disclosure that took place between the health-care professional and the parents directly affected the patients' experiences of secrecy associated with being affected.

Given the paucity of studies of disclosure in DSD, we may turn to other models for a more comprehensive appraisal of the process of disclosure. The best fit appears to be the two cases of adoption and donor conception where parents are faced with informing their child that s/he is genetically unrelated to both parents. While adopted and donor-conceived individuals are not learning of a potential life-long disability, in both cases the disclosure information pertains to the essence of identity. These children are different to other children in a fundamental way much like children with DSD.

The extant adoption literature demonstrates that full disclosure, and as early as possible, is the best policy. Children are believed to fare better given the chance to integrate adoption status within the sense of self. Conversely, studies of donor conception suggest that many parents are not in favour of disclosure.[22,23] One of the most recent studies reports that as many as 43% of parents indicated they would never tell their donor-conceived child of his/her status.[23] Reasons cited include that 'disclosure is not necessary' or that 'disclosure may damage family relationships'.

Together with the three studies of DSD, these studies suggest that disclosure of fundamental and potentially stigmatising information is a difficult process and must be considered carefully. There is evidence of negative effects of non-disclosure; however, the process by which disclosure does, or should, take place has not been investigated. Current investigations are under way and we anticipate that these studies will not only elucidate a process which has never been fully recorded or reported, but will also provide a basis for establishing a protocol to formally guide the process. There, very likely, is an optimal pace and order to the process. The classic case in DSD, for example, is how and when does one disclose karyotype status to a young CAIS patient? While opinions abound, systematic evaluation should inform an established protocol.

Disclosure is of great concern to the parents of a DSD child, both in terms of their own experience in learning of the child's condition and in conveying the information to the child in due course. Considering the patient and family in a holistic framework, which incorporates the psychological and emotional needs of the child and family, is at the heart of the Consensus Statement. While we may use common sense and borrow from the literature in similar cases, we still do not know the extent of the effects of timing and manner of disclosure on patients and families. It is our intention to elucidate such nuanced effects.

Summary

In sum a consensus statement which professes above and beyond the most recent literature review provides valuable guidance for the scientist and practitioner alike. A brief scan of the current DSD literature suggests that the 'Consensus Statement for the Management of Intersex Disorders' is highly regarded as a clinical guideline. However, we now know that, beyond endorsement of ideas as a matter of scientific discourse, it appears that practitioners have put into practice the Statement's recommendations. Psychologists have been employed, not only to assess potential psychosocial/psychosexual outcomes, but also to offer immediate support to families in distress. Furthermore, and perhaps the most remarkable product of the Statement, is the complete overhaul and adoption of a new medical lexicon pertaining to DSD. Such a rapid uptake is unparalleled in clinical medicine. Finally, as the protocol for case management becomes a part of routine practice, it seems appropriate to turn to the meta-cognitive task of assessing how we think about and disclose the diagnosis of DSD to patients and their families in the earliest stages of interaction. To explicate the process and incorporate a best practices protocol should be a new focus for improving patient care.

Practice points

- Evaluation and long-term management must be carried out at a centre with an experienced multidisciplinary team.
- Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management to promote positive adaptation for the patient.
- Open communication with patients and families is essential and participation in decision making in encouraged.
- Patient and family concerns should be respected and addressed in strict confidence.

Research agenda

- Research should be conducted to devise appropriate disclosure strategies for parents and for child patients as they develop both emotionally and psychologically.

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