Disorders of Sex Development (DSD): Networking and Standardization Considerations

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Abstract

Syndromes resulting in Disorders of Sex Development (DSD) are individually rare. Historically, this fact has hindered both clinical research and the delivery of evidence-based care. Recognizing the need for advancement, members of European and North American medical societies produced policy statements, notably the Consensus Statement on Management of Intersex Disorders, which recognize that optimal healthcare in DSD requires multidisciplinary teams in conjunction with networking of treatment centers and continued development of patient registries. This paper summarizes efforts in Europe and the U.S. toward creating networks focused on expanding discovery and improving healthcare and quality of life outcomes in DSD. The objectives and function of registry-based networks (EuroDSD/I-DSD), learning collaboratives (DSD-net), clinical outcomes research (DSD-Life), and networking hybrids (DSD-TRN) are reviewed. Opportunities for, and barriers to standardization in research and care are highlighted in light of practical considerations, for example, limitations in reliably classifying anatomic phenotypes and gaps in behavioral health staffing resources. The role of patient-reported outcomes is considered, with emphasis on integrating patient perspectives, given findings of limited agreement in outcome ratings by healthcare providers and patients. Finally, the characteristics of clinical centers likely to deliver the highest quality outcomes are discussed.

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Bibliography
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Introduction

Disorders of Sex Development (DSD) are prevalent in the aggregate but individually rare a fact that has hindered the conduct of clinical research and the delivery of evidence-based care. The Consensus Statement on Management of Intersex Disorders [1] (hereafter referred to as the Consensus) recognized that optimal healthcare services for people affected with DSD requires a broad range of expertise typically found only at tertiary healthcare centers.

General principles in the clinical management of patients with rare diseases have been extended to the creation of multidisciplinary healthcare teams specific to DSD [2]. The current review summarizes efforts in Europe and in the U.S. toward creating networks focusing on comprehensive healthcare delivery and outcomes in DSD. There are different examples of networking initiatives; all share the goal of extending discovery of the mechanisms and processes involved in the pathophysiology of DSD (medical or psychosocial). Variability from one initiative to the other is possibly most readily discerned when it comes to translation of research (basic and clinical) into ongoing clinical practice.

This review also addresses the topic of standardization in DSD. Standardization is critical to scientists in the discovery of generalizable evidence. The importance of standardization is not diminished when it comes to the translation of scientific discovery to patient care. Unfortunately, the rapid pace of medical science and technology has frequently overtaken the capacity of healthcare systems to reliably integrate such advances. Improvement in the quality and safety of healthcare, whether in DSD or other conditions, implies that variability driven by specialty or individual provider preferences, independent of patient presentation, is replaced by evidence-based care tailored to patient needs and values [3]. The formation of networks in DSD entails adoption of common terminologies, increased reliability in descriptions of biochemical and anatomic phenotypes, and narrowing of variability in the

delivery of care that is not directly tied to the patient's presentation or needs. Standardization of terminology and procedures is an essential component of quality improvement in healthcare delivery leading to improved outcomes.

Networking

The earliest European DSD networks (Germany, www.netzwerk-is.de; Scotland, www.sdsd.scot.nhs.uk) were formed over a decade ago. Recognizing the importance of this approach, the Consensus encouraged continued development of multi-site collaborations and patient registries [1]. Single site efforts are inherently incomplete due to limited numbers of patients with discrete conditions, the range of factors assessed because of local expertise and scarcity of infrastructure to enable adequately powered prospective studies. **Table 1** provides an overview of European and U.S. networks and collaborations focusing on DSD.

EuroDSD and I-DSD (www.i-dsd.org)

With initial support from the European Society for Paediatric Endocrinology (ESPE), a web-based registry was developed to facilitate collaborative research projects (www.eurodsd.com). This organization is currently the International DSD (I-DSD) Registry, promoting research on the biochemical and genetic characteristics of DSD. In its present form, the registry does not capture on-going clinical management nor incorporate psychosocial data. It is also unknown how representative cases in the registry are of the total population of patients with the same condition seen at referring sites [4]. These shortcomings notwithstanding, I-DSD has proven itself an effective platform for researching questions that can only be answered through creation of a patient registry [5,6]. The registry is open to researchers and clinicians who can apply to analyze data and/or enroll patients. I-DSD serves the role of a virtual network facilitating collaboration among healthcare centers and specialists and forms the backbone of initiatives such as DSD-Life and DSDnet (**Table 1**). Beginning in 2015, registered participants (and their legal guardians) will be able to access aspects of their personal record via a secure login.

DSD-Life (www.dsd-life.eu)

DSD-Life assesses the influences of clinical care strategies and decision-making on long-term health-related quality of life outcomes by conducting a set of uniform physical and psychological assessments on affected people (16 years or older), across the full range of DSD diagnoses. The evaluation includes a physician-completed medical questionnaire, details of the surgical history, hormone therapies and psychosocial counseling. Participants also receive a physical exam accompanied by hormonal and metabolic testing. Finally, psychosexual development and psychosocial adaption are assessed by standardized questionnaires completed online. With participant informed consent, DSD-Life data will be added to the I-DSD registry and, thereby, greatly expand the breadth of information available for secondary data analysis.

The scope of this investigation, both in terms of the number of participants (≥1 500) and range of variables assessed makes DSD-Life a very ambitious project. Patient reports regarding events prior to age 16 are based on recall. Also, the study does not include the reports of parents close in time to when decisions, some irreversible, are made regarding clinical management, nor does it assess the attitudes, beliefs and preferences contributing to parenting decisions and their influences on subsequent parenting strategies. Assuming that any clinical decision is associated with variability in outcomes, studying early interactions between parents and the child's healthcare providers, or between parents and their child as they mature, creates the opportunity to examine factors that mediate or moderate outcomes within diagnostic groups [7].

Table 1 Major DSD networks and collaborations.

Name	Founding year	Number of Sites/ Location	Funding source	Structure	Specific characteristics
I-DSD (EuroDSD until 2011)	2008	33 Across 4 continents	UK Medical Research Council (I-DSD) European Commission (EuroDSD)	Patient registry	– No restrictions on inclusion: patients of all ages, no defined length of time between initial presentation or diagnosis and entry into the registry – Cross-sectional data (genetic, biochemical and phenotypic – no psychosocial data)
DSD-Life	2012	15 Europe only	European Commission	Clinical outcomes research	– Patients aged 16 year or older – Study recruitment at each participating site as well as through DSD patient support organizations – Medical and surgical history review, physical exam, and hormonal and psychosocial assessment – Potentially supplements I-DSD registry with psychosocial data, with patient/parent assent/consent
DSD-TRN	2012	7 US only	National Institute of Child Health and Human Development, NIH	Learning collaborative/quality improvement intervention patient registry and biobank	– Guide diagnosis and ongoing clinical management (medical, surgical, and psychosocial) via standardized clinical forms – All patients receive single standard of clinical care regardless of participation in registry – Inclusion in registry restricted to <18 years at initial clinical encounter
DSD-net	2013	28 19 European and 9 International Partners	European Cooperation in Science and Technology (COST)	Learning collaborative	– Five work groups cover broad range of topics (from standardization of clinical phenotyping, genetics and laboratory assessment to perceptions of research and dissemination) – Sharing knowledge, promoting research, improving care

DSD-net (www.dsdnet.eu)

An example of a DSD learning collaborative is the recently created DSD-net. Collaborative learning is an educational method where 2 or more participants or organizations work together to acquire skills or achieve an outcome. Key in this process is that participants are responsible for one another's learning as well as their own. DSD-net (a project under the framework for European Cooperation in Science and Technology, COST) links researchers from a broad range of specialties to encourage exchange of ideas and methods to promote harmonization of research, diagnostic and clinical management strategies. The network plans to achieve its objectives by organizing international workshops, researcher-industry round tables, visits of junior faculty to established clinical and research programs, and workshops for advocacy groups.

DSD-TRN (dsdtrn.genetics.ucla.edu)

The DSD-Translational Research Network represents a hybrid of a learning collaborative and DSD patient registry and is the sole U.S. network. In contrast to other DSD initiatives, the DSD-TRN is designed to capture the "process" of ongoing care using a comprehensive combination of prospectively applied genetic, biochemical, phenotyping, and psychosocial approaches to inform the diagnosis and clinical management of the individual patient and family. Standardized forms guide longitudinal clinical assessments and care, from the initial point of contact to the present. If parents (and patient) consent, details of the patient's medical record are uploaded to the registry for research purposes. Participation in the registry also includes the option of patients and biological parents contributing a blood sample to a biobank for exome sequencing. Importantly, families choosing not to be involved in research still receive the same model of care promoted by the network in the interest of continuous quality improvement.

The DSD-TRN serves as a platform for hypothesis-driven research by creating a clinical network that can participate in research protocols that are either integrated into the model of care (e.g., a decision support tool) or conducted as stand-alone projects conducted in parallel to ongoing care (e.g., functional studies of newly identified genetic variants). Monthly, multisite video case conferences create the opportunity for providers from all DSD teams in the DSD-TRN to review challenging cases and receive comments and suggestions from team members at other sites. Finally, the DSD-TRN incorporates the distinctive and valuable input from patient advocacy and support groups through collaboration of the Advocacy Advisory Network (AAN) led by Accord Alliance (www.accordalliance.org).

Standardization

Lack of standardization and reliability in multiple aspects of DSD diagnosis and clinical management sets a ceiling on scientific discovery, quality of healthcare delivery and associated health and quality of life outcomes. Variability exists in both the process of diagnosis and clinical management. For example, it remains the case that apart from adrenal disorders or atypical sex chromosomes that result in DSD, a specific molecular diagnosis is identified in only a minority of patients [8, 9]. Inconsistency across clinical centers in the approach taken toward arriving at a genetic diagnosis is one factor that maintains the status quo [10]. Partially as a consequence of this situation, there is limited research linking known genetic mutations responsible for specific DSD and a range of outcomes, including risk of gonadal tumors, fertility potential, or even stability of gender identity across the lifespan.

Problems of standardization extend to deficiencies in description of the anatomic phenotype (genital ducts and external genitalia). There are no firmly established classification systems for many pediatric urogenital conditions, creating a significant barrier to advances in the field, including identification of genotype-phenotype associations. A research meeting sponsored by the U.S. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), entitled a Strategic Plan for Pediatric Urology Research, identified limitations in reliable classification of anatomic phenotype as a barrier to clinical outcomes research [11].

Apart from the call in the Consensus for integration of behavioral health services in the delivery of care to patients with DSD and their families, little is available by way of guidelines for psychosocial evaluation or management [12]. The dearth of prospectively collected behavioral data, such as reactions of healthcare providers and parents to the child's birth and the process of medical decision making, prevents researchers and clinicians from learning about ways in which the medical and broader social environments potentially modulate outcomes for people with DSD.

The standardization process needs to extend beyond adoption of common pathways in diagnosis or reliable descriptions of phenotypes. Evaluating subjective appraisals of patient/family experience and the results of hormonal or surgical interventions is an additional important feature of ongoing care that should be systematically and prospectively captured. Patient-reported outcomes are increasingly being adopted as endpoints in assessing value in clinical care (for example, see guidelines endorsed by the U.S. Food and Drug Administration [13], the European Medicines Agency [14], and resources available at the website for the National Institutes of Health Patient Reported Outcomes Measurement Information System, PROMIS®; www.nihpromis.org).

Clinician and patient-reported outcomes frequently diverge. For example, in one long-term follow-up study of women with 46,XX DSD due to classic congenital adrenal hyperplasia, participants reported "moderate" satisfaction with cosmetic appearance of the external genitalia following genitoplasty. No difference in cosmetic outcome was reported between women who were salt-losers (SL, with more atypical genital anatomy at birth) compared to those who were simple-virilizers (SV, born with less atypical genitalia). In contrast, physician ratings were more positive for cosmetic outcomes in the SV group compared to the SL group, and were better overall for all participants compared to patients' self-ratings, regardless of SL or SV designation [15]. In another study of cosmetic outcomes of genitoplasty in people with diverse 46,XY DSD conditions, physician ratings for patients who received feminizing genitoplasty were more positive than for patients who received masculinizing surgical procedures [16]. The importance of the patient perspective was underscored in this study by participants reporting that the appearance of their genitalia was the greatest factor contributing to dissatisfaction with their body image, regardless of type of genitoplasty they received. Thus, the limited data available at this time reveal that physician assessment of cosmetic outcomes following genitoplasty for people born with atypical genitalia due to 46,XX or 46,XY DSD does not necessarily reflect patient

self-assessment. Limited agreement within and between surgeons and discordance in patient-physician cosmesis ratings is not limited to the genitoplasty.

Research is beginning to emerge on factors influencing the level of agreement between patient and surgeon ratings of outcomes. Although ratings for functional outcomes of procedures generally agree [17,18], greater disagreement is observed for cosmetic outcomes. For example, surgeons rate abdominal and breast scarring worse than patients [19], whereas patients rate cosmetic outcomes of orthopedic trauma [20] and scoliosis [21] surgeries worse than surgeons. When patients rate cosmetic outcomes worse than surgeons, factors associated with this discordance include female sex of the patient and general dissatisfaction with medical care [20].

Studies of surgeon ratings of cosmetic outcomes for the procedures they perform reveal considerable variability. For example, orthopedists' cosmetic ratings of the neck and back prior to and following spinal fusion for idiopathic scoliosis show fair to poor intra- and inter-rater reliability [21]. The most consistent orthopedist who participated in this study rated pre-operative photos similarly only 56% of the time when repeat ratings occurred following a 6-week interval. The same orthopedist rated post-operative photos similarly only 59% of the time when repeated views were separated by 6 weeks. Differences in ratings of scarring contributed most significantly to the poor intra-rater reliability among the 6 surgeons studied. Inter-rater reliability was just as poor in this investigation, with the greatest variability due to orthopedists' scores of cosmetic deformity. Patients' satisfaction with their surgery was not associated with surgeons' ratings of scars, deformity or pre- to post-operative change [21]. Thus, poor agreement exists within and between surgeons when assessing cosmetic outcomes and surgeons' cosmetic ratings do not correlate with patient satisfaction.

Considering differences in perceptions between physician-physician and patient-physician ratings of cosmesis following surgical procedures of the spine, breasts or abdomen, it is unsurprising that disagreement extends to outcomes for genitoplasty. We lack data on whether or not pediatric surgeons, pediatric urologists and adolescent gynecologists consistently rate cosmetic outcomes of masculinizing or feminizing surgeries over time. Additionally, we know little about the degree of overlap between surgeons' ratings and patients' perceptions of genital appearance. We also do not know if gender of rearing impacts surgeons' and patients' perceptions of genital appearance, nor do we know if parents' satisfaction with their child's DSD-related medical care is related to patients' cosmetic ratings of the genitals.

The different DSD networks and learning collaboratives have each responded in distinctive ways to address the variability existing in both the process of diagnosis and clinical management across network sites. **Table 2** summarizes efforts at standardization, either through assessment of care (e.g., DSD-Life), via research initiatives (e.g., I-DSD, DSD-net), or both (e.g., DSD-TRN). In the DSD-TRN, for instance, each workgroup (genetics, anatomy/surgery, endocrine, psychosocial) is tasked with the creation of clinical data collection forms to establish uniformity in descriptions of diagnosis and treatment. These forms serve as "templates" for documenting encounters in the patient's electronic health record across network sites, reducing the need for effort on the part of the individual clinician beyond the routine task of documenting assessments and procedures at the time of the visit. Adding burdens on already taxed clinicians may serve as barrier to sustaining any quality improvement or longitudinal research initiative. A guiding principle of the DSD-TRN is concerted effort at standardization of diagnosis and clinical management. The goal is to have all patients (and families) seen at the network sites provide consent for details from the medical record to be uploaded to the registry. This objective assumes efforts, across sites, at delivering reliable (i.e., reproducible) descriptions of the anatomic, biochemical and psychosocial phenotypes, as well as the procedures applied to manage the care of patients and families.

In the I-DSD initiative, collection of standard data elements (e.g., external masculinization score, gender assignment, genetic diagnosis, etc.) has made it possible to discern secular changes in gender assignment practices across medical centers [5] and to make statements about associated anomalies in DSD, based on large samples [6]. For those participants agreeing to have their data included, findings from the standardized DSD-Life assessment protocol will complement medical data in the I-DSD registry by adding details regarding psychosocial and psychosexual development, patients'/parents' perspectives regarding care, ethical considerations and cultural context.

Standardization efforts remain challenging: priorities and incentives in healthcare delivery can be misaligned with the goals of quality improvement. Substantial uncompensated and incremental effort on the part of individual clinicians at network sites is required at each stage of efforts to harmonize approaches to diagnosis and treatment. Factors contributing to clinician or site-specific variability in practice include individual training and experiences and access to particular specialty services. For example, recent reviews and surveys of surgical practice for DSD show an astounding range of procedures without accompanying data to support such variety [22,23]. It is also a challenge to identify qualified behavioral health providers with prerequisite training and experience in the clinical management of DSD.

Translating Evidence to Quality Care

The European Union Committee of Experts on Rare Diseases (EUCERD) established criteria for designation of a site as a "center of expertise" [24]. The criteria include (among others): the capacity to produce and adhere to clinical practice guidelines; propose quality care indicators; measure outcomes, including patient satisfaction; demonstrate high levels of expertise as evidenced by volume of referrals and second opinions; make contributions to research in the design and implementation of studies; demonstrate capacity to deliver comprehensive and integrated care, including attention to psychosocial factors; and attend to transition from pediatric to adult care. These criteria provide guidance on establishing a center equipped to manage the care of individuals with rare diseases, including DSD.

Collaboration among professionals from different specialties has been shown to be problematic [25]. The terms "multidisciplinary" and "interdisciplinary" are often used interchangeably; however, meaningful distinctions need to be emphasized. Although a multidisciplinary approach ensures that the assessment and recommendations are comprehensive, this approach does not guarantee that the team is functioning synergistically or harmoniously [26]. In fact, the "multidisciplinary team" described in the Consensus is more accurately characterized as "interdisciplinary" rather than "multidisciplinary." A multidisciplinary team approach is discipline-oriented, with all providers working in parallel and with clear role definitions, specified

Table 2 Structure and function of DSD research networks/learning collaboratives and efforts at standardization of clinical care.

	I-DSD	DSD-Life	DSD-net	DSD-TRN
Network governance	Project management group (PI, co-investigators n = 2, project manager n = 1, software engineers n = 2) Steering committee (clinicians/researchers n = 10, rep of patient organizations n = 2)	Management committee (PI, clinicians/researchers (n = 15), work packages leaders n = 7) Scientific Advisory Board (clinicians/researchers n = 5, rep of patient organizations n = 1)	Management Committee (Chair and vice-chair n = 2, clinicians/research members n = 30)	Network "Leadership Group" (PIs n = 2, co-investigators from each site n = 10) Accord Alliance and Advocacy Advisory Network (reps of patient support/advocacy orgs n = 4)
Criteria for membership	Centers of Expertise for DSD, following the EUCERD Recommendations on Quality Criteria for Centers of Expertise for Rare Diseases in Member States	EU Consortium members with expertise in DSD	EU Consortium members with expertise in DSD	Eligibility restricted to pediatric centers that include, at a minimum, pediatric endocrinology, pediatric urology, and behavioral health (psychology, psychiatry or social work)
Criteria for use of registry	Registry available to clinical users and researchers approved by a Registry panel within the Steering Committee. From 2015 onwards, also by patients/guardians	NA	NA	Registry available to members of participating sites
Professional Expertise	Pediatric endocrinology, pathophysiology, urology, psychology, genetics (multidisciplinary)	Endocrinology, surgery, psychology, and ethics (multidisciplinary)	Pediatric endocrinology, urology, surgery, psychology, genetics (multidisciplinary)	Pediatric endocrinology, urology, psychology, genetics (adolescent gynecology, surgery, nursing, social work, child life at select sites) (interdisciplinary)
Usual care assessment	Optional, e. g., longitudinal assessment of CAH medical management	Yes, cross-sectional	No	Yes, longitudinal
Standard operating procedures (SOP)	Yes, for research, e. g., SOP to access registry	Yes, for research, e. g., physicians, psychologists and nurses receive training to deliver research protocol in standardized manner	No	Yes, for research and clinical care, e. g., behavioral health providers receive training in administration and interpretation of psychosocial questionnaires and translation of findings to interventions (psychoeducational and others) for patients/families
Number of cases participating	n > 1390	Recruitment started in Feb 2014	NA	n > 300
Domains covered	Mandatory Diagnostic (genetic)	Mandatory Psychosocial adaptation Psychosexual develop Patients'/parents' view, ethics and cultural context Surgery Hormones and metabolism	Mandatory Harmonization and standardization of clinical phenotyping and clinical management; biology and genetics; harmonization of laboratory assessment Patient experiences and perceptions of participation in research, dissemination and capacity building	Mandatory Genetics Anatomy/surgery Endocrinology Psychosocial
	Optional/planned: Surgical/anatomical Biochemical Transition Longitudinal module for CAH medication management		Optional: Education: E-learning portal, training school Short-term scientific missions (institution or lab visits to other participating COST member to learn new techniques or gain access to specific instruments and/or methods not available at their own institutions)	Optional: Biobank: DNA samples from patient and parents
Publications (examples)	EuroDSD [32, 33] I-DSD [5–6]	[34]		[4, 10, 35–36]

Table 2 Continued.

	I-DSD	DSD-Life	DSD-net	DSD-TRN
Ongoing studies (selected)	– Novel mechanisms in adrenal and reproductive biology – Outcome of preserved gonads in adults with AIS – Evaluation of puberty in girls with pAIS – Improving long-term medical management outcomes in congenital adrenal hyperplasia by establishing a CAH-registry – Exome sequencing of DSD – Language, reading and communication problems in children with sex chromosome trisomy (47,XXY, XXX, XYY)	– Attention to the long-term effects on health, quality of life, sexual functioning and psychological well-being, with the principal purpose of developing European guidelines for treatment and care – To explore how satisfied patients are with their treatment, as well as to solicit their views on how society (and especially medical professionals) respond to their disorder – To provide information and education on the needs and care of patients	– Consensus building regarding anatomic phenotyping (time-dependent morphology) – Application of novel molecular technologies in DSD, e.g., assess genotype-phenotype correlations – Identification of optimal lab assessments in DSD diagnostics – Explore models of clinical care that facilitate good clinical practice and research – Development of patient educational materials – Dissemination of results to public	– Mitigation of negative experiences related to genital exams – Medical photography to enhance descriptions of phenotype – Exome sequencing of DSD – Endocrine, e.g., monitoring use of prenatal dexamethasone in CAH; use of DHT cream for penile growth in 5αRD-2 deficiency) – Psychosocial, e.g., identifying individual and family characteristics modulating psychosocial adaptation with associated interventions – Transition to adult care – Educational resources for patient/families – Informed consent (attention to legal issues) – Decision support tools

tasks, and hierarchical lines of authority. In contrast, providers on an "interdisciplinary team" meet regularly in order to discuss and collaboratively set treatment goals for the patients and jointly carry out the treatment plans. Ideally, they are on the same hierarchical level and with a high degree of communication and cooperation among the team members. A by-product of this model is that team members learn how the goals of their own discipline may require modulation when taking into account considerations of the other specialties and the agreed-upon goal for the patient [27].

The different teams of the DSD networks and collaboratives reflect a range of working relationships on the multidisciplinary-interdisciplinary continuum. Interprofessional education (IPE) is an intervention in which the team members learn interactively together with the purpose of improving collaboration and patient health and well-being outcomes. As noted in a recent Cochrane review [28], the key elements of IPE remain to be determined and the authors call for studies assessing the effectiveness of IPE interventions compared to profession-specific interventions; clinical trials with the inclusion of qualitative research methods examining processes relating to the IPE and practice changes; and cost-benefit analyses contrasting traditional with interprofessional approaches. Finally, transferring successful or promising strategies used in other chronic pediatric fields and adapting these for discovery and quality improvement in the area of DSD may prove valuable [29–31].

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Conflict of Interest

The authors declare no conflict of interest.

References

1 *Lee PA*, *Houk CP*, *Ahmed SF*, *Hughes IA*. Participants in the International Consensus Conference on Intersex. Consensus statement on management of intersex disorders. Pediatrics 2006; 118: e488–e500
2 *Moran ME*, *Karkazis K*. Developing a multidisciplinary team for disorders of sex development: Planning, implementation, and operation tools for care providers. Adv Urol 2012; 2012: 604135
3 *Institute of Medicine*. Committee on Quality of Health Care in America. Crossing the quality chasm: A new health system for the 21st century. Washington, DC: The National Academies Press, 2001
4 *Hanauer DA*, *Gardner M*, *Sandberg DE*. Unbiased identification of patients with disorders of sex development. PLoS One 2014; 9: e108702
5 *Kolesinska Z*, *Ahmed SF*, *Niedziela M*, *Bryce J*, *Molinska-Glura M*, *Rodie M*, *Jiang J*, *Sinnott RO*, *Hughes IA*, *Darendeliler F*, *Hiort O*, *van der Zwan Y*, *Cools M*, *Guran T*, *Holterhus PM*, *Bertelloni S*, *Lisa L*, *Arlt W*, *Krone N*, *Ellaithi M*, *Balsamo A*, *Mazen I*, *Nordenstrom A*, *Lachlan K*, *Alkhawari M*, *Chatelain P*, *Weintrob N*. Changes over time in sex assignment for disorders of sex development. Pediatrics 2014; 134: e710–e715
6 *Cox K*, *Bryce J*, *Jiang J*, *Rodie M*, *Sinnott R*, *Alkhawari M*, *Arlt W*, *Audi L*, *Balsamo A*, *Bertelloni S*, *Cools M*, *Darendeliler F*, *Drop S*, *Ellaithi M*, *Guran T*, *Hiort O*, *Holterhus PM*, *Hughes I*, *Krone N*, *Lisa L*, *Morel Y*, *Soder O*, *Wieacker P*, *Ahmed SF*. Novel associations in disorders of sex development: Findings from the I-DSD registry. J Clin Endocrinol Metab 2014; 99: E348–E355

7 *Sandberg DE*, *Gardner M*, *Cohen-Kettenis PT*. Psychological aspects of the treatment of patients with disorders of sex development. Semin Reprod Med 2012; 30: 443–452
8 *Arboleda VA*, *Lee H*, *Sanchez FJ*, *Delot EC*, *Sandberg DE*, *Grody WW*, *Nelson SF*, *Vilain E*. Targeted massively parallel sequencing provides comprehensive genetic diagnosis for patients with disorders of sex development. Clin Genet 2013; 83: 35–43
9 *Arboleda VA*, *Sandberg DE*, *Vilain E*. DSDs: Genetics, underlying pathologies and psychosexual differentiation. Nat Rev Endocrinol 2014; 10: 603–615
10 *Baxter RM*, *Arboleda VA*, *Lee H*, *Barseghyan H*, *Adam MP*, *Fechner PY*, *Bargman R*, *Keegan C*, *Travers S*, *Schelley S*, *Hudgins L*, *Mathew RP*, *Stalker HJ*, *Zori R*, *Gordon OK*, *Ramos-Platt L*, *Pawlikowska-Haddal A*, *Eskin A*, *Nelson SF*, *Delot E*, *Vilain E*. Exome sequencing for the diagnosis of 46,XY disorders of sex development. J Clin Endocrinol Metab 2015; 100: E333–E344
11 *National Institute of Diabetes and Digestive and Kidney Diseases*. Research progress report – strategic plan for pediatric urology. NIH Publication No. 06-5879 2006; February
12 *Meyer-Bahlburg HFL*. Treatment guidelines for children with disorders of sex development. Neuropsychiatrie de l'Enfance et de l'Adolescence 2008; 56: 345–349
13 *U.S. Department of Health Human Services FDA Center for Drug Evaluation Research, U.S. Department of Health Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health Human Services FDA Center for Devices and Radiological Health*. Guidance for industry: Patient-reported outcome measures: Use in medical product development to support labeling claims: Draft guidance. Health Qual Life Outcomes 2006; 4: 79
14 *European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP)*. Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products. Cpmp/ewp/139391/04 2006; January
15 *Wisniewski AB*, *Migeon CJ*, *Malouf MA*, *Gearhart JP*. Psychosexual outcome in women affected by congenital adrenal hyperplasia due to 21-hydroxylase deficiency. J Urol 2004; 171: 2497–2501
16 *Migeon CJ*, *Wisniewski AB*, *Gearhart JP*, *Meyer-Bahlburg HF*, *Rock JA*, *Brown TR*, *Casella SJ*, *Maret A*, *Ngai KM*, *Money J*, *Berkovitz GD*. Ambiguous genitalia with perineoscrotal hypospadias in 46,XY individuals: Long-term medical, surgical, and psychosexual outcome. Pediatrics 2002; 110: e31
17 *Lattig F*, *Grob D*, *Kleinstueck FS*, *Porchet F*, *Jeszenszky D*, *Bartanusz V*, *O'Riordan D*, *Mannion AF*. Ratings of global outcome at the first postoperative assessment after spinal surgery: How often do the surgeon and patient agree? Eur Spine J 2009; 18: 386–394
18 *Roitberg BZ*, *Thaci B*, *Auffinger B*, *Kaplan L*, *Shen J*, *Brown FD*, *Lam S*. Comparison between patient and surgeon perception of degenerative spine disease outcomes – a prospective blinded database study. Acta Neurochir 2013; 155: 757–764
19 *Kerrigan CL*, *Homa K*. Visual assessment of linear scars: A new tool. Plast Reconstr Surg 2009; 124: 1513–1519
20 *O'Toole RV*, *Castillo RC*, *Pollak AN*, *MacKenzie EJ*, *Bosse MJ*, *LEAP Study Group*. Surgeons and their patients disagree regarding cosmetic and overall outcomes after surgery for high-energy lower extremity trauma. J Orthop Trauma 2009; 23: 716–723
21 *Buchanan R*, *Birch JG*, *Morton AA*, *Browne RH*. Do you see what I see? Looking at scoliosis surgical outcomes through orthopedists' eyes. Spine 2003; 28: 2700–2704
22 *Springer A*, *Krois W*, *Horcher E*. Trends in hypospadias surgery: Results of a worldwide survey. Eur Urol 2011; 60: 1184–1189
23 *Steven L*, *Cherian A*, *Yankovic F*, *Mathur A*, *Kulkarni M*, *Cuckow P*. Current practice in paediatric hypospadias surgery; a specialist survey. J Pediatr Urol 2013; 9: 1126–1130
24 *European Union Committee of Experts on Rare Diseases*. EUCERD recommendations: Quality criteria for centres of expertise for rare diseases. 2011; October 24. Available http://nestor.orpha.net/EUCERD/upload/file/EUCERDRecommendationCE.pdf
25 *Institute of Medicine*. Establishing transdisciplinary professionalism for improving health outcomes: Workshop summary. In: Washington, DC: The National Academies Press, 2014
26 *Pless I*. Editorial: 'Interdisciplinary' and 'multidisciplinary' are not synonymous. Injury Prevent 1995; 1: 65–66
27 *Health Canada*. Interdisciplinary education for collaborative, patient-centred practice.Research and findings report. 2004; February 20. Available http://www.ferasi.umontreal.ca/eng/07_info/IECPCP_Final_Report.pdf
28 *Reeves S*, *Perrier L*, *Goldman J*, *Freeth D*, *Zwarenstein M*. Interprofessional education: Effects on professional practice and healthcare outcomes (update). Cochrane Database of Systematic Reviews 2013, doi:10.1002/14651858.CD002213.pub3
29 *Colletti RB*, *Kappelman MD*, *Crandall WV*, *Margolis PA*. Quality improvement in inflammatory bowel disease. In: Mamula P, Markowitz JE, Baldassano RN (eds.). Pediatric Inflammatory Bowel Disease. 2nd ed. New York: Springer, 2013; 547–554
30 *Godfrey MM*, *Oliver BJ*. Accelerating the rate of improvement in cystic fibrosis care: Contributions and insights of the learning and leadership collaborative. BMJ Qual Safety 2014; 23: i23–i32
31 *Weiss KB*, *Mendoza G*, *Schall MW*, *Berwick DM*, *Roessner J*. Improving asthma care in children and adults. Boston, MA: Institute for Healthcare Improvement, 1997
32 *Ahmed SF*, *Rodie M*, *Jiang J*, *Sinnott RO*. The European disorder of sex development registry: A virtual research environment. Sexual Develop 2010; 4: 192–198
33 *Bashamboo A*, *Ledig S*, *Wieacker P*, *Achermann JC*, *McElreavey K*. New technologies for the identification of novel genetic markers of disorders of sex development (DSD). Sexual Develop 2010; 4: 213–224
34 *Köhler B*, *Jürgensen M*, *Kleinemeier E*, *Thyen U*. Psychosexual development in individuals with disorders of sex development. In: Kreukels BPC, Steensma TD, de Vries ALC (eds.). Gender dysphoria and disorders of sex development. Springer, US: 2014; 115–134
35 *Akhavan A*, *Merguerian PA*, *Grady RW*, *DiSandro M*, *Shnorhavorian M*. Digital photographic measurement in hypospadias: Validation and comparison to intraoperative measurement. J Pediatr Urol 2014; 10: 312–316
36 *Sandberg DE*, *Mazur T*. A noncategorical approach to the psychosocial care of persons with DSD and their families. In: Kreukels BPC, Steensma TD, de Vries ALC (eds.). Gender dysphoria and disorders of sex development. Springer, US: 2014; 93–114