

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
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Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)

Growing up with Disorders of Sex Development (DSD): Critical Developmental Issues for Children and Families Affected by DSD

Natcher Conference Center (Building 45), Room D
NIH main campus, Bethesda, Maryland
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Summary Responses to Request for Information (RFI)

This document summarizes responses to an RFI issued on December 17, 2014, by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD)¹ in conjunction with planning the scientific research workshop, *Growing Up with Disorders of Sex Development (DSD): Critical Developmental Issues for Children and Families Affected by DSD*.²

The workshop’s goal is to identify research questions in the understudied area of DSD and child development, broadly defined. The purpose of the RFI was to solicit comments, particularly from affected individuals and families but also from other interested parties, that would help inform workshop planning. An additional purpose was to gather information for future consideration by NICHD and other NIH Institutes and Centers (ICs).

[Note: This summary was provided to participants in the workshop, which took place on March 26-27, 2014, at the Natcher Conference Center, NIH main campus, Bethesda, Maryland. The workshop was supported by the NICHD and the Office of Rare Diseases Research, National Center for Advancing Translational Sciences, NIH. A summary of the workshop is available at: <http://www.nichd.nih.gov/about/meetings/2014/Pages/032614.aspx>.]

The NICHD would like to thank all respondents to the RFI. It is not possible for a summary to capture the richness, depth, and detail of the responses, but all comments will be retained in their entirety to supplement the summary in drafting workshop proceedings and other uses.

RFI respondents identified themselves in the following nonexclusive categories: individuals with a DSD, and/or parents or spouses of such individuals with DSD; advocacy groups, activist groups, and individuals working on behalf of such individuals; researchers who specialize in DSD; and research-oriented professional societies. Responses included descriptive accounts of

¹ <http://grants.nih.gov/grants/guide/notice-files/NOT-HD-13-019.html>

² Terminology in this summary: “DSD” in this document should be understood to encompass alternative terms that may be preferred, including “intersexuality” and specific diagnostic categories; “family” may include an affected individual’s parents, spouse, siblings, or other relatives; “parents” may refer to birth or adoptive parents or other caregivers.

growing up with and living with DSD, as well as recommendations for improved clinical care and ideas for research. Some responses included peer-reviewed articles, book chapters, and links to Australian policy on DSD. Responses were generally consistent with the intersex-related comments in responses to a broader, June 2014 NIH RFI that sought comments on health and health research needs of lesbian, gay, bisexual, transgender, and intersex populations.³ The workshop RFI responses summarized below do not reflect a representative sample of affected populations, because federal RFIs are not scientifically designed survey instruments.

Please note that responses provided here do not necessarily represent the opinions of the NICHD, the NIH, or the HHS.

The RFI was structured to elicit responses on certain DSD-related issues: diagnosis, decision-making, living with a DSD (including what might be learned from children and families living with other challenging conditions), clinical management, and social factors. Responses are summarized below within four major themes that emerged from the comments:

- Affected individuals and their clinicians need a stronger evidence base to identify diagnoses, determine prognoses, and assess outcomes.
- Full, accurate, and readily understandable communication should take place among affected individuals, families, and clinicians to ensure informed clinical decision-making and promote overall well-being for those affected by DSD.
- Peer support and psychological support are both important for affected individuals and families.
- Future research on DSD should address a wide range of design and implementation issues, including participation of affected individuals and families and incorporation of the patient perspective.

Comments were often related directly or indirectly to more than one theme or subtheme. For example, the concept of engaging children with DSD to discuss clinical options is shown under the theme of communication, but it might also be helpful to consider it under the themes of psychological support or research design.

Affected individuals and their clinicians need a stronger evidence base to identify diagnoses, determine prognoses and assess outcomes. Instead of lumping dissimilar conditions together, researchers should develop scientific evidence that is specific to each DSD condition.

Diagnosis

- Availability of accurate and affordable genetic and molecular diagnostic tools that would improve timeliness of diagnoses, with less patient pain and discomfort, is an important priority.

³ Unpublished analysis (forthcoming) of responses by a working group of the NIH LGBTI Research Coordinating Committee to the RFI at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-13-076.html>.

- Diagnostic consultation, specific to each type of DSD, at regional centers of excellence, including NIH, before, during, and after diagnosis could be helpful to affected individuals and their families.
- The risks and benefits for children of genital exams and genital photography, especially as the psychological impacts of such procedures at different developmental stages are not well considered. Experiences with similar medical procedures (e.g., urological interventions) may be informative.
- Controlled, sensitive photography to standardize anatomical description (quantitative measurement) for use by multiple clinicians should be considered as an alternative to repetitive examinations.
- Conscious sedation could be considered for genital examination.

Gender

- A better understanding of the molecular pathogenesis of DSD could improve the ability to predict gender preference and gender role behavior.
- Further research is needed on the relative influence of biological (e.g., hormones) and nonbiological (e.g., parenting style, peer influence, and/or cultural factors) on gender identity, gender role behavior, and psychological well-being.
- An overall bioassay of androgen responsiveness for use, *in vivo* or *in vitro*, with newborns would be helpful in treatment planning. Existing methods limit prediction of future development of a genetically male infant with partial androgen insensitivity syndrome (PAIS), for example.
- Masculinization of genitalia and masculinization of the brain: New methods are needed for clinical measurement of prenatal androgen priming of the brain and for forecasting the implications for gender of rearing. Scientists need to better understand how specific brain regions are related to gender identity development.
- Primate studies of genital virilization and surgical outcomes would be helpful.
- Research is needed to identify biological and psychosocial factors affecting newborns with a DSD that can help predict long-term acceptance of sex of rearing.
- Scientists should consider longitudinal studies of individuals who have been raised with a neutral sex of rearing to identify outcomes. Germany has recently granted legal recognition of neutral sex.
- Evidence is needed to understand the effects of interactions among timing of diagnosis and gender assignment (especially if delayed and/or discordant) on patient health-related quality of life and family well-being.
- The experiences of transgender youth may help inform research on individuals with DSD with gender dysphoria. Researchers may want to consider the similarities and differences in clinical experience and developmental evolution, and the applicability of intervention paradigms such as WPATH (World Professional Association of Transgender Health).

Gonads

- Individuals with certain DSD may face increased cancer risk of *in situ* gonads. Proteomic prediction of cancer and identification of its manifestations could help identify cases earlier.
- Sensitive, specific genomic and/or serum markers for gonadal malignancy are needed. Specific immunohistochemical markers for primordial germ cells/genocytes, in

conjunction with morphology and clinical parameters, could help estimate germ cell tumor risk.

- Protocols are needed for monitoring the health of abdominal or inguinal testes in girls and women. Methods based on improved imaging or serum biomarkers should be developed.
- Clinicians need tools to optimize endogenous hormone production and preserve fertility from puberty onward for patients with *in situ* gonads.
- More information is needed to identify the optimal clinical regimen to manage symptoms of individuals who have had orchidectomies. Research is also needed to address bone health for these individuals.

Hormones

- Improved understanding of the molecular etiology of DSD could be employed to better predict response to therapies, such as exogenous hormone therapy.
- The implications of pediatric and adolescent hormone replacement therapy (HRT) for a broad range of DSD conditions are not well understood, and more data are needed to identify the appropriate formulation, type, dosage and delivery options.
- Studies of the efficacy and safety of HRT in women may inform treatment planning for DSD and transgender women; for example, European studies of testosterone in women with complete androgen insensitivity syndrome should be consulted.
- Efficacy trials of rational, mutation-specific selection of androgens for patients with PAIS are needed. To facilitate research in this area, new methods are needed to identify PAIS patients reared as male who might respond to large doses of androgens during puberty.
- Natural history information is lacking to adequately describe symptoms and characteristics associated with lack of hormones prior to puberty. Clinical information is needed to best manage the adverse effects of lack of hormones.
- Several adults with DSD reported that, in retrospect, they would have preferred delaying decisions about gender assignment and/or clinical intervention. Outcome studies of puberty blockers and other techniques for enabling children to delay decisions about clinical interventions could be especially useful, for individuals with DSD as well as for transgender individuals.
- Research should address hormone treatment and breastfeeding. The effect of concurrent estrogen and prolactin treatment in adults should be determined in clinical studies.

Psychological issues

- Natural history studies should be conducted to describe the cognitive and general mental health status of children with DSD.
- The contribution to multidisciplinary teams of psychologists and other mental health professionals with DSD-specific training should be assessed, especially to understand the impact on the health and well-being of affected children and families.
- Scientific data are needed to address how gonadectomy and genitoplasty can affect psychosocial and psychosexual development in adolescents and adults.
- Information is needed to assess how family sharing of DSD information with social networks affects child and family well-being.
- Some commenters pointed out that individuals may have forms of atypical reproductive tract development that may not be considered as DSD (e.g., hypospadias), but that these

individuals may also experience adverse surgical outcomes, shame, and stigma, and researchers and clinicians should consider their experiences as well.

- Multiple commenters pointed out that as children with DSD develop, they experience distinct, age-related challenges for social interactions.
- Evidence-based interventions specific to DSD are also needed to address parental depression, anxiety, and specific parenting challenges.

Reproductive potential

- Diagnosis-specific understanding of reproductive potential is needed. Several commenters with DSD reported that reproductive potential and sexual function were treated dismissively by some clinicians.
- Methods to retrieve and store germ cells or gonadal tissue and studies of best ways to mature germ cells for later use could be helpful for individuals with a number of different types of DSD.

Resources (clinical, other)

- Patient adherence (or lack thereof) with medication can be an issue in DSD clinical practice and research. Adherence issues may reflect a conscious choice or external barriers to care.
- More subspecialty clinical and research training (medical, mental health, surgical) in care of affected individuals and families is needed.
- Evidence-based protocols to support the transition from pediatric (family-centered) to adult (patient-centered) care are needed. Including adult-care clinicians in multidisciplinary pediatric and adolescent medicine team care could facilitate transition.
- Interdisciplinary care in primary care settings for emerging adults with DSD is important, but current practice needs improvement.

Surgery

- A stronger evidence base is needed to support decisions on the optimal timing of feminizing surgery.
- The effects of surgical techniques should be identified through long-term somatic and psychological follow-up.
- Several commenters affected by DSD reported dissatisfaction with their surgeries and suggested that surgery should be delayed until an individual is able to participate in clinical decisions and/or avoided altogether.
- A systematic review of existing literature could help inform decisions about earlier versus later surgery.
- The need for and risks and benefits of intersex surgery for individuals older than age 25 are difficult to assess with current information and should be studied further.
- It would be useful to determine whether a delay in assuming major responsibilities may be appropriate following adult intersex surgery, to permit stabilization of mood and other effects of surgery and hormone therapy.
- A child's potential sexual orientation is not an appropriate diagnostic criterion for decisions about surgical or hormonal intervention.

Full, accurate, and readily understandable communication should take place among affected individuals, families, and clinicians to ensure informed clinical decision-making and promote overall well-being for those affected by DSD.

Communication

- Several commenters stressed parental education to promote “forthrightness” about a child’s condition, “from the beginning,” with the child, family members, social contacts (school, sports), primary care physicians, and others. “Secrets do not help anyone. Keeping them only causes problems for people later in life.” Some individuals with DSD stressed the importance of being fully accepted and appreciated for who they are.
- Parents, patients, and clinicians need access to resources “to meet day-to-day challenges in life, relationships, school, and the medical clinic.”
- A DSD diagnosis often involves uncertainty about a child’s medical prognosis, gender identity, and psychosocial adjustment. Commenters stressed the need for clinicians to be honest about the degree of uncertainty and sensitive to that uncertainty’s impact on the family.
- Standardized biological, medical, and psychosocial information for structured communication among affected individuals and families would be helpful, especially if developed with the involvement of patient-advocates and DSD-specialized ethicists. A commenter reported hurtful and incorrect assumptions a clinician had made about an affected child and family. Standardized and structured information could limit the impact of such assumptions.
- Several commenters cautioned against the assumption that adverse psychological effects of DSD would be minimized by very early treatment and minimizing or concealing potentially disturbing information.
- Researchers and clinicians should consider the effect of the quality of clinician/family/patient discussions on care, decision-making and the psychological impact of a patient’s clinical experiences.

Ethical issues and informed consent

- Several commenters raised the issue of child assent, and whether it would be ethically preferable to postpone life-altering decisions, such as gender reassignment surgery, until a child is old enough to assent or consent. Genetic and molecular information that could inform such decisions should be considered by clinicians and made available to families.
- Interventions to help individuals to participate more effectively in research and clinical care decisions would be helpful.
- Ethical and legal guidance is needed for parents regarding conditions posing specific challenges for children’s participation in sports and other extracurricular activities.
- A variety of factors should be considered for family decision-making and informed consent. These include “urgency” (i.e., whether decision-making could be delayed); regional, religious, racial, ethnic, and socio-economic status; parental stress; strategies to reduce parental distress on learning of a child’s DSD; and outcomes of a structured “think period” for family/clinician discussions before decisions on non-urgent care.
- Ethical guidelines may be needed for research data storage and sharing.
- Adherence to and impact of ethics guidelines should be researched.

- Risks and implications of treatment for adult sexual partnerships should be thoroughly explored with an affected individual and/or family, to ensure fully informed consent.

Information-sharing resources

- Information-sharing tools for children with certain other medical conditions (e.g., HIV) have proved helpful and should be considered for children with DSD.
- “Engage the child” to better understand appropriate language to discuss DSD and possible treatments at all development stages and teach this approach to families and clinicians.
- An accurate and current informational website, preferably maintained by NIH, would be helpful. This might include assessment tools and decision aids for families and clinicians.
- Data are needed to better understand the impact on the family of clinician communication of diagnosis and etiology.
- The extent of family understanding of DSD and factors that promote family understanding, are not well understood. Cognitive and emotional management of clinical information should be investigated further.
- Patients, families, and clinicians may hold divergent views on clinical concerns (e.g., physical function vs. medication management). This possibility should be recognized and addressed.
- For some DSD, the condition may not be diagnosed until early adolescence and may not be characterized by clinicians in a way that families can easily understand. The currency and comprehensiveness of clinical subspecialists’ knowledge in providing care for individuals with DSD should not be taken for granted. Additional training, to update clinician knowledge, may be needed.
- Some clinicians may be biased with regard to clinical options or resistant to fully informed consent.

Peer support and psychological support are important for affected individuals and families.

Peer support

- Long-term peer (and psychological) support can be valuable for parents in decision-making and in management of children with DSD.
- When referring individuals and families to national organizations, clinicians should consider the quality of the information that may be provided.
- Information is needed about the characteristics of patients and parents that lead to their participation in peer support groups, the characteristics of effective peer support, and how peer support helps affected individuals and families understand complex medical information and become more confident in making clinical decisions.
- Data are needed about the rates of clinician referral of affected individuals and families to peer groups and other sources of support, and what factors influence clinicians’ decisions to refer families or otherwise facilitate family support.
- The effects of including a person with a DSD on the multidisciplinary care team should be considered, including effects on team functioning and patient well-being.

- The use of support group meetings as a new venue for delivering care through interventions “aimed at participants” should be explored.

Psychological support

- Design and delivery of mental health services for affected children and families should be based on comprehensive, scientifically valid evidence of their psychological needs.
- Data are needed on mental health comorbidities in children and families affected by DSD, assessed in the diagnostic process and across developmental stages. Research is needed to identify appropriate points for intervention.
- Child, adult, and family success in negotiating challenges in the diagnostic process should be studied, to inform guidance for others affected by DSD.
- Psychosocial aspects of DSD should be included in collaborative studies, with a goal of optimizing patient and family outcomes in diagnosis and promoting family well-being.
- Ethnic/cultural group differences should be incorporated into DSD research, with special attention to secrecy/shame dynamics associated with atypical anatomies and reproductive potential, as well as potential family violence, family sexual abuse, and incidence of suicides.
- Ethnic/cultural group factors that may contribute to acceptance of genital variance should be identified, especially in ethnicities or cultures where attitudes could discourage treatment.
- Anger and grieving in an individual with a DSD (of any age) and parents should be considered.
- Attachment theory is necessary but not sufficient for understanding psychosocial dynamics in families affected by DSD and their decision-making.
- Several commenters stated that surgical treatment could be very damaging to children with DSD and their families and that alternatives to surgical treatment should be considered to mitigate psychological damage.
- Specialized resources for psychological support are needed, including recommendations for spouses and children of intersex individuals when diagnosis and surgery occur during a marriage.

Terminology and identity

- Terminology associated with DSD can have a negative impact on individuals with DSD and their families. Some respondents strongly prefer nonsexualized terminology to characterize a specific diagnostic category or as an umbrella term for DSD. “[S]exual’ is always going to hit a nerve in a population that feels self-conscious about ... their sexuality [per se] ... Could [there] be a very clinical term such as disorder of the endocrine system? ... Some teens and women struggle with sexual identity ... due to the need for medication to become ‘feminine.’ They fear that misconceptions about them will influence their future in negative ways. What if a significant other reads up on [the condition] and finds information that is not true or interpreted incorrectly?”
- “I will use the term ‘born with difference’ as a substitute for the pathologizing term ‘DSD’ ... I self-identify as ‘intersex,’ a hated term among parents.”

Future research on DSD should address a wide range of design and implementation issues, including participation of affected individuals and families and incorporation of the patient perspective.

Research design (including outcomes)

- Prospective measurement, with objective quality criteria, of multidisciplinary care at centers of excellence would improve care for affected individuals.
- Patient outcomes from centers of excellence should be compared with outcomes from other clinical sites.
- Effectiveness of integrated (“multimodal”) pharmacological, psychological, surgical treatment in “pragmatic, patient-centered trials” should be assessed, as an approach to reducing problems in recruiting cohorts of “adequate” size for randomized trials.
- Affected individuals should be asked to participate from “earliest stages of research design,” including IRB reviews.
- Retrospective study data should be investigated for its potential use in developing guidance in clinical decision-making, because prospective studies cannot yield such guidance for many years and because controlled, double-blind research trials cannot be done.
- Researchers should seek early engagement of DSD advocates and activists in research planning and study design. Community support should be sought for studies addressing patient needs, of which researchers may be less informed.
- Patients’ characterization of “satisfactory” outcomes of hormonal, psychological and surgical interventions should be included in longitudinal studies, without conflation of specific functional or social outcomes. Researchers should also include as outcomes the quality of personal relationships and individuals’ happiness with sexual functioning in a relationship, instead of measures specifically of heterosexuality.
- Additional “patient satisfaction” outcomes should be studied, including self-esteem (including comfort with or shame about one’s body); “happiness with [gender] of assignment, [gender] of rearing, gender presentation”; pain (physical and emotional) related to management of intersexuality; impacts on parental, familial, and social relationships; romantic/sexual relationships, including shame/comfort, capacity/incapacity for sexual sensation, and fear of rejection; experiences in bathrooms, locker rooms, and other “binary sex-specified settings”; and institutional requirements for sex designation (birth certificates, driver’s licenses, etc.).
- Study “health, not sex” in affected individuals (i.e., “all the things studied and measured in *any* child”) and “map results against DSD syndrome,” with special attention to identified risks (e.g., bone health, growth, weight, and mental health).

Research resources

- A “large-scale registry with assessment of clinical cases” could facilitate research. A national registry based on data from diagnostic testing with the NIH gene sequencer was suggested.
- Standardized CPT coding could facilitate assessment of interventional data in registries and elsewhere.

- A centralized registry of clinical and histopathological data, from assessment of gonadal histopathology in biopsy and gonadectomy samples collected at centers of excellence, should be developed to support evidence-based management of gonads in individuals with DSD.
- Any North American registry should preferably be partnered with European efforts, to “increase power of database.”

Research topics

- Include siblings of children with DSD, both those with and those without other health issues, in research, to study sibling-related physical, emotional, and psychological development of children with DSD.
- Conduct research in school settings, including parental perceptions of competence of school nurses and other school officials, and the influence of such perceptions on parental involvement with and decisions about a child’s education.
- Research should be conducted on school management of a child’s adrenal crises and effect on “child’s outlook on life.”