Sexual Development

9th I-DSD Symposium

Bern, Switzerland, 14–16 July, 2022

Abstracts

Disclosure Statement Guest Editors
All guest editors have no conflicts of interest to declare.

The organising committee declares that it is authorised to submit these abstracts on behalf of all participating authors.

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Sex Dev 2022;16(suppl 1):1–91
DOI: 10.1159/000525564
Published online: June 30, 2022

Programme

I-DSD Symposium

Thursday 14th - Saturday 16th July 2022

All Sessions in the Ettore Rossi Auditorium

SYMPOSIUM DAY 1 (THURSDAY, JULY 14TH 2022)

Registration & Coffee from 11:30 (Foyer)	
13:00	Opening
Session 1 – Setting the Scene (13:00-13:35) **Chair: Anna Nordenström, Stockholm, Sweden**	
13:00 – 13:05	Welcome - Christa Flück, Bern, Switzerland
13:05 – 13:20	Patients' experiences in Switzerland
13:20 – 13:35	Patient support & advocacy – Arlene Smyth, Turner Syndrome International
Session 2 – International Collaboration (13:40-14:15) **Chair: Faisal Ahmed, Glasgow, UK**	
13:40 – 13:45	Endo-ERN – Olaf Hiort, Lübeck Germany
13:45 – 13:50	ESPE DSD working group – Tülay Güran, Istanbul, Turkey
13:50 – 13:55	APEG DSD Working Group – Michele O'Connell, Melbourne, Australia
13:55 – 14:00	PES DSD Working Group – Courtney Finlayson, Chicago, USA
14:00 – 14:05	I-DSD/I-CAH – Christa Flück, Bern, Switzerland
14:05 – 14:15	Discussion
Oral Communications 1 (OC1) (14:20-15:30) **Chairs: Rade Vukovic, Belgrade, Serbia, Angela Lucas-Herald, Glasgow, UK**	
14:20 – 14:30	Current management of acute adrenal insufficiency related adverse effects in children with congenital adrenal hyperplasia – results of an international

	survey of specialist centres – Salma Ali, Glasgow, UK
14:30 – 14:40	Identification of small regions of overlap from copy number variable regions reveals candidate genes and novel chromosome loci for hypospadias – Ina Amarillo, Hershey, USA
14:40 – 14:50	The international SF1 next project: Description of a cohort of 107 individuals with SF-1/NR5A1 variants – Chrysanthi Kouri, Bern, Switzerland
14:50 – 15:00	Pathway to Care among People with Disorders of Sex Development: Cohort Profile – David E Sandberg, Ann Arbor, USA
15:00 – 15:10	Designing a best-worst scaling survey for defining successful outcomes and trade-offs in DSD care – Erica Weidler, Phoenix, USA
15:10 – 15:20	A novel POR variant recurrently found in Argentine patients results in a wide spectrum of undervirilised phenotypes in 46,XY patients – Jimena Lopez Dacal, Buenos Aires, Argentina
15:20 – 15:30	Timing of reconstructive surgery for individuals with differences of sex development (DSD): Stakeholder views on successful outcomes – Kathleen van Leeuwen, Phoenix, USA

Coffee Break 15:30 – 16:00

Session 3 – Reaching A Genetic Diagnosis In The Era Of NGS (16:00-17:30)

Chair: Olaf Hiort, Luebeck, Germany

16:00 – 16:25	The clinical approach – Ruth McGowan, Glasgow, UK
16:25 – 16:50	Advances in insilico analysis – Katie Ayers, Melbourne, Australia
16:50 – 17:15	Functional analysis – Anu Bashamboo, Paris, France
17:15 – 17:30	Discussion

Free Evening

SYMPOSIUM DAY 2 (FRIDAY, JULY 15TH 2022)

Session 4 –Adrenal & Gonadal Development (08:15-09:45)

Chair: Amit Pandey, Bern, Switzerland

08:15 – 08:40	Mouse models for DSD – Serge Nef, Geneva, Switzerland
08:40 – 09:05	Novel therapeutic models for adrenal disorders – Leo Guasti, London, UK
09:05 – 09:30	Novel models of the gonads – Anna Lauber-Biason, Fribourg, Switzerland
09:30 – 09:45	Discussion

Oral communications 2 (OC2) (09:50-11:00)

Chairs: Meilan Rutter, Cincinnati, USA, Grit Sommer, Bern, Switzerland

09:50 – 10:00	Caregiver Perceptions of Stigma Associated with their Child's Difference of Sex Development – Kristina I. Suorsa-Johnson, Salt Lake City, USA
10:00 – 10:10	Sexual Development and prenatal growth. Analysis of the prevalence of being born Small for Gestational Age (SGA) in a large DSD cohort, and the genotypic frequency of GHR gene polymorphism in non-disgenetic undiagnosed 46,XY DSD patients – María Celeste Mattone, Buenos Aires, Argentina
10:10 – 10:20	"I believe God doesn't make mistakes, and I am wonderfully made in His image": The intersection of religion/faith and clinical care in Differences of Sex Development – Meilan Rutter, Cincinnati, USA
10:20 – 10:30	Experiences and needs of variation in sex characteristics peer support members in the prenatal setting – Michele O'Connell, Melbourne, Australia
10:30 – 10:40	46,XY Partial gonadal dysgenesis; diagnosis and long-term outcome at puberty – Rieko Tadokoro Cuccaro, Cambridge, UK
10:40 – 10:50.	Genital skin wound healing is associated with the extent of external virilisation in boys with hypospadias – Angela Lucas-Herald, Glasgow, UK
10:50 – 11:00	Psychological impact on parents of children born with atypical genitalia in India – Tanvi Bindal, New Delhi, India

Coffee Break 11:00 – 11:30

Session 5 – Hypospadias – a disorder of sex development or not (11:30 – 13:00)

Chair: Margarett Shnorhavorian, Seattle, USA

11:30 – 11:50	Acquired or genetic – Jorma Toppari, Turku, Finland
11:50 – 12:10	The views of an endocrinologist – Sabine Hannema, Amsterdam, Netherlands
12:10 – 12:30	The views of a psychologist -Norma Ruppen, Zurich, Switzerland
12:30 – 12:50	The views of a surgeon – Emilie Johnson, Chicago, USA
12:50 – 13:00	Round table

Lunch 13:00 – 14:00

Session 6 – Debate (14:00 – 15:15) 'This house believes that clinical psychology care should be provided proactively in every case of atypical genitalia'

14:00 – 14:05	Introduction and poll – Christa Flueck, Bern, Switzerland
14:05 – 14:25	For – Vickie Pasterski, Cambridge, UK
14:25 – 14:45	Against – David Sandberg, Ann Arbor, USA
14:45 – 15:15	Discussion & poll

Coffee and Posters 15:15 – 15:30

15:30 – 17:30 **Guided poster rounds (Ground floor)**

19:30 – Social Evening

SYMPOSIUM DAY 3 (SATURDAY JULY 16TH 2022)

Session 7 – Endocrine aspects at transition & beyond (09:00 – 10:45)

Chair: Carla Bizzari, Rome, Italy

09:00 – 09:25	Importance of transition for long term care – Philippe Touraine, Paris, France
09:25 – 09:50	Management of hypogonadotropic hypogonadism – Julia Rohayem, Munster, Germany
09:50 – 10:15	Assisted conception in Klinefelters -Claus Gravholt, Aarhus
10:15 – 10:40	Long-term psychosocial outcome – Baudewijntje Kreukels, Amsterdam, Netherlands
10:40 – 10.50	Discussion

Coffee Break 10:50 – 11:15

Session 8 – Future Directions (11:15 – 13:15)

Chair: Hedi Claahsen, Nijmegen, Netherlands

11:15 – 11:40	Incorporating DSD concepts in the undergraduate curriculum – Ina Amarillo, St Louis, USA
11:40 – 12:05	The role of patient organisations in influencing care and research – Johan de Graaf, Netherlands
12:05 – 12:30	Incorporating the ethical dimension into clinical practice – Jürg Streuli, Zurich, Switzerland
12:30 – 12:55	Benchmarking of care in DSD & CAH – Justin Davies, Southampton, UK
12:55 – 13:15	Discussion

13:15 – Close (Faisal Ahmed)

Optional Small Group Networking Breakout With Packed Lunch 13:15-14:30

The 9th International DSD Symposium, Bern, Switzerland, 14/07/2022-16/07/2022 has been accredited by the European Accreditation Council for Continuing Medical Education (EACCME®) with 11 European CME credits (ECMEC®s). Each medical specialist should claim only those hours of credit that he/she actually spent in the educational activity.

Feedback survey https://link.webropol.com/s/idsd2022feedback

I-DSD Training Workshop

Thursday July 14th 2022 **(09:00 -12:30)**

Ettore Rossi Auditorium, Course Rooms 1, 2 & 3

The I-DSD/I-CAH/I-TS registries Angela Lucas-Herald/Salma Ali Glasgow, UK	Bioinformatic analysis Amit Pandey Bern, Switzerland	Communication with a new parent or patient Katie Traino Oklahoma City, USA	Interpretation of endocrine tests Tülay Güran Istanbul, Turkey

The Training Workshop is an additional event. The full programme is available to registered workshop participants

A Clinical Approach to the Diagnosis of DSD

Ruth McGowan[1]

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Differences or disorders of sex development (DSD) are a heterogeneous group of rare conditions characterised by a variation in chromosomal, gonadal or phenotypic features that define sex development. Identifying a definitive diagnosis is essential for the long term management of an affected individual potentially providing information about long term fertility, adrenal health, tumour risk, chance of recurrence for the individual, their parents and may inform future reproductive options. The role of genetic testing in the diagnosis of DSD has changed over the years and is increasingly performed at an earlier stage, often alongside or indeed, prior to biochemical investigations. The introduction of high sequencing technique techniques using a targeted gene panel, whole exome or genome sequencing (WEGS) has increased diagnostic yield to up to two thirds in XY, DSD.

In Glasgow, the initial investigation of XY, DSD focuses on careful clinical phenotyping, family history, standard genetic testing (56 DSD gene or 21 hypogonadotrophic hypogonadism (HH) panel) and biochemical investigations, done in parallel. The results are discussed at the DSD Diagnostic Board. If no causative gene variant is identified, WEGS is considered depending on phenotype and family history.

In a local review of boys with XY, DSD who underwent standard testing, variants were found in, 9/59 (15%) and 39/99 (39%) had who had a limited 7 gene or 56 gene panel, respectively. Between 2016 and 2020, 14/30 (47%) individuals with suspected HH had gene variants (ACMG, class 3-5). WEGS was applied through the Genetic Investigation of Rare Disorders (GIRD) study as well as the Scottish Clinical Exome, identifying novel variants (CKAP2L, SEC3A1, TXNRD2, RLIM and WDR11) in 5/17 (30%) of families with XY, DSD.

I will describe case vignettes from the Glasgow DSD clinic demonstrating that clinical phenotype, multidisciplinary input and research collaboration is crucial in the diagnosis of DSD.

Advances in in silico analysis

Katie Ayers[1,2]

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Differences of sex development (DSD) represent a major paediatric concern and clinical management of these conditions can be difficult. Providing a molecular diagnosis for patients with a DSD and their families can serve multiple purposes: naming the underlying cause contributes to acceptance, reduces stigma or blame, and provides crucial clues and guidance for clinical management, including information on the malignancy risks associated with some types of DSD. A diagnosis is integral to genetic counselling and family planning, and in conditions where DSD is part of a wider congenital syndrome, diagnosis can allow early clinical intervention or access to essential support.

Our group has previously created a targeted DSD gene panel of 64 known diagnostic DSD genes and sequencing of a cohort of more than 300 patients identified a likely genetic diagnosis in 43% of patients with 46,XY DSD. In patients with 46,XY disorders of androgen synthesis and action the genetic diagnosis rate reached 60%. We have now established this test as a clinical diagnostic test at the Victorian Clinical Genetics Services, Melbourne, Australia where it is run as a virtual gene panel on an exome sequencing backbone. This is the most comprehensive DSD test available to patient in Australia and New Zealand.

We are now working to identify novel genetic causes in patients negative for a diagnostic finding, including for those with conditions such as premature ovarian insufficiency that are poorly understood at the molecular level or unrepresented in clinical testing. This work includes using advanced bioinformatics to interrogate whole exome and whole genome sequencing for cryptic genomic changes or copy number variants in DSD genes that may have been previously missed, as well as identifying novel causative genes. This also includes work to identify variants affecting the regulatory regions of gonadal genes. I will discuss these technologies and our genetic findings as well as the importance of robust in silico analysis during diagnostic gene curation and gene discovery.

Functional analysis

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Large scale high-throughput sequencing studies are revealing new genes and loci that may be involved in the development of DSD. Strong genetic evidence supported by experimental data is imperative for establishing the causality of these candidate genes/loci in DSD. The absence of rigorous analysis of the newly discovered genes/loci results in questionable data, that may be confusing or misleading both for the clinicians and patients and their families. Therefore critical evaluation of the evidence to support causality for new genes/ variants causing DSD is imperative. Emerging data suggests that numerous genes are responsible for DSD and each gene explains a small number of cases. For certain genes, such as DHX37, pathogenicity is established by robust human genetics data, even in the absence of functional studies, animal models or a biological context that is relevant for gonad formation. However, the evidence in support of causality should be addressed by a combination of following questions-

-Is the transmission of the variant compatible with DSD?

-Does human population genetics data support a role for the gene/variant in DSD?
-Is the gene/variant associated with other human congenital disorders that do not include DSD?
-What is the known biological role(s) of the gene?
-Is there robust experimental evidence or animal/cellular model to support pathogenicity?

In-vitro cell based assays are a popular experimental tool to understand the effect(s) of a variant on the biological function of the protein. These assays may indicate a change in the biological activity of the protein but rarely give an insight into the mechanism(s) of disease initiation or progression. Animal models, especially mice can be highly informative, however there is a increasing number of genes or variants which cause human DSD that cannot be modelled in mice. An attractive alternative is the development of in-vitro human cellular models, that can recapitulate human gonad development in-utero. These systems can act as a surrogate for gonad development and provide a biologically relevant and accesible system for functional analysis of candidate genes/variants that may cause DSD.

Identification and characterization of a novel and rare somatic lineage in the developing mouse gonad

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Background/Aims:
A complete characterization of the different cell lineages forming the bipotential gonad is essential for our understanding of the process of sex determination. We investigated the origin, specification and subsequent sex-specific differentiation of a previously uncharacterized population of supporting-like cells (SLC) in the developing mouse gonads.

Methods:
We used a combination of single cell RNA sequencing (scRNA-seq) analyses, immunofluorescence, gene expression analysis, in vivo cell lineage tracing and loss-of-function experiments.

Results:
The SLC lineage is closely related to the coelomic epithelium and specified as early as E10.5, making it the first somatic lineage to be specified in the bipotential gonad. SLC progenitors are localized within the genital ridge at the interface with the mesonephros. SLCs become sexually dimorphic around E12.5, progressively acquire a more Sertoli- or pre-granulosa-like identity and contribute to the formation of the rete testis and rete ovarii.

Conclusion:
We describe a rare gonadal cell lineage at the origin of the rete testis and rete ovarii

Novel therapeutic models for adrenal disorders

Leonardo Guasti[1]

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Background:
Adrenal insufficiency (AI) is a serious condition associated with a significant increase in morbidity and mortality, and a reduction in quality of life. AI arises from pathology directly affecting the adrenal gland, the pituitary/hypothalamus, or via suppression of the hypothalamic-pituitary adrenal axis by exogenous glucocorticoid therapy. The current gold-standard treatment for patients with AI is life-long replacement with exogenous steroids; despite recent new formulations, patient management is an ongoing challenge for clinicians, as no regimen suitably mimics the diurnal pattern of cortisol noted in healthy individuals, and objective variables to measure replacement quality are lacking.

Aims:
We will discuss how new gene and cell-based approached are promised to revolutionise the treatment of patients with AI. Gene therapy targets patients with congenital adrenal disorders, such as congenital adrenal hyperplasia (CAH) and familial glucocorticoid deficiency: in this system, the functional gene is delivered to adrenocortical cells via adeno associated viruses (AAVs). Investigational gene therapy is currently being developed for patients with mutations in CYP21A2, resulting in classic salt-wasting and simple virilizing forms of CAH. The main hurdles associated with gene therapy is the ability of AAVs to target adrenocortical stem-progenitor cells, allowing for a long-term cure, rather than a transient one if mature fully differentiated steroidogenic cells were to be targeted only. Theoretically, gene editing tools could also be delivered to adrenal cells to correct mutations in loco. Cell-based therapied could be applicable to a larger cohort of adrenal disorders and aims at replacing non-functional adrenocortical cells with a cell product generated in the laboratory: this is currently still in preclinical phase and the main obstacles are the generation of an appropriate number of clinically relevant adrenocortical-like cells via reprogramming (either via lineage conversion, differentiation of pluripotent stem cells or establishment of organoids), which are expandable as well as functional after transplantation.

Novel models of the gonads

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Animal models and cell lines derived from gonadal tumors had been so far the main alternatives to study the mechanisms leading to differences of sex development (also called variations of sex characteristics, VSC). Such models, though, show important differences with proper human gonadal cells due to their tumoral origin and the fact that sex development pathway is not always well conserved among species.

Two revolutionary new technologies now offer the possibility of tackling this complex problem in an appropriate manner. Firstly, the ability to transform terminally-differentiated cells into induced pluripotent cells (iPSCs), developed by Nobel Laureate Shinya Yamanaka, is the basis for the consequent creation of high-quality cell lines that resemble gonadal cells better than currently available cell models. Secondly, the 3D cell culture methodology that has been largely developed over the past century experiences now a new flourishing resulting from the ability to grow organoids from cells or tissues derived from human subjects, with promising applications in the area of personalized medicine. The combination of these technologies allows the creation of robust and highly complex human-derived gonadal models where germ cells and the different somatic supporters interact and regulate each other in an organotypic manner. These organoids should advance the understanding of gonadal development and its variations. Also,reproducible gonadal organoids might become an excellent platform for screening of substances that potentially affect reproduction in humans.

Acquired or Genetic?

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Development of penile urethra is regulated by sex hormones. Normal development is critically dependent on androgen action in the fetus. In the absence of sufficient androgen action, the penis remains small and the urethral folds do not fuse properly. Dihdrotestosterone can provide strong enough androgen signal for penile development, whereas testosterone alone is insufficient. Thus, children with 5-alpha reductase defect and any defect in androgen biosynthesis preceding this step can cause hypospadias, as well as androgen insensitivity due to receptor mutations. These and several gene defects underlying testicular dysgenesis are well-known genetic reasons for hypospadias. However, in the majority of hypospadias cases, no hormonal defect can be identified after birth. This points to the possibility that environmental effects on the regulation system could cause hypospadias. Indeed, in experimental animals, exposure to antiandrogenic compounds cause hypospadias. Furthermore, the effects of the compounds are additive, rendering even low levels of single chemicals harmful when they act together in a mixture of antiandrogens. In human epidemiological studies, exposure to chlorinated pesticides have been associated with an increased risk of hypospadias, but the results are not conclusive. Small sample sizes of the studies have been a major limitation. Nevertheless, besides known genetic reasons for hypospadias, environment may have a major impact particularly on mild forms of hypospadias, such as glanular and coronal defects.

Hypospadias – a disorder of sex development or not. The views of an endocrinologist

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Differences/disorders of sex development (DSD) have been defined as congenital conditions in which development of chromosomal, gonadal or anatomical sex is atypical. In the broadest sense this would include all forms of hypospadias, but in the 2006 consensus statement on DSD only perineal hypospadias, or milder forms of hypospadias with undescended testes, were listed as criteria suggesting DSD. For individuals with DSD, multidisciplinary care is recommended with a diagnostic evaluation including genetic, endocrine and radiological investigations. Several recent studies have shown that conditions characterised by deficient androgen production or action, including gonadal dysgenesis, androgen biosynthesis defects and androgen insensitivity, may also underlie proximal hypospadias with descended testes. Recognising these conditions has important therapeutic and prognostic consequences. This supports the practice of offering endocrine and genetic evaluation to all boys with proximal hypospadias. The potential benefits of this approach will be discussed, as well as possible drawbacks. Further studies are required to refine diagnostic recommendations for boys with hypospadias.

Need of psychological support in hypospadias patients

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The question will be discussed whether children and adolescents with hypospadias should receive psychological support as it is the "gold standard" for individuals with a "common" DSD diagnosis. In doing so, the concept of psychological support for hypospadias patients at the University Children's Hospital Zurich will be presented. This project has been implemented since 2016. It involves providing children and adolescents with hypospadias as well as their relatives with not only medical but also psychological support. Based on clinical experience and case studies, the concerns of children and adolescents with operated or non-operated hypospadias will be presented. Furthermore, the question will be addressed whether these concerns change depending on the age of the patients and the severity of the hypospadias.

Is hypospadias a disorder of sex development? A surgeon's view

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When a baby is born with hypospadias, the first referral made is often to a surgical specialist (urologist or pediatric surgeon). It is therefore up to the surgeon to determine whether the baby's anatomy most likely represents an isolated anatomic condition, or whether the hypospadias may indicate a defined DSD condition or other important genetic abnormality. The surgeon must then decide whether to order endocrine and genetic testing, and/or whether to refer the family for further discussion with multidisciplinary colleagues. From my reading and clinical experience, classification of the hypospadias itself as "a DSD" without more granularity is unhelpful, as this gives patients a label without direct clinical benefit. The goal of suggesting endocrine and genetic testing is to determine if patients have a defined DSD diagnosis that could affect gender identity, fertility, or tumor risk, or a systemic health condition that could benefit from improved prognosis and screening recommendations is. However, only about 1 in 3 boys with hypospadias who pursue additional testing are found to have a definitive diagnosis, so the cost and stress of pursuing additional testing must be balanced with a high likelihood of non-diagnostic results. The current approach at our institution is to offer a standard set of endocrine and genetic tests to all patients with proximal hypospadias, and to others on an individual basis (e.g., distal hypospadias with undescended testes or multiple other congenital anomalies). We are hopeful that advanced genetic testing options such as whole genome sequencing will improve diagnostic yield and ability to prognosticate outcomes for patients with hypospadias.

Importance of Transition for Long Term Care

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There is evidence that the process of transition from pediatric to adult health services is often associated with deterioration in the health of adolescents with chronic conditions. Transitional care is the term used to describe services that seek to bridge this care gap. It has been defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems." This process entails interventions, such as providing structured and repetitive patient education, counseling services of patients regarding lifestyle issues and health behaviors, and care and skill demonstration provided by transition coordinators . The number of young people with chronic illnesses and disabilities entering adulthood, who may be in need of support services to achieve their physical, social, and psychological potential, is on the increase. This may be a burden for the department of adult medicine if not enough resources are dedicated to these cohorts of patients undergoing transition of care from the pediatric system to the adult medicine one. In Pitie Salpêtrière Hospital, Departments of Endocrinology, Nutrition and Diabetology, Centers for Rare Endocrine Disorders and Rare Gynecological Disorders have set up a healthcare pathway called TRANSEND. Its aims are to promote a personalized medicine to all patients referred from pediatric departments and presenting endocrine and metabolic chronic diseases. This healthcare pathway is based on 3 different directions: the relationship with pediatric departments, the development of programs of education within the Pitié Salpêtrière Hospital to enable the development of autonomy of the young adult and finally the setup of a personalized

network between the tertiary care departments and the health actors outside of the hospital. The main objective is to ensure a long-term follow up of these patients with chronic diseases, a better adhesion to their own management of their diseases, a better compliance to their treatments. Besides the medical involvement, the objective of such networks is also to permit to the young adult with chronic disease to be fully integrated among others in his own social, professional, sexual life and to avoid any marginalization due to their chronic disease.

Le Roux et al, Endocr Connect, 2021
Le Roux et al, Eur J Endocrinol, 2022

Management of hypogonadotropic hypogonadism

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Background:
The most prevalent cause of delayed puberty in males is self-limited constitutional delay of growth and puberty (CDGP); congenital hypogonadotropic hypogonadism (CHH) is present only in a modest proportion in affected adolescents. Hormonal treatment is necessary only in the latter; it involves the use of testosterone, combined hCG/FSH, or GnRH. Acquired hypogonadotropic hypogonadism (HH) is rarely the cause of pubertal delay, the origins include cranial trauma or surgery, tumour, irradiation, inflammation or ischemia.

Objective and hypotheses:
This presentation will focus on the pros and cons of different treatment options for HH.

Method:
IM testosterone esters are the most frequently prescribed formulation for pubertal induction in male adolescents. Transdermal testosterone or IM testosterone undecanoate (TU) is suitable to maintain male secondary sexual characteristics in older patients. However, with such regimens, testicular maturation is not initiated. Treatment with gonadotropins is indicated, if testicular growth and fertility are desired. Pulsatile subcutaneous application of GnRH may alternatively be used, however this modality is effective only if pituitary LH- and FSH-secretion is uncompromised.

Results:
Long-term data show that rates of successful initiation of spermatogenesis for HH with a 2-3 year replacement regimen of gonadotropins or GnRH range around 91-95 %, but only 60% reach a normal semen quality. However, subnormal sperm counts in semen do not preclude spontaneous conceptions. Testicular growth is successfully initiated in nearly all males on central hormone replacement, but less than 75% eventually achieve normal adult gonadal sizes. Transfer to testosterone replacement is indicated for life-long replacement, once testicular maturation is accomplished. Rarely, spontaneous remission of congenital GnRH failure is observed.

Conclusion:
Pediatric patients with delayed puberty due to HH should be considered for treatment with hCG/rFSH. In boys with an exclusive hypothalamic origin of HH, pulsatile GnRH may alternatively be used. These approaches may be especially useful for boys aiming for complete normalization of their pubertal development, including testicular maturation.

Assisted conception in Klinefelter syndrome

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Although described 80 years ago, Klinefelter syndrome (KS) continue to be a difficult diagnosis for clinician to make, and many patients are still misdiagnosed, or remain undiagnosed. Only about 25% of KS patients are ever diagnosed, and most of these diagnoses are not made until adulthood, where most are diagnosed during fertility work-up. Classic characteristics of KS include small testes, infertility, hypergonadothropic hypogonadism, and cognitive impairment. The pathophysiology behind KS is not well understood, including the background for the testicular catastrophe that sets in during puberty or even earlier. Recent genetic studies have shown pervasive changes at all levels, including methylation changes, with primarily hypermethylation, but also areas with hypomethylation, global changes in mRNA expression, but also changes in other types of regulatory RNA, such as miRNA and circRNA. A number of candidate genes have been identified, some of which may be involved in testicular function, and results also suggest that our concept for the genetic changes underlying phenotypic traits in KS will have to change.

KS is associated with higher morbidity and mortality rates, and lower socio-economic status. Some of the conditions seen in KS include, in addition to hypogonadism, the metabolic syndrome, type 2 diabetes, cardiovascular disease, and other conditions known to affect fertility. Medical treatment typically focuses on testosterone replacement therapy for hypogonadism, and fertility intervention. Germ cell loss seems to accelerate as early as during childhood, while it seems to be normal in fetus' with KS. In most adults the seminiferous tubules are usually degenerated, but in about half of all KS small areas with normal tubules and apparently normal spermatogenesis can be found. Such tubules can be harvested during testicular sperm extraction (TESE) procedure and later used for intra cytoplasmatic sperm injection (ICSI) to achieve pregnancy. Newer studies have shown that in about half of adults with KS it is possible to find spermatozytes, while fewer achieve pregnancy and again fewer achieve a child birth.

Long-term psychosocial outcome in DSD

Baudewijntje Kreukels[1]

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Differences of sex development (DSD) are congenital conditions in which the development of chromosomal, gonadal or genital characteristics is atypical. Most people with DSD adapt well to their life circumstances and report a good Quality of Life. The individual's health status is reported to be an important predictor of QoL. Mental health is reported to be compromised in a substantial minority of adults with DSD, in particular individuals with Klinefelter Syndrome. Across DSD conditions adults may share feelings of shame. Condition openness is an important predictor of levels of anxiety and depression in individuals with a DSD condition. Developing a positive self-esteem and body image may be challenging. Sexuality, including adequate sexual function and good sexual wellbeing, is acknowledged to be an important aspect of quality of life. In individuals with DSD, sexuality may be influenced by sex-atypical physical appearance, sex hormone replacement therapy, past genital surgeries, as well as psychological issues such as identity questions, body image and self-esteem. In several DSD conditions gender variance and gender dysphoria may occur more often compared to individuals without DSD. Gender variance may be associated with lower levels of self-esteem and higher levels of anxiety and depression. To tailor care for individuals with DSD to their specific needs, the study of long term psychosocial outcome and its associations with various factors is needed.

Advancing DSD/Intersex health care through inclusive and affirmative medical training program

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There has been an ongoing advocacy focused on eliminating disparity and achieving equity in health outcomes of individuals with differences of sex development and intersex (DSD/intersex) conditions. To attain such goals, the creation of a DSD/intersex-centered training program dedicated to future physicians, educators, researchers, and other trainees across medical disciplines is of utmost importance. Here we describe systematic approaches in achieving inclusive and affirmative learning spaces and services in various areas and levels of medical training: 1) determination of essential learning pearls, 2) identification of curricular gaps and needs assessment, 3) development of strategies and methods to address such gaps, 4) funding and implementation, and 5) sustained engagement of advocates and relevant stakeholders. These efforts will better equip future health care providers with excellent and competent knowledge and skills in providing accessible and equitable care to DSD/intersex individuals.

The role of patient organisations in influencing care and research

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During a traditional development process a patient organisation (PO) undergoes a number of phases. In the first phase a PO provides contact opportunities for fellow sufferers and in the second phase POs start with providing information about the disorder(s) via newsletters, patient magazines, websites, webinars and meetings. In the third phase a PO gains awareness to be part of a broader healthcare environment and starts with advocating in the field of politics, medicines reimbursement processes, regulatory activities and seeks cooperation with other POs to find common goals. The demarcation of these phases are not always that sharp, but roughly this shows the development of a PO.

There is though a fourth phase to be distinguished. Patient representatives gain knowledge by training, for example in the field of medicine development processes. This training and other trainings prepare patient representatives for their role to fulfil equal partnerships with HCPs and researchers. The establishment of European Reference Networks for rare conditions gave a boost to the professionalisation of patient representatives. The ERNs provide in an extensive network of colleague patient representatives and HCPs and give the opportunity the to do research together, taking the patients perspective into account. This unique cooperation improves the quality of care and research, because the result is a co-production benefitting both patients and HCPs.

The Ethics of Intersex and Variations in Sex Characteristics: Do's and Don'ts based on a Minireview and the Shared Optimum Approach

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Clinical management of Intersex or Variations in Sex Characteristics (VSC) has undergone fundamental change in principles over the past 30 years but kept being highly complex and contested. With this fundamental shift of care over the past three decades, health care professionals, activists and supporters are currently finding themselves having to choose between the lesser of two evils: on the one hand, deferring decisions to adolescence or adulthood, and thereby treating a child as a small, incomplete adult with a limitation of parental rights, on the other hand limiting potential options of a future adult; thus creating the retrospective interpretation of medical treatment as unnecessary, coerced or even mutilating. Based on a mini review with a summary of present ethical recommendations, the article presents a comprehensive set of do's and don'ts based on mid-level principles in combination with the recently introduced shared optimum approach. All stakeholders should focus on specific and general thresholds of harm in a transparent and democratic manner, based on changing values, regional law as well as children's and human rights. At the same time, within the threshold, the field of shared optimum arises, where parents and growing children have discretion to find successful ways of implementing VSC into a child's and a future adult's life and

identity. Transprofessional teams, including supporting and advocacy groups, are a crucial part on the spectrum of shared decision-making and should become an essential part of a future concept of professionalism in VSC.

Benchmarking of care in DSD and CAH

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Background:
Benchmarking in healthcare improves efficiency, quality of care, patient safety and patient satisfaction. The process involves developing standards, sharing of best practice and evidence-based practice and then identifying potential areas of improvement. Key priorities for benchmarking include collecting a meaningful dataset, engaging clinicians, patients and families and using the findings to inform healthcare policy. The development of user-friendly tools to capture prospective data is essential. Benchmarking care for rare disease presents several challenges.

Discussion:
The I-DSD and I-CAH registries provide an opportunity to not only collect information about conditions but also to provide centres a perspective on their clinical care outcomes compared to other centres – potentially providing useful information to identify local care deficits enabling targeting of resources and driving improvement in care overall. Preliminary studies using real world data from the I-DSD and I-CAH registries have shown it is possible to use information from the registry to generate individualised centre-specific reports for aspects of care, such as adrenal insufficiency adverse events. Benchmarking data was fed back to individual centres and the majority found this information beneficial.

Conclusions:
Understanding the reasons for variation in care in DSD and CAH may provide insights into enhancing care in the future. Further work is needed to demonstrate whether benchmarking can improve care quality over time. This lecture will provide an overview of the developments in this area.

Oral Communication Abstracts – Session 1

OC 1.1

Current management of acute adrenal insufficiency related adverse events in children with congenital adrenal hyperplasia- results of an international survey of specialist centres

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Background:
There is wide variation in reported rates of acute adrenal insufficiency (AI) related adverse events (sick day episodes and adrenal crises) between centres. This study aimed to evaluate the level of consensus on criteria considered essential for defining and managing these events in children with Congenital Adrenal Hyperplasia.

Methods:
Active users of the I-CAH/I-DSD Registries (n=66), non-active users of I-CAH/I-DSD (n=35) and the EuRRECa e-Reporting Registry (n=10) were approached to complete an online survey.

Results:
56 clinicians from 27 countries responded to the survey; response rates for the three Registry groups were 42 (65%), 11 (31%) and 3 (30%), respectively. Written corticosteroid management plans and one to one patient/parent education were provided by 54 (96%) and 51 (91%) clinicians, respectively; 33 (59%) provided steroid-aware emergency cards. 56 (100%) and 55 (98%) clinicians advised an increase in glucocorticoid dosing (sick day dosing) in the event of fever or severe infection (eg. pneumonia). Less common indications for sick day dosing included vaccination and mild afebrile intercurrent illness, recommended by 17 (30%) and 9 (16%) clinicians, respectively. The most frequently reported sick day dosing regimen was tripling the total daily dose of hydrocortisone and administering 3 times daily, reported by 24 (43%) clinicians. 40 (71%) specified the duration of sick day dosing as ≥48 hours for severe infections. Vomiting and diarrhoea were the most common indications for intramuscular hydrocortisone, reported by 34 (61%) and 25 (45%) clinicians, respectively. Over 50% of respondents indicated that essential clinical criteria for adrenal crisis should include fatigue and nausea or vomiting and over 60% indicated that the criteria should include hypotension, hyponatraemia, hyperkalaemia and clinical improvement following parenteral glucocorticoids. A bolus parenteral injection of hydrocortisone and glucose infusions were the most frequently administered medications, reported by 50 (89%) and 32 (57%) of clinicians, respectively.

Conclusions:
Although there is considerable variation in the definition and management of AI related adverse events in children amongst specialist centres, there is also good evidence of consensus on specific aspects that can be used to develop standardised criteria and lead to greater benchmarking of care.

OC 1.2

Identification of small regions of overlap from copy number variable regions reveals candidate genes and novel chromosome loci for hypospadias

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Background:
Hypospadias is a common form of congenital atypical sex development, and it is often associated with other congenital comorbidities. Since chromosome microarray analysis (CMA) has not been historically considered first-line testing, the most common genetic findings implicated in hypospadias have been single sequence variations. Investigations of recurrent and overlapping copy number variations (CNVs) detected by CMA have resulted in the identification of genes and chromosome regions associated with various forms of differences of sex development (DSD).

Aims:
In this study, we identify smallest regions of overlap (SROs) from overlapping CNVs of individuals with hypospadias that may contain novel genes and regulatory regions.

Methods:
In this retrospective study, we investigate the DECIPHER database, as well as an internal institutional database, to identify overlapping CNVs among individuals with isolated and syndromic hypospadias. From such CNVs, we identify SROs and determine the genes and gene deserts within. We also analyze for the first time additional common phenotypes among individuals with hypospadias and overlapping CNVs.

Results:
We identified 75 SROs on 18 chromosomes, with highest frequencies on 22 (17 SROs) and 1 (9 SROs), and none on Y, 3, 14, 19, 20, or 21. These SROs contained 40 candidate genes and 14 candidate regions without protein-coding genes, or gene deserts, that had never been associated with hypospadias. We identified comorbidities across nearly all organ systems; however, the most common sexual development-related comorbidity was micropenis (3 SROs) and in other developmental pathways was neurodevelopmental abnormality (24 SROs).

Conclusion:
Increased utilization of CMA has resulted in an explosion of CNV data, mostly large CNVs. Further investigation of these CNVs through defining SROs provides a method to discover potential candidate genes and regions associated with hypospadias and, occasionally, additional comorbid phenotypes. These findings illuminate many novel candidate genes never previously thought to contribute to hypospadias.

These data may aid genetic counselling and management of individuals with hypospadias, as well as improve understanding of its underlying genetic aetiology and human genital development overall.

These results also demonstrate the powerful potential of microarray-based analysis in the discovery of genetic contributors of phenotypes with complex aetiologies, including DSD.

OC 1.3

The international SF1 next project: Description of a cohort of 107 individuals with SF-1/NR5A1 variants

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Background:
Variants in Steroidogenic Factor 1 (NR5A1/SF-1) lead to a broad spectrum of phenotypes, but data on the whole picture of phenotypes are currently lacking. We aimed to investigate the phenotype of individuals with SF-1 variants in a large international cohort.

Methods:
We identified the individuals through the international I-DSD network and through contacting researchers from previous publications on SF-1. Collaborators from 27 centres retrospectively entered phenotyping data according to the I-DSD registry and the Human Phenotype Ontology project in a REDCap database.

Results:
Clinicians provided comprehensive phenotype data of 107 individuals. Of those, 96 (90%) were 46,XY, nine were 46,XX (8%), and two were 47,XYY and 47,XXY respectively (1% each). Median age at follow-up was 12 years (range 0-54 years). Sex assignment at last follow-up was male in 62/107 (58%) and female in 45/107 (42%) individuals. Ten individuals had sex reassignment during the follow-up period (eight from female to male, one from male to female, one from other to male). Most (101/107, 94%) had differences of sex development (DSD), including 83/101 (82%) with disorders of gonadal development, 12/101 (12%) with non-specific XY DSD, disorders of androgen synthesis/action (2/101, 2%) or other types of DSD (4/101, 4%). In 95 individuals, we had sufficient data on overall health problems. Thirty-six of 95 individuals (38%) had health problems which were not DSD-related in the following organ systems: urinary (10/95, 11%), blood and spleen (each 9/95, 9%), skeletal and central nervous system (each 7/95, 7%), head/neck (3/95, 3%), adrenal, metabolism/homeostasis and psychosocial (each 4/95, 4%), integument and muscle (each 3/95, 3%), immune and endocrine (each 2/95, 2%), cardiovascular, connective tissue and peripheral nervous system (each 1/95, 1%). There were no abnormalities in abdomen, breast, vasculature or respiratory system.

Conclusion:

More than one third of individuals with SF-1 variants had multiple organ abnormalities, with a broad spectrum of phenotypes. Comprehensive gene profiling will allow to assess genotype-phenotype correlation and identify likely disease-causing variants in additional genes that might impact the phenotype. Genotype-phenotype patterns may help to identify individuals at risk for additional health problems.

OC 1.4

Pathway to Care among People with Disorders of Sex Development: Cohort Profile

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Background/Aims:
The "DSD Pathways" study was initiated to assess health status and patterns of care among people enrolled in large integrated health care systems and diagnosed with disorders (differences) of sex development (DSD). The objective of this cohort profile is to describe methods of cohort ascertainment for two specific DSD conditions: classic congenital adrenal hyperplasia with 46,XX karyotype (46,XX CAH) and complete androgen insensitivity syndrome (CAIS).

Methods:
Using electronic health records, we developed an algorithm that combined diagnostic codes, clinical notes, laboratory data, and pharmacy records to assign each cohort candidate a "strength-of-evidence" score supporting the diagnosis of interest. A sample of cohort candidates underwent a review of the full medical record to determine the score cutoffs for final cohort validation.

Results:
Among 5,404 classic 46,XX CAH cohort candidates, strength-of-evidence scores ranged between 0 and 10. Based on sample validation, the eligibility cutoff for full review was set at the strength-of-evidence score of ≥7 among children under the age of 8 years and ≥8 among older cohort candidates. The final validation of all cohort candidates who met the cutoff criteria identified 115 persons with classic 46,XX CAH. The strength-of-evidence scores among 648 CAIS cohort candidates ranged from 2 to 10. There were no confirmed CAIS cases among cohort candidates with scores <6. The in-depth medical record review for candidates with scores ≥6 identified 61 confirmed cases of CAIS.

Conclusion:
As the first cohort of this type, the DSD Pathways study is well-positioned to fill existing knowledge gaps related to management and outcomes in select DSD populations. Analyses will examine diagnostic and referral patterns, adherence to care recommendations, and physical and mental health morbidities examined through comparisons of DSD and reference populations, and analyses of health status across DSD categories.

OC 1.5

Designing a best-worst scaling survey for defining successful outcomes and trade-offs in DSD care

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Background/Aims:
Divergent views about successful care practices for differences of sex development (DSD) may lead to treatment decisions that do not align with the interests and priorities of patients and parents, negatively impacting quality of life. Novel to DSD, best-worst scaling (BWS) has been used in healthcare and other fields to measure preferences and acceptable trade-offs between attributes (e.g., treatment options). In the Defining Successful Outcomes and Trade-offs study, we developed a BWS survey to compare and contrast how individuals with DSD, parents of a child with DSD, DSD healthcare providers, and allied professionals define and differentially value DSD care processes and outcomes.

Methods:
The BWS survey was developed in several steps. In-depth interviews with DSD stakeholders (teenagers and adults with DSD, parents, DSD healthcare providers, and allied professionals; n=110) identified attributes related to (1) the process of achieving and (2) successful outcomes associated with DSD care. These attributes were iteratively refined throughout the interview process and used to create the BWS survey. Initial drafts of the BWS survey were pre-tested by stakeholders (n=17) via interview, followed by pilot testing of the survey by additional stakeholders (n=44).

The final survey was fielded to stakeholders (n=499) recruited through three pediatric medical

centers, each with an interdisciplinary DSD team, between May 2021 and March 2022. Importance scores for each attribute were calculated as follows: (number of times an attribute was selected as “most important”) - (number of times an attribute was selected as “least important”).

Results:
The final BWS survey comprised questions that encompassed a selection of 14 process attributes and 16 outcome attributes related to successful DSD care. Process attributes included “good communication between care team and patient/family” and “delay non-urgent treatments that cannot be reversed.” Outcome attributes included “patient satisfaction” and “successful treatment with surgery.”

Conclusion:
We report novel methodology for DSD through the development and application of BWS to examine preferences and trade-offs in clinical decision-making, across and between stakeholders. Using BWS, we hope to gain insight into traditional or shifting perspectives and priorities to guide clinical care and improve outcomes for those with DSD.

OC 1.6

A novel POR variant recurrently found in Argentine patients results in a wide spectrum of undervirilised phenotypes in 46,XY patients

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Background:
Cytochrome P450 oxidoreductase (POR) deficiency results in defective steroid production in the gonads and adrenals. Mutations in POR cause ambiguous genitalia in both 46,XX and 46,XY patients and adrenal insufficiency with/without bone malformations resembling Antley-Bixler syndrome.

Methods:
To report a novel p.Gly88Ser variant in POR identified in 4 Argentine families.

Results:
All index cases had 46,XY karyotype; patients 1-3 were assigned male and patient 4, female.

Patient 1 had micropenis, perineoscrotal hypospadias, partially fused labioscrotal folds, and inguinal gonads. External Genital Score (EGS) was 4.5 and he had bulbous nose and auricular skin tags.
Patient 2 had micropenis without hypospadias, fused and bifid labioscrotal folds with palpable gonads and EGS of 9. He had imperforate anus and colo-vesical fistula.
Patient 3 had micropenis, perineoscrotal hypospadias, partially fused labioscrotal folds with palpable gonads, and EGS of 7. His affected sister (46,XX) presented with primary hypogonadism at pubertal age.
Patient 4 presented with genital tubercle length within female range, one genital orifice and a left inguinal gonad. She had unilateral kidney agenesis and dysmorphic features (bulbous nose, flat nasal bridge, arachnodactyly, thoracic kyphosis).

All patients showed elevated basal ACTH, 17-OH progesterone and progesterone, normal cortisol without response to ACTH, and low androstenedione and testosterone without response to hCG. POR deficiency was suspected. None presented radiographic signs of Antley-Bixler syndrome. A novel homozygous variant NM_000941.3:c.262G>A/p.Gly88Ser in POR was found in all four patients and patient 3's sister. The variant was also detected in the heterozygous state in the parents that could be studied. No common ancestors have been found between the families.
The variant was classified as likely pathogenic (PM1, PM2, PS4, PP3) according to ACMG. Functional studies in vitro showed severe effects of the Gly88Ser variant on POR activity supporting the defect in steroid and drug metabolism

Conclusion:
The suspicion of a POR defect was mainly based on the characteristic biochemical pattern in undervirilised patients with 46,XY DSD. The p.Gly88Ser variant in POR presents a wide phenotypic spectrum. The existence of the same variant, not previously described, in 4 Argentine families raises the possibility of the existence of a founder effect.

OC 1.7

Timing of reconstructive surgery for individuals with differences of sex development (DSD): Stakeholder views on successful outcomes

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Background/Aims:

Few topics within pediatric medicine are as controversial as surgical management of newborns and young children with a difference of sex development (DSD). Disagreements exist both between and within stakeholder groups. The present study aimed to explore viewpoints regarding timing of urogenital and gonadal surgery in different stakeholder groups.

Methods:
Adolescents and adults with DSD (n=24), parents (n=19), healthcare providers (n=37) and non-healthcare professionals (n=30) shared their opinions about urogenital and gonadal surgeries. Interviews were transcribed and coded thematically; surgery-related codes and keywords were analyzed.

Results:
Many participants across stakeholder groups recommended parents decide against early non-emergent/elective surgery for their child, with intent to revisit the topic with their child as they age. However, other parents opted for early surgery. Common reasons cited for early surgery included: "improving" genital appearance, reducing stigma and shame, less painful recovery when younger, facilitating "normal" physical and sexual function, and cultural attitudes. Providers stated that parents favor typical genital appearance in their decision-making, though parents valued child happiness the most, whether they were for or against surgery. The most cited reason for not performing early surgery was irreversibility, though some affected individuals also listed pain and "hating" surgery. Most stakeholders stressed the importance of patient/family education (e.g., clinicians explaining all options, pros, cons, potential complications, and likelihood of future surgeries), and noted a preference for surgical decision making occurring during adolescence. Discussing options with affected peers was also listed as a valuable element of decision-making.

Conclusion:
The patient's participation in shared decision-making regarding surgery, when old enough, was considered important for successful care, and this was consistent across all stakeholder groups. Patients desired autonomy and parents expressed conflict over tradeoffs regarding timing of surgery. Providers and other allied professionals stressed the importance of process and education around surgical decisions.

Oral Communication Abstracts – Session 2

OC 2.1

Caregiver Perceptions of Stigma Associated with their Child's Difference of Sex Development

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Background/Aim:
Stigma is frequently reported as an accompanying feature of a difference of sex development (DSD); however, most reports involve convenience samples and first-person accounts of affected adults.

Qualitative research has shown that caregiver worries center on the child being stigmatized due to their DSD, prompting decisions for early urogenital surgeries and/or withholding information about the child's diagnosis from friends and family. In contrast, one survey of caregivers of chart-selected children and adolescents found that caregiver stigma ratings are generally low. Nevertheless, a subset reported experiencing moderate to high levels of stigma that linked to protectiveness of their child and wanting to keep the DSD private. To broaden our understanding of the prevalence of experienced or anticipated DSD-related stigma in clinic populations, we interrogated relevant stigma variables in the US-based DSD Translational Research Network (DSD-TRN) patient registry.

Methods:
The DSD-TRN is a network of pediatric medical centers providing interdisciplinary care to patients and families affected by DSD. Member sites contribute clinical data to a centralized registry. Caregivers (n=324; 79% women) of children/adolescents with a DSD (n=333; Mage=7.4 years, SD=6.5; 59% girls) completed a battery of psychosocial measures, including 3 stigma-specific questions: "My child will be treated differently because of his/her condition," "People will look down on us/treat us differently," and "Having a urogenital condition attaches a stigma or label to my child." Questions were answered using a 4-point Likert scale (1="not true for me" to 4="very true for me").

Results:
Caregivers generally reported that it was not true to a little true that their child will be treated differently because of their condition (M=1.8; SD=1.0), that people will look down on the family or treat them differently (M=1.4; SD=0.7), and that having a urogenital condition attaches a stigma/label to their child (M=1.6; SD=0.8).
However, a subset (n=96; 29%) also reported that at least one of these statements was mostly or very true.

Conclusion:
Approximately one quarter of caregivers with a child receiving DSD care at a tertiary care facility in the US indicated that stigma accompanied the condition. Providers should screen for the presence of and address implications of these experiences/expectations on clinical management decision making and psychosocial adaptation.

OC 2.2

Sexual Development and prenatal growth. Analysis of the prevalence of being born Small for Gestational Age (SGA) in a large DSD cohort, and the genotypic frequency of GHR gene polymorphism in non-disgenetic undiagnosed 46,XY DSD patients.

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Background:
Being born SGA is an associated condition to DSD, especially in those patients with non-specific disorders of undermasculinization. The relationship between the presence of genital abnormalities and intrauterine growth restriction is unknown. The GH-IGF system might be involved in mice and human sex differentiation. Furthermore, the GHR gene polimorfism (d3-GHR) has been associated with decreased fetal growth and lower birth weight.

Aims:
To evaluate the prevalence of being born SGA in a cohort of DSD patients evaluated in a single tertiary pediatric center, and its relationship with karyotype, molecular diagnosis, and phenotype. To analyze the genotypic frequency of d3-GHR gene polymorphism in the undervirilized undiagnosed 46,XY DSD group according to fetal restriction.

Methods:
Patients were classified according to karyotype. Birth Weight and length standard deviation SDS were calculated according to gestational age (Intergrowth21). Genotypic frequency of d3-GHR was also compared with the allelic frequency in control subjects (n=159).

Results:
We evaluated a cohort of 556 DSD patients classified as DSD46,XY 33%, DSD 46,XX 37%, and chromosomal DSD 29%. SGA was found in 25.4% of DSD 46,XY, 7% of 46,XX, and in 31% of chromosomal DSD. Molecular diagnosis was achieved in 38% of 46,XY and 95% 46,XX DSD patients. Accordingly to molecular diagnosis among 46,XY DSD patients, the frequency of SGA was higher in non-disgenetic patients without molecular diagnosis and apparently normal testicular function ($p < 0.05$).In the latter, no difference was found in the frequency of d3-GHR allele polymorphism among SGA and non-SGA, neither the control group (p=ns).

Conclusions:
The frequency of being born SGA in 46,XY DSD group was higher in non-dysgenetic patients with unknown etiology. The allelic frequency of the d3-GHR gene polymorphism might not be involved in this association. Finally, intrauterine growth retardation in DSD 46,XY patients remain poorly understood. Further studies to assess the role of other factors involved in early embryonic growth and development, and in gonadal differentiation are needed.

OC 2.3

"I believe God doesn't make mistakes, and I am wonderfully made in His image": The intersection of religion/faith and clinical care in Differences of Sex Development.

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Background/Aims:
Individuals with differences of sex development (DSD) and their families are subject to social and cultural factors impacting their perspectives and decision-making around their condition and clinical care. Religious beliefs are important for most of the United States (US) population. The 2006 DSD Consensus Statement recognized that religious factors can influence treatment choices. However, literature exploring the role of religion/spirituality in this population is scant and these factors are inconsistently integrated during DSD care delivery. As part of the Defining Successful Outcomes and Trade-offs (DSOT) study, we explored the intersection of religion, faith and spirituality within DSD care delivery.

Methods:
US stakeholders (n=110), comprising individuals with DSD (n=24; aged 15-39y), parents (n=19), DSD healthcare providers (n=37), and other allied professionals (n=30), participated in semi-structured interviews. Participants were asked what constituted successful outcomes for those with DSD and how to achieve them. We identified transcript passages with keywords relating to religion, faith and spirituality, and reviewed overarching themes and significant topic areas therein.

Results:
Religion was identified as an important factor in how individuals understood DSD and in decision-making regarding care delivery. Discussion of religion during interviews varied based on role, from 0% (urologists/surgeons) to 100% (gynecologists, parents involved in support organizations). Participants with minimal/no religious affiliation reported more freedom in decision-making. For those with religious affiliations and faith, some found comfort and purpose (creational intent) through religion; others expressed guilt or rejection if choices led to "sin". A major theme encompassed foundational beliefs underpinning gender - including social order, sexuality and reproductive potential. These, in turn, influenced clinical decision-making regarding gender of rearing, genital surgery and fertility options. While religious communities may offer support and acceptance, some participants reported ignorance and rejection by religious leaders and schools.

Conclusions:
Integrating religion/faith is important in optimizing patient- and family-centered DSD care and outcomes. More education is needed for both providers and religious communities. Involving hospital chaplaincy may provide a bridge to promote spiritual health and resilience and complement DSD team care.

OC 2.4

Experiences and needs of variation in sex characteristics peer support members in the prenatal setting

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Background/Aims:
Advances in genomic technologies have led to a greater proportion of variations in sex characteristics (VSC) being detected prenatally. Prospective parents in this setting may choose to continue or terminate their pregnancy. In this context, they can turn to peer support group (PSG) members, people directly connected to VSC, for information and support. Yet we do not know the experiences of these PSG members, and what additional needs they may have, to fulfil this role. To address this knowledge gap, our aim was to explore the experiences and needs of VSC PSG members who have provided support to prospective parents who 1) have received a prenatal VSC diagnosis, and/or 2) are considering undergoing prenatal testing for VSC.

Methods:
In this exploratory qualitative study, we conducted semi-structured interviews with VSC PSG members to understand and describe their experiences and needs. Interview transcripts were analysed via thematic analysis to generate themes strongly linked to the data.

Results:
We interviewed five Australian-based participants, identifying eight themes related to three domains of enquiry: 1) current practice: personal link to VSC is both a benefit and a burden, respecting decisions, providing tailored information; 2) gaps/challenges: limited capacity to support, variable training; and 3) wishes/priorities: need for improved healthcare services, need for validated peer support training, and incorporating peer support into holistic care.

Conclusions:
We found that whilst PSG are perceived to play an important role in the prenatal setting, there are several challenges which impede their capacity to provide support. Accordingly, we identified multiple ways healthcare professionals and PSG can potentially improve VSC peer

support and care for prospective parents in the prenatal setting. Implementing these strategies could help to ensure PSG are well-supported and equipped to provide prenatal peer support. Importantly, this may also increase the chances of prospective parents receiving sufficient support and information at this sensitive time.

OC 2.5

46,XY Partial gonadal dysgenesis; diagnosis and long-term outcome at puberty

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Background
46,XY Gonadal dysgenesis (GD) is classified as complete (CGD) or partial (PGD) based on gonadal morphology and function. The diagnosis of PGD is based on clinical, biochemical, histological and genetic findings. This study aims to evaluate clinical features of GD and pubertal outcomes of PGD in a large cohort, with CGD as a comparator.

Methods:
Patients with 46,XY GD were identified from the I-DSD Registry and data on phenotype,

genetics, puberty and histology were collated. CGD inclusion criteria; (1) 46,XY (2) typical female genitalia (3) presence of Mullerian duct derivatives, and (4) if pubertal, elevated LH/FSH. PGD; (1) 46,XY (2) atypical genitalia (3) at least 1 of the following:

(A) evidence of gonadal dysgenesis (Testosterone level after HCG < double the basal value, AMH in-between male and female references or low inhibin B or Mullerian derivatives), (B) histology consistent with PGD, or (C) pathogenic variant in gene associated with GD. Group categories were: CGD, PGD assigned female at birth (PGDf), PGD (PGDm) assigned male at birth.

Results:

	CGD (n=109)	PGDf (n=82)	PGDm (n=109)
Presenting complaint	Delayed puberty 53/95 (56%); Incidental karyotype findings 25/95 (26%); Germ cell tumour symptoms 10/95 (11%)	Atypical genitalia 56/74 (76%); delayed puberty 9/74 (12%); primary amenorrhea + virilisation 4/74 (5%)	Atypical genitalia 103/103 (100%)
Presence of uterus	94/105 (90%)	46/79 (58%)*	31/100 (31%)*
Genetic cause identified	48/109 (44%)	40/82 (49%)	45/109 (41%)
Associated health issues	48/101 (48%)	48/74 (65%) #	37/99 (37%)
virilisation with gonad(s) (>=14y)	N/A	9/24 (38%)	33/59 (56%)

Conclusion:
This large study of 300 patients with GD highlights the heterogeneous phenotype of PGD compared with CGD and the consequent diagnostic challenge. Many PGD patients with preserved gonads have the potential to develop puberty spontaneously. Further studies should evaluate the role of histological data in diagnosis and prediction of the risk of germ cell malignancy in PGD.

OC 2.6

Genital skin wound healing is associated with the extent of external virilisation in boys with hypospadias

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Introduction:

Surgical repair of hypospadias is associated with high rates of surgical complications, including wound dehiscence. It is not clear whether any clinical factors predispose to impaired wound healing in boys with hypospadias.

Aims:
To identify if cell migration and proliferation in genital skin is altered in boys with hypospadias.

Methods:
Genital skin (GS) samples were collected from boys undergoing hypospadias repair (cases) or routine circumcision (controls) for GS fibroblast culture. Cells were seeded onto a 6-well plate at a density of 100,000 cells/well using a haemocytometer and grown until 80% confluence. A sterile pipette tip was used to scratch a wound. Cells were imaged using an EVOS XL Core microscope immediately after the wound was made and 48 hours later. Cell migration was determined by averaging 3 measurements within the centre of the scratch using ImageJ software. Cell proliferation was measured using a commercial Cell Count Kit-8 (Abcam, UK).

Results:
Seven cases (median age (range) 1.8 (1.2, 6.3) years) and seven controls (median age 1.6 (1.2, 6.1) years) were recruited. Of the boys with hypospadias, 3 (43%) had proximal hypospadias and 4 (57%) had distal hypospadias. The median EMS of cases was 10 (3, 11). There were no statistically significant differences in endocrine biochemistry between the 2 groups at the time of surgery. Genetic testing had been performed in all proximal hypospadias cases, with no variants identified. Boys with hypospadias had impaired cell migration with reduced % wound closure at 48 hours (26.3 vs 41.3 %, p=0.049) and reduced cell proliferation (0.16 vs 0.21 nm, p=0.01). External Masculinisation Score was positively correlated with % wound closure (r=0.7, p=0.008) and cell proliferation (r=0.6, p=0.007). There were no statistically significant correlations between birthweight, gestation at birth or endocrine biochemistry.

Conclusions:
There is an association between wound healing and virilisation of the external genitalia in boys. Further research is required to elucidate the underlying mechanism for dysfunctional wound healing in boys with hypospadias. Understanding this association may lead to improved surgical outcomes.

OC 2.7

Psychological impact on parents of children born with atypical genitalia in India

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Background:
Parents of children with DSD (Disorders of sex development) are known to suffer from psychosocial and mental issues including depression, anxiety, and post-traumatic stress at the

time of diagnosis. Apart from uncertainty and limited information about child's condition, there is an additional social stigma to bear. Through this study, we have analysed the prevalence of anxiety and depression in Indian parents of children with DSD and associated risk factors. We elicited the experiences and perceptions of the parents, and their expectations from the healthcare systems.

Methods:
This is a cross sectional study including parents of 40 children of age less than 6 years with confirmed diagnosis of 46XY DSD (N= 22) or 46 XX DSD (N=18) with atypical genitalia (Prader stage of 3-5 in females or external masculinisation score of less than 9/12 in males). Children with known co-morbidities or parents with known psychological disorders were excluded. Data was collected through face-to-face semi-structured interview using specially designed questionnaire consisting of closed as well as open-ended questions. Depression and anxiety have been assessed using PHQ9 and GAD7 scales respectively.

Result:
DSD was diagnosed at birth in 12/40 patients. 5/18 patients with 46, XX DSD were raised as males and 3/22 of 46, XY DSD raised as females. The mean age of diagnosis of DSD was 15 months. Moderate to severe depression was found in 23% (7/30) and 24% (8/33) fathers and mothers respectively whereas moderate to severe anxiety was seen in 16% (5/30) fathers and 27% (9/33) mothers. Parents with a 45 XX child with virilisation had higher rate of psychological morbidity due to the concerns of future marriage and infertility whereas parents with support of extended family seemed to be well adjusted. Gender was assigned at birth to 35/40 children without a karyotype report. Other issues included parental guilt, blaming of mother, and myths surrounding DSD with inability to distinguish between transgender and DSD conditions. Majority of patients feared sending their children to school and 26/40 parents wanted an early surgical correction.

Conclusion:
There is a high level of depression and anxiety amongst Indian parents of children born with atypical genitalia. Parents are in need of psychological support and guidance regarding diagnosis, management and prognosis of DSD. Future studies should assess the impact of psychological counselling on mental health of parents.

Poster Presentations

PO 1
A digital network for professionals providing psychosocial care in DSD

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Background:
DSD have a large impact on psychosocial wellbeing. Variances in sex development, either somatic in behaviour or identity, makes one vulnerable for social stigmatization. Psychosocial care is provided to support acceptance and optimize chances for self-actualization and social participation. Changes in medical knowledge, clinical practices and parental and patients' attitudes and expectations will change practice in psychosocial care.

A survey1 conducted under COST Action BM1303 revealed a large diversity among providers of psychosocial care and a lack of common grounds for evidence based psychological interventions. An organizational body to stimulate collaboration and professionalization is missing. Online meetings in a secured digital environment facilitate the start of such an organization.

Aim:
Building an organizational body for providers of psychosocial care by starting a digital learning network for professionals providing psychosocial care in DSD.

Methods:
Presentations of our ideas a working group held at two online conferences in 20212 to investigate the need
among colleagues to participate in such an organization. Application for ERN Exchange stipends for short visits to Rotterdam and Stockholm.

Results:
Our workshops were visited by colleagues who supported our ideas and shared our plans among colleagues locally.
ERN-Exchange stipends facilitated us to collaborate intensively to work out our plans.
The kick-off meeting was organized the 28th of January 2022. The meeting was attended by 24 participants from Europe and the USA, all involved in psychosocial care in multidisciplinary DSD-teams. Colleagues presented their DSD team and their ideas for this network. Ideas were discussed and an agenda for the next meetings was set up. A dropbox was installed to share presentations, meeting notes, references, etc. A second meeting will be organized the 20th of May.

Discussion:
Our initiative is welcomed by many colleagues. With participating colleagues, we shared our need to discuss, develop and evaluate our professional practice. In future meetings, we hope to welcome colleagues we did not reach yet.

PO 2
Sexual self-concept in women with DSD

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Background
Many women born with disorders or differences of sex development (DSD) report sexual problems, in particular women who have undergone extensive genital reconstruction. Examining cognitions and emotions that hinder or promote sexuality (i.e. sexual self-concept) may facilitate understanding these sexual problems and may contribute to the development of specific interventions.

Aim
Investigation of sexual self-concept, body image and sexual functioning in relation to genital surgery.

Methods
Study 1 Evaluation of the psychometric properties of our Dutch translation of the Women's Sexual Self-Concept Scale (WSSCS) in a sample of 589 healthy Belgian and Dutch women aged 18-65, median age 23, participating in an anonymous web-based survey.
Study 2 Follow-up study in women with DSD (N=99, aged 17-60, median 26y) and control women. Main outcome measures: questionnaires on sexual self-concept (WSSCS-D), body image (Body Image Scale), sexual functioning (Female Sexual Functioning Index) and sexual distress (Females Sexual Distress Scale-Revised).

Results
Study 1 Evaluation of the Dutch version of the WSSCS (WSSCS-D) revealed a three-factor structure that corresponded largely to that of the original version.

Study 2 Compared to control women, women born with a DSD described themselves as being less interested in sex and less sexually active. These women also harboured more negative emotions and cognitions regarding their sexuality and were less satisfied with their external genitalia. In women with a DSD, sexual self-concept was associated with compromised outcomes on sexual functioning and distress. Women who were in a steady relationship and/or had been sexually active in the past four weeks had a more positive sexual self-concept, took a more active role in their sexual relationship, experienced more sexual desire and arousal and less sexual distress, than women who were not involved in a partner relationship.

Discussion
Findings in this study indicate that cognitions and emotions related to sexual self-concept play a role in sexual functioning of women with a DSD. A cognitive behavioural counselling approach

with focus on coping and exploration of the own sexual needs could prove useful in this group. This study is accepted for publication in Archives of Sexual Behaviour.

PO 3

Cognitive executive functioning in relationship to karyotype in children with monosomy x

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Background

Women born with complete or partial monosomy X report an excess of behavioral, emotional and social difficulties compared with typical females of the same age. Affected psychosocial wellbeing and obstacles in social functioning become impairing during adolescence and continues into adulthood. Factors that explain the psychosocial backlog are unknown yet. Most females with Turner syndrome have intellectual abilities in normal ranges, but poor skills in executive functions are common and are associated with impairments in attention, working memory, cognitive flexibility, processing speed and social cognitions such as ability of face recognition, recognition of facial emotional expression and difficulties to comprehend other people's feelings and intentions.
It is assumed that the combination of deficits in social-cognitive processing and executive function predispose these females into social interaction difficulties. Peer relationships are not a concern during childhood, most social difficulties emerge and become impairing during adolescence. The lack of estrogen may contribute to impaired executive and social-cognitive processing in adolescence, possibly because it occurs during a critical period for brain development. In young children executive functioning and social cognition received less attention and studies are scarce.

Aim

Investigation of executive functioning in relation to genetic loss in school-aged children with complete and partial monosomy X.

Methods

Design Retrospective cohort study
Patients Children with complete or partial monosomy X (45,X; 45,X/46,XX; 45,X/46,XY) aged 5-12 years old visiting the Turner outpatient clinic of the Sophia Children's Hospital of Erasmus MC. Children with mental retardation were not included.

Outcome measures
Executive functioning: Digit Span (working memory) 'Symbol Search and Coding (processing speed) from WPPSI- III/IV-NL and WISC-III/V-NL; Auditory Attention and Response set (selective and sustained auditive attention, Inhibition (suppress impulsive reactions) and Word Generation (cognitive flexibility) from NEPSY-2-NL; Key Search, Zoo Map and Six Parts (planning and time management) from BADS-C-NL and BRIEF questionnaire (executive functioning problems in daily life).Karyotypes from cytogenetic analysis in peripheral blood cultures.IQ-scores from WPPSI-III/IV-NL and WISC-III/V-NL intelligence scales for children)

Results
Findings will be presented on poster presentation at I-DSD 2022.

PO 4
Information Sharing in DSD: The Creation of a Caregiver-Support Tool

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Background/Aims:
Social support can protect against negative mental health outcomes experienced by some parents/caregivers of a child with a difference of sex development (DSD). Parent hesitancy to share information isolates them from established social supports and may set the stage for an unhealthy sense of shame or secrecy within the family. Healthcare providers can assist parents to feel more comfortable sharing information with the important people in their lives. This presentation will (1) describe clinician needs assessment results regarding information sharing among DSD Translational Research Network (DSD-TRN) Psychosocial Workgroup (PWG) members, and (2) summarize the subsequent development of a clinical tool to help providers facilitate discussions regarding information sharing with caregivers of children with DSD.

Methods:
DSD-TRN PWG members (N = 19; 70% response rate) completed a survey about their experiences facilitating information sharing discussions with parents of children with DSD. Results were reviewed with PWG members to clarify the needs of providers to facilitate the creation of a clinician tool. The clinician tool was created and iteratively reviewed with the PWG for feedback and refinement.

Results:
The results of the survey indicated that providers believe information sharing discussions are important and that their ability to facilitate these conversations could be improved with more

experience/education, having a written resource, more research, peer support, and more time with parents. The clinical tool included the following elements: (1) an evidence-based rationale for facilitating information sharing conversations with caregivers along with references, (2) common clinical considerations and potential behavioral communication interventions, and (3) a series of prompts to help caregivers explore their social support networks for the purpose of identifying potential recipients of shared information.

Conclusion:
The DSD Sharing Health Information Powerfully – Team Version (SHIP-T) is a resource for DSD healthcare providers to utilize in hospital and ambulatory settings to help caregivers of children with DSD share information with their social support networks. Future directions include transitioning the SHIP-T to a caregiver handout and expanding the resource to other aspects of information sharing (e.g., caregiver sharing information with their child about their condition).

PO 5

Defining Successful Outcomes and Trade-offs in Differences of Sex Development: Parlaying Stakeholder Valuations into Educational Resources for Healthcare Providers

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Background/Aims:
Clinical management of differences of sex development (DSD), congenital conditions in which chromosomal, gonadal, or anatomic sex development is atypical, is in a state of flux. There are disagreements within and between professional, advocacy, and patient communities regarding optimal healthcare delivery. The Defining Successful Outcomes and Trade-offs (DSOT) study seeks to identify unique and overlapping perspectives of teenagers and adults with a DSD, parents of a child with a DSD, providers, and other professionals regarding clinical practices and

outcomes in DSD care.

Methods:
The ongoing mixed methods DSOT study comprises three phases: (1) identifying what constitutes successful clinical management practices and outcomes through in-depth, semi-structured interviews with members of diverse stakeholder groups (n=110); (2) ascertaining trade-offs that stakeholders make using best-worst scaling methods (n=497); and (3) designing provider educational content, informed by Phases 1 and 2, that clarify and integrate medical evidence with patients' or families' values and preferences to facilitate shared decision making (SDM).

Results:
Seven themes (e.g., understanding diagnosis and self-efficacy in management are necessary but complex) leading to successful outcomes for individuals with a DSD emerged from Phase 1. Phase 2 queried two major areas: process (14 attributes) and outcome (16 attributes). Together, Phases 1 and 2 identified an area of need that could be improved through the educational resources being created in Phase 3: shared decision making, as facilitated through the creation of decision aids for parents of infants/young children with DSD. Decision aids are focused on choosing a gender of rearing (boy/girl/gender neutral), genetic testing, urogenital surgery, and gonadal surgery. Curriculum modules include: (1) an introduction to SDM; (2) how to apply patient decision aids to improve the process and outcomes of SDM; (3) practicing/implementing SDM within specific clinical scenarios; and (4) SDM with proxy (or multiple) decision makers.

Conclusion:
The approach utilized in the DSOT study to understand differential valuation of clinical management elements and develop data-driven educational materials is generalizable to other pediatric conditions involving multidisciplinary care in which treatments are elective and dependent on patient or family values and preferences.

PO 6
Optimizing delivery of care for individuals with differences of sex development (DSD): Defining successful outcomes and trade-offs

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Background/Aims:
Clinical care of individuals with differences of sex development (DSD) is complex, challenging and controversial. Expert Consensus in 2006 called for an experienced multidisciplinary team that integrates psychosocial care, recognizing the complementary role of peer support groups, in optimizing DSD care. While these ideals are widely accepted, the care model often falls short due to divergent levels of implementation, deficient care coordination, inadequate education and communication, deficiencies in transition to adult care, and suboptimal advocacy organization and provider collaboration. In the Defining Successful Outcomes and Trade-offs Study, we aimed to: 1) evaluate how individuals with DSD, parents, healthcare providers and allied professionals perceive success in the delivery of DSD care; and 2) identify associated trade-offs and challenges.

Methods:
Teenagers and adults with DSD (n=24), parents (n=19), DSD healthcare providers (n=37), and allied professionals (n=30) completed audio-recorded interviews exploring features of successful outcomes and how to achieve them. Recordings were thematically coded and analyzed using NVivo software. Quotes specific to delivery of DSD-related healthcare services were analyzed.

Results:
Participants (n=110) underscored a coordinated interdisciplinary team of experts (including a psychologist) who communicate and collaborate well as central to success in the delivery of DSD care. Team care should be patient-centered: holistic, individualized (including attending to patients' cultural and religious values), empowering and supportive. Teams should present all management options, including psychological support, and the value of non-surgical providers in balancing decision-making around surgical and non-surgical choices was key. Participants endorsed the importance of peer/family support and discussed potential incorporation into team care.
Trade-offs and challenges included financial cost and lack of psychological services, feeling overwhelmed by a large team, dearth of adult care, and facilitating peer/family support.

Conclusion:
Patients with DSD need long term, coordinated, individualized, interdisciplinary care. Future directions include incorporating patient and family voices and support into DSD team care. Participants' values and preferences will contribute towards creation of resources for healthcare providers to facilitate clinical decision- making and improve outcomes for individuals with DSD.

PO 7
Defining success in the delivery of fertility-related care for patients with differences of sex development

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Background/Aims:

Individuals with differences of sex development (DSD) experience complex, often competing, medical and psychosocial challenges. Among these challenges, the perception and importance of fertility to individuals with DSD, parents, healthcare providers and other stakeholders are not well characterized. These perspectives are paramount to providing comprehensive care. As part of the Defining Successful Outcomes and Trade-offs Study, we aimed to characterize stakeholders' perceptions of the importance of fertility, including how "success" in fertility is defined and how this can be achieved.

Methods:
DSD stakeholders (n = 110) participated in small-group or individual, audio-recorded, semi-structured interviews discussing the clinical care of patients with DSD. Primary questions included: "What is a successful outcome in DSD care?" and "How do you achieve it?" Fertility also was a suggested topic to discuss. Transcripts were examined qualitatively utilizing a phenomenological approach; themes were coded using NVivo software. This analysis focuses on the extracted themes related to fertility.

Results:
Fertility was discussed by 19/24 individuals with DSD, 12/19 parents, 35/37 healthcare providers, and 19/30 other stakeholders. Success related to fertility included knowledge of the DSD condition, associated fertility potential, and options for fertility preservation, as well as the realization of parenthood (biologic or other), if desired. Important components to achieving this success included the following:

1) timing of care (early introduction, reintroduction in adolescence and young adulthood, and discussion on multiple occasions)
2) information provided (DSD condition, associated fertility potential, options for fertility preservation, options for fertility through assisted reproductive technology, and alternative family-building)
3) quality of communication (culturally, developmentally, and age appropriate). Trade-offs identified included anatomic form versus sexual or reproductive function, fertility preservation versus cancer risk reduction, and balancing the different priorities of stakeholders (e.g., the priorities of individuals with DSD versus their parents).

Conclusions:
A wide range of DSD stakeholders cited fertility as important to achieving successful outcomes for individuals with DSD. These stakeholder perspectives should guide fertility-related information-sharing, decision- making, and clinical care.

PO 8

Frequency analysis of ten years' experience in a multidisciplinary clinic of pediatric patients with differences of sexual development in Mexico City

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Background:
Differences of sexual development (DSD) are medical conditions in which the sex chromosome, gonads, or genitalia are different. They frequently occur in newborns with atypical genitalia. The international prevalence of newborns with atypical genitalia is approximately 1 in 3,000. In whom sex assignment is delayed after birth, it is 1 in 11,000 births. DSD are classified depending on the karyotype result into three subclasses: 46,XY DSD, 46,XX DSD, sex chromosome DSD. Currently, there is no report about DSD frequency in the Mexican population. This project aims to analyse DSD frequency in a Mexican pediatric population in ten years.

Methods:
This project was performed in the "Hospital Infantil de México Federico Gómez". We identified the DSD patients from the records of the karyotype results from 2011 to 2021. The inclusion criteria were patients with atypical genitalia, bilateral cryptorchidism, micropenis, proximal hypospadias, clinical diagnosis of congenital adrenal hyperplasia, or apparently females with inguinal hernias.

Results:
In ten years, we had a total of 446 patients with DSD; of these, 261 patients (58%) corresponded to a 46,XY DSD, 141 patients (31%) were 46,XX DSD, and 44 patients (9.8%) had a sex chromosomal alteration. The 46,XY patients´ main clinical characteristic was atypical genitalia in 98 cases, representing 38% of the 46,XY DSD. Followed by 33 patients (12.6%) with bilateral cryptorchidism. As reported in the literature, the most frequent diagnosis in patients with XX DSD was congenital adrenal hyperplasia in 57 patients. Six patients had a diagnosis of ovotesticular XX DSD, and one patient with testicular DSD. The main karyotype of the patients with sex chromosome DSD was 45,X/46,XY in 12 patients (27%). We had nine patients with atypical genitalia and a 47,XXY karyotype.

Conclusions:
Our hospital is a centre of reference in which patients from all over the country are studied. Therefore, knowing the frequency in this population may indicate the number of patients with DSD in Mexico. This will help develop clinical diagnosis strategies and highlight the importance of genetic analyses to obtain an accurate diagnosis. Ultimately, our project will impact the development of public health strategies in our country.

PO 9

Exploring Prenatal Testing for Difference of Sex Development from a Genetic Healthcare Providers' Perspective

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Background/Aims:
During pregnancy, non-invasive prenatal testing may suggest an increased chance of sex chromosome aneuploidy (SCA), while other Differences of Sex Development (DSD) may be suspected on ultrasound or confirmed with targeted pre-implantation or antenatal genetic testing. Genetic healthcare providers (HCP) facilitate result disclosure, informed decision-making and referral to specialists and peer support groups (PSG). The primary aim of this research was to explore the perceptions and experiences of genetic HCP when supporting parents who have received a prenatal test result that suggests an increased chance of a DSD, with a secondary focus on PSG involvement.

Methods:
Genetic HCP from services across Australia with recent experience delivering prenatal test results for DSD were invited to participate in semi-structured interviews. Inductive thematic analysis was performed combined with a phenomenological approach, to enrich understanding of the lived experience. Two transcripts were co-coded independently by two researchers for academic rigour.

Results:
Eleven genetic HCPs from five Australian states participated in this study: three clinical geneticists and eight genetic counsellors.
Experience discussing results relating to SCA was described by all participants.
Three key themes were identified.
1) Delivering information: "trying to paint them a balanced view";
2) Counselling for uncertainty: "it just leaves them with uncertainty";
3) Using resources for support: "directing them to the right source".
Genetic HCP commonly referred to resources developed by PSG to provide insight into the lived experience of
DSD and facilitate meaningful synthesis of information. However, they were mindful that this information may not always be relevant and may cause unnecessary concern for some families.

Discussion/Conclusions:
Genetic HCP sought to provide balanced and accurate information about DSD and their anticipated associations, often with referral to written resources. The broad phenotypic associations of SCA and uncertainties predicting outcomes in individuals where SCA is identified antenatally made this challenging for HCP; similarly, these issues were also perceived to somewhat undermine the value of resources and PSG in this cohort. This study highlights the challenges that arise during prenatal counselling for DSD and supports the need for improved resources for HCP and prospective parents/people who receive prenatal results.

PO 10

Prenatal ultrasound and genetic evaluation of atypical genitalia in possible Disorders/ Differences of Sex Development - Counseling aspects and outcome

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Objective:
To report uptake of genetic counseling and prenatal genetic testing after the finding of atypical genitalia on prenatal ultrasound and the clinical and genetic outcome of these pregnancies as little is reported on this topic so far.

Methods:
A retrospective cohort study (2017-2019) of atypical fetal genitalia in our DSD expert center. We describe counseling aspects, invasive prenatal testing, genetic and clinical outcome of fetuses without (group 1, n=21 ,(36%)) or with (group 2, n=37, (64%)) additional anomalies on ultrasound.

Results:
In group 1, 86% of parents opted for genetic counseling versus 73% in group 2, and respectively 56% and 27% of these parents refrained from invasive testing. Atypical genitalia were postnatally confirmed in 90% (group 1) and 65% (group 2). At birth additional anomalies were present in 19% of group1 fetuses and not confirmed in 11% of group 2 fetuses. Four postnatal genetic diagnoses were established in group 1 (19%) and eight prenatally plus two postnatally in group 2 (27%). The total genetic diagnostic yield was 24%. No terminations of pregnancy occurred in group 1.

Conclusions:

For optimal care, referral for an expert fetal ultrasound scan, genetic counseling and invasive diagnostics including broad testing should be offered after prenatal detection of isolated atypical genitalia.

PO 11

Testosterone or DHT treatment during first year of life had no effect on behavior in boys with 46,XY DSD

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Background/Aims:
Hypospadias and micropenis is common in boys with XY,DSD. Treatment with testosterone or dihydrotestosterone (DHT) have been performed during the first year of life with the aim to promote penile growth. Prenatal androgen exposure is known to affect behavior in masculine direction. However, the effect of treatment with early postnatal androgens on behavior is not previously studied. The aim was to investigate the effect of androgen treatment during first year of life on later behavior in boys with hypospadias using play observation and parental questionnaires.

Methods:
42 boys with hypospadias, aged 2-6 years, were included. Patients were excluded due to genetic karyotype (46 XX), assigned gender and missing data. The boys were recorded playing with a set of toys valued as either masculine, feminine or neutral. The boys and parents answered questionnaires concerning their behavior. The results were compared between the boys treated with testosterone or DHT and those non-treated and also related to the severity of hypospadias.

Results:
Treatment did not significantly affect toyplay. Parents reported less active behavior, e.g. less energetic and prefers quiet games compared to active ones, in the treated boys at 3 but not at 5 years. Boys with more proximal (severe) hypospadias played more with feminine and less with masculine toys regardless of treatment.

Discussion/Conclusions:
This study showed no clinically significant effects of androgen treatment during first year of life on behavior in boys with hypospadias, nor did we see effects of androgen exposure on attention span and ability to concentrate. The severity of hypospadias seemed to affect toyplay, suggesting the importance of prenatal androgens rather than postnatal androgens for development of gender typical behavior.

PO 12

Understanding and implementing the new German legislation on "protecting children with variation of sex development" – psychological and sociological perspectives

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Background/Aims:
In May 2021, the German parliament passed a new, long-debated and controversial law "to protect children with a variation of sex development/sex characteristics" from medically unnecessary surgeries until they are old enough to decide for themselves. This law joins various laws passed in other countries in recent years and recognizes the rights to self-determination and bodily autonomy, especially genital autonomy of newborns with variations of sex development. In this paper, we address details of the new legislation from psychological and sociological perspectives and focus on these questions: How is the law perceived in the general public as well as by professionals and families involved? What is the new role of psychosocial professionals in implementing the new law? Which implementation strategies can be used / are fruitful to bring legislation into live and to include both medical professionals' competences as well as families affected?

Methods:
We present recent data of different qualitative study methods including discourse analysis of the law's versions; participant observation of committees and discussions around the enactment of the law, as well as expert interviews with medical professionals.

Results:
Although this legislation enables the "wait and see" approach, which overwhelms the traditional "social emergency" policy to quickly "repair" atypical genitalia, it overlooks many questions and has significant blind spots. E. g. it is unclear which VSD conditions require immediate surgical intervention and which not; it ignores the important distinction between genital appearance, genital function, and gender identity as well as the meaning of bodily autonomy for children with VSD.

PO 13

Digital photography in the evaluation and management of female patients with congenital adrenal hyperplasia: a standardized protocol for quality improvement

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Background/Aims:
Digital photography can be securely stored in the medical record and enhance documentation of physical exam findings and monitor wound healing. A standardized protocol that respects the dignity of the patient and maintains the fidelity of objective documentation is needed for patients with differences in sexual development (DSD) and congenital adrenal hyperplasia (CAH). The purpose of this study was to evaluate the feasibility, acceptability, and applications of a HIPAA-compliant digital photography protocol in the care of female patients with CAH.

Methods:
A protocol for standardized digital imaging including consent, permission, data capture, and storage in the electronic medical record (EMR) was implemented. Patients undergoing physical examination during multidisciplinary CAH clinic visits, preoperative evaluation, and postoperative follow-up from October 2020 through May 2021 were included. Male patients with CAH, patients with clitoromegaly or urogenital sinus not from CAH, and patients seen through telehealth were excluded. Consent was obtained from caregivers and permission from patients. Images of the exam were taken during clinic visits or at the time of surgery with no identifying features included. Images were directly uploaded into the patient's chart in the HIPAA-protected EMR separate from other clinical documentation and not stored on personal devices

Results:
There were 17 patients with CAH seen with median age 6 years (range 2 weeks – 18 years). There was a median of 3 photos per patient during the study period with cooperation from both the patient and their caregiver. Amongst the patients seen, 6 patients underwent reconstruction with a median of 10 photos per patient. Images were available and used for preoperative planning and counseling. Patients with previous images did not require repeat examinations and were subjected to fewer genital examinations. Fewer providers were present during exams. Images taken by providers and caregivers during the postoperative period were used to monitor wound healing and surgical outcomes.

Discussion/Conclusions:
Implementation of standardized digital photography was feasible and acceptable to patients and caregivers. Digital images reduced the need for repeat physical examination and provided a visual means of enhancing clinical documentation.

PO 14

Integration of Child Life services in the delivery of multi-disciplinary Differences in Sexual Development (DSD) and Congenital Adrenal Hyperplasia (CAH) care

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Background/Aims:
Multiple studies have demonstrated the benefit of incorporating certified child life specialist (CCLS) services in various aspects of pediatric care. Although the significance of psychosocial support of patients with Disorders of Sexual Development (DSD) and Congenital Adrenal Hyperplasia (CAH) is increasingly recognized, the involvement of CCLS services into the DSD and CAH multidisciplinary care model has yet to be described. The purpose of this study was to evaluate the feasibility, acceptability, and patient and family experience of incorporating CCLS services into the multidisciplinary DSD and CAH care model.

Methods:
As part of a quality improvement initiative, CCLS services were routinely incorporated in the multidisciplinary DSD and CAH clinics at our institution. Encounters for patients seen in clinic between July 2018 through October 2019 were reviewed for demographic information, DSD diagnosis classification, CCLS documentation, and whether an exam under anesthesia (EUA) was required due to an incomplete clinical exam. CCLS documentation was reviewed for assessments, interventions, whether patients tolerated their physical exams, time of CCLS services, and additional CCLS support beyond the physical exam. All patients were limited to one physical exam per clinic visit.

Results:
Out of the 45 encounters with CCLS involvement, 42 (93.3%) exams were well-tolerated. CCLS assessments considered patient development, communication considerations, temperament, medical stressors, coping preferences, and patient preferences for activities and distractions. Interventions included preparing patients for their physical exams, encouragement before and during exams, addressing patient stressors, distractions and coping mechanisms, and advocating for the patient. No patients required an EUA.

Discussion/Conclusion:
This study demonstrates the feasibility, acceptability, and positive impact of CCLS services in the delivery of patient and family-centered care for patients with DSD and CAH as part of the multidisciplinary team model.

PO 15

Cross-Cultural Disparities in Psychosocial Research of Individuals with Classical Congenital Adrenal Hyperplasia: A Scoping Review

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Background/Aims:
Calls for research and clinical interventions addressing psychosocial needs among individuals with 21-hydroxylase deficiency, or Classical Congenital Adrenal Hyperplasia (CAH), are receiving increased attention. However, across countries and cultures, there are disparities in diagnostic practices (e.g., newborn screening) and amount of psychosocial research that may impact the cross-cultural applicability of existing evidence-based recommendations. The present scoping review aims to quantify the disparity between CAH rates and rates of CAH psychosocial research across countries/regions to better guide international research and clinical efforts.

Methods:
Searches were conducted in six electronic databases for (1) CAH Incidence/birth/prevalence rates (CAH rates), and (2) published psychosocial research with individuals with CAH and their families. Queries used search terms developed by the authorship team, yielding 580 and 719 articles, respectively. Two authors reviewed each abstract for inclusion criteria: peer-reviewed journal articles, written in English, reports on 21-hydroxylase deficiency separately, and assesses (1) birth/incidence/prevalence or (2) psychosocial adjustment. Discrepancies between reviewers were resolved by re-rating content and consulting with senior authors until agreed upon final classifications. Process was repeated for full-text reviews. Final full-texts included 64 CAH rates articles and 89 CAH psychosocial articles from which geographic region/country was derived.

Results:
The regions with the highest reported rates of CAH are predominantly non-Western (e.g., Thailand, Ghana, and India), yet the regions with the greatest number of psychosocial publications are from Western regions (e.g., United States, Germany, and United Kingdom).

Conclusion:
Our findings highlight a discrepancy between those countries with the highest rates of CAH and those conducting psychosocial research. In other words, individuals with CAH are present worldwide, however, the predominate psychosocial literature is not globally representative. Specifically, due to cultural differences between these regions (e.g., religion/spirituality, gender norms and expectations, child rearing practices, economics, health care, research capacity resources), increased global collaboration is needed to inform and drive representative psychosocial research for those affected by CAH as well as the translation of findings to optimize care for people worldwide.

PO 16

A single-institution retrospective chromosome microarray analysis of copy number variations in non-coding regions of genes detected in patients with differences of sex development

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Background/Aims:
Differences of sex development (DSD) are a phenotypically diverse group of conditions involving atypical development of hormonal, gonadal, or anatomical sex in relation to sex chromosomes. There are many known genes whose copy number variations (CNVs) can lead to DSD, such as the Y-linked SRY and SOX9 on chromosome 17. Most of the previous research into the genetic basis of DSD has focused primarily on variants found within coding regions of genes, while less attention has been devoted to the relevance of non-coding variants. Even though these non-coding regions are gene deserts, they are known to contain regulatory elements that can enhance or suppress gene expression. This study involves copy number analysis of noncoding regions detected in patients with DSD.

Methods:
Retrospective studies were performed using the data obtained from patient samples (n=7,789; 2008 to present) sent to Washington University Cytogenetics Laboratory for chromosome microarray analysis (CMA). We analyzed the 39 overlapping and distinct non-coding variations described in (Atlas et al 2021; PMID: 34634785). This data set was used to create an analysis track to identify any copy number variations overlapping with non-coding regions in our set of DSD patients. We identified the DSD features as well as the non-DSD phenotype observed in our patients.

Results:
The number of copy number variations described in each of the 8 genes ranged from 2 (AR, DMRT1, GATA4, NR0B1) to 22 (SOX9). Using our CMA track, we identified CNVs involving 5 genes: AR, DMRT1, NR0B1, SOX3, and SRY. The specific DSD phenotypes of these individuals were ambiguous genitalia, atrophic testicle, micro-penis, X-linked adrenal hypoplasia, and features of Turner and Klinefelter syndromes. We also observed non-DSD phenotypes, most commonly involving cardiovascular and skeletal defects

Discussion/Conclusion:
This genotype-phenotype study emphasizes the importance of investigating non-coding regions that are too often ignored in many genomic analyses. Data obtained from this study will assist with future genetic diagnoses, genetic counselling, and management of patients with various DSD conditions.

PO 17

Clinical and genetic analysis of six patients with atypical testicular development

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Background:
Testicular development requires the formation of the bipotential gonads and their differentiation into multiple sex-specific cell types through precise coordination of the expression of pro-testis and anti-ovary genes. Alterations in this process can lead to differences of sex development (DSD). Currently, the diagnostic rate of patients with XY DSD is around 40%. This low rate is due to clinical and genetic heterogeneity and because many of the genes involved in testicular development are yet to be discovered. Many of the known genes that participate in testicular development were discovered by genomic analysis of patients with atypical gonads or genitalia. This project provides genetic analyses and a detailed clinical description of six patients with atypical testicular development, and aims towards an increase in diagnostic yield and new insights into testicular development and DSD.

Methods:
The clinical evaluation included endocrine, genetic, and urological assessments. Whole-exome sequencing (WES) was performed from the patients´ peripheral blood.

Results:
Patient 1: proximal hypospadias, vanishing testis, and hypergonadotropic hypogonadism. Karyotype: 46,XY. WES: heterozygous variant in MYRF:c.789delC(p.Ser264fs), pathogenic.
Patient 2: small testes, hypergonadotropic hypogonadism, clinodactyly, and asymmetric lower extremities. Karyotype:46,XY. WES: heterozygous variant in FGFR1:c.318delC(p.Ser107fs), pathogenic.
Patient 3: proximal hypospadias and tetralogy of Fallot, low levels of testosterone and dihydrotestosterone.
Karyotype:46,XY. WES: heterozygous variant in ESR2:c.268G>C(p.Val90Leu), variant of unknown significance (VUS) and another heterozygous variant in ZFPM2 (FOG2):c.679A>G(p.Ile227Val), likely benign.
Patient 4: bilateral cryptorchidism, cleft lip and palate, epicanthus, ptosis, and thoracic hemivertebrae. Karyotype:46,XY. WES: heterozygous variant in FOXL2:c.211G>C(p.Ala71Pro), VUS. Patient 5: atypical genitalia. Karyotype: 47,XXY. WES: heterozygous variant in SPRY4:c.593C>T(p.Thr198Met), VUS. Patient 6: female external genitalia, primary amenorrhea. Karyotype: 46,XY. WES: heterozygous variant in MAP3K1:c.919C>T (p.Arg307Cys), VUS.

Conclusion:
The clinical and genetic assessment of patients with differences of sex development has revealed potential causative genes for typical and atypical testicular development that await functional validation

PO 18

Two novel mutations in MCM8 gene in a 46, XX female with short stature, primary ovarian insufficiency and kidney dystopia

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Primary ovarian insufficiency (POI) affects about 1% of females under 40 and represents a major cause of female infertility. Approximately one third of POI are of genetic in origin, including FMR1 premutation, Turner syndrome and approximately 60 other genes, involved in development, hormonal signalling, cell division and survival, immunity, and metabolism. MCM8 is a recently discovered gene that plays an important role in homologous recombination and DNA repair and only up to ten mutations have been described in the medical literature so far.

We describe a 13-year-old girl, born term from non-consanguineous parents. Her linear growth delay was noticed from 8 years and by 11 years it was -2SDs. She has mild cubitus valgus, hypermobile joints, mild shortening of the 4th metacarpals, hypertrychosis, normal chest, neck and body proportions, and age-appropriate intelligence.

Ultrasound examination revealed rotation of the right kidney and dystopic left kidney, but kidney function remains normal on annual control. Pelvis MRI showed agenesis of ovaries and small hypoechogenic uterus. Bone age was delayed. Thyroid status, serological markers of celiac disease, IGF-1, IGFBP-3 were normal, FSH as well LH were markedly elevated, AMH was extremely low. Cytogenetic analysis confirmed 46,XX karyotype. Whole exome sequencing (WES) was performed, which revealed two novel heterozygous variants in MCM8 gene: c.278_271del, p.(Ile93Argfs*22) classified as likely pathogenic and c.703T>C, p.(Cys235Arg) classified as variant of unknown significance. Currently the patient is on transdermal oestrogen treatment for 6 months. Her bone age is still delayed with two years, and height velocity remains in prepubertal range, but breast development started, and the size of the uterus increased and became more structured.

The presented case is noteworthy in several ways. Firstly, it highlights the importance and diagnostic utility of WES in the context of unexplained POI. Secondly, we describe two novel mutations in MCM8 gene, broadening the mutation spectrum of the MCM8-related disorder. And finally, presented case broadens the phenotypic spectrum of this rare disease prompting clinicians to suspect genetic aetiology of POI in the context of short stature and kidney malformations.

PO 19

Whole exome sequencing advances a genetic diagnosis in patients with differences of sex development and corroborates the role of RXFP2 in autosomal recessive bilateral cryptorchidism and infertility

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Background/Aims:
Differences of sex development (DSD) are heterogeneous conditions affecting the development of chromosomal, gonadal or anatomical sex. Although over 75 genes are associated with DSD, the diagnostic yield of whole exome sequencing (WES) studies typically does not exceed 35% in a clinical setting. Here, we investigated the benefits of WES for the genetic diagnosis in patients with DSD.

Methods:
Between 2016 and 2022, 144 unrelated index patients with a clinical diagnosis of DSD or the broader DSD umbrella underwent WES-based panel testing interrogating the coding regions of 130 genes implicated in DSD, primary ovarian insufficiency, and hypogonadotropic hypogonadism. Variants were extracted and classified according to the ACMG guidelines. Copy number variant (CNV) analysis was performed using the ExomeDepth algorithm. Structural modeling and a cyclic AMP (cAMP) reporter gene assay was used to assess the pathogenicity of an RXFP2 (NM_130806.5) missense variant.

Results:
In 13% of patients, we identified a likely pathogenic (LP) or pathogenic (P) rare variant in 12 distinct DSD genes, including AR (6), NR5A1 (2), WT1 (2), ATRX, CYP21A2, DHX37, HSD3B2, HSD17B3, RXFP2, SRD5A2, SRY, and TXNRD2. The majority are sequence variants, four of which are CNVs identified using ExomeDepth. Interestingly, in two brothers displaying bilateral cryptorchidism and infertility, an intragenic RXFP2 deletion was found in trans with a heterozygous missense variant c.229G>A, p.(Glu77Lys). The RXFP2 receptor binds INSL3 and is involved in testicular descent. The pathogenicity of the missense variant was substantiated by in silico modelling and in vitro functional analysis. The missense variant showed normal expression and ability to bind the ligand INSL3, but the absence of a cAMP signal in response to INSL3 supported loss-of-function.

Conclusion:
We demonstrate the benefit of WES-based genetic testing of DSD in a clinical context and illustrate the important additive value of CNV assessment on WES data. The low detection rate emphasizes, on the one hand, the need for advanced genome analysis to solve missing heritability in DSD, and on the other hand, the need for more stringent inclusion criteria and delineation of this condition to allow transparent reporting and comparison.
This finding corroborates the role of RXFP2 in autosomal recessive bilateral cryptorchidism and supports that infertility is part of the phenotype.

PO 20

Can noncoding NR5A1 gene variants explain phenotypes of Disorders of Sex Development?

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Background:
Steroidogenic factor-1 (SF1), encoded by NR5A1 gene, is an essential transcription factor that regulates several target genes involved in reproduction and endocrine function. Pathogenic variants in NR5A1 gene are responsible for a wide spectrum of disorders/differences of sex development (DSD).

Methods:
All NR5A1 exons including ~750 bp of the 5'-upstream flanking region were amplified and sequenced by Sanger method, in vitro functional analyses were performed to investigate the impact of NR5A1 noncoding variants on promoter activity and whole exome sequencing (WES) were done in order to exclude coding variants in other genes involved with DSD phenotypes. Results: Four variants were identified within the NR5A1 noncoding region, three in the upstream promoter region (c.-762C>T, c.-413G>A, and c.-207C>A) and one in the 5´UTR within noncoding exon 1 (c.-133G>A), in three patients with 46,XY DSD. In vitro functional analyses showed that transactivation activity was affected in all cases. 125 target genes for 46,XY DSD were analyzed through WES results and revealed few relevant variants in WDR11, WWOX, SRA1, RET, MYO7A and SMAD6; genes that are known to be somehow involved in sex development pathways, but were never reported as oligogenic cause of gonadal dysgenesis.

Discussion/Conclusion:
Little is known about variants located at NR5A1 noncoding region associated with DSD. Although a correlation with DSD is still elusive, it is feasible to consider that those variants might influence the phenotype, especially because they are located in an important region for the interaction with different co-factors essential to promote gene expression and appropriated sex determination and differentiation. The results from in vitro assays and WES analyses also corroborates with our hypothesis. Considering the number of DSD cases that remain idiopathic after analyses of the mainly responsible genes for the pathophysiology, we emphasize the importance of a careful molecular analysis of NR5A1 noncoding region as some of DSD cases might be explained by variants in this commonly neglected region

PO 21

Three novel NR5A1 variants in individuals with 46,XY DSD fail to activate a SOX9 enhancer

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Aims:
Steroidogenic factor 1 (NR5A1/SF1) is a key transcription factor in gonadal development and numerous pathogenic NR5A1 variants have been reported in individuals with differences of sex development (DSD). We investigated three novel mutations in NR5A1, in individuals with DSD, and assessed the ability of the mutants to activate eALDI, an enhancer of SOX9.

Methods:
Three novel NR5A1 mutants (found in 46,XY DSD patients) were identified using a targeted DSD gene panel. The mutants were generated in vitro using site-directed mutagenesis. To test for SF1 activation of eALDI, mutant and wild-type NR5A1 constructs, either alone or in combination with SOX9, were transfected with eALDI into a monkey kidney cell line (COS7) and in vitro luciferase assays were performed.

Results:
The first patient was a 46,XY female with complete gonadal dysgenesis and was found to have a missense mutation (p.L401V) in the ligand-binding domain (LBD). The second patient was an undervirilised male with a 46,XY karyotype and a family history of undescended testes and hypospadias. This patient had a missense mutation (p.V369F) also in the ligand binding domain. The third patient was a 46,XY male with partial gonadal dysgenesis and was found to have a nonsense mutation(p.Q362*). All three mutants showed reduced activation of eALDI when compared to wildtype NR5A1 and NR5A1/SOX9 combined. These mutations were modelled on wild type NR5A1 protein structure and were predicted to cause an alteration of the LBD.

Conclusion:
Three novel NR5A1 mutations are reported, all in individuals with a varying degree of severity of 46,XY DSD. The missense mutations and the nonsense mutation all showed a reduction in eALDI activation. Since NR5A1 and its activation of SOX9 play a key role in gonadal development, this disruption highlights a likely mechanism in the development of DSD for these individuals. Disruption of the LBD by these variants could negatively impact on ligand binding and subsequent NR5A1 function. With a large variation in clinical phenotypes for those with a pathogenic NR5A1 mutation, it is a critical gene to include in screening for individuals with DSD.

PO 22

Genetic diagnosis of DSD : NRC Experience

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Disorders of sex development (DSD) comprise a heterogeneous group of heritable abnormalities of sexual determination and differentiation. In Egypt the incidence of DSD is 1 in 5,000, due to the high rate of consanguinity

Aim of study:
This study showed our activity at NRC for proper classification of DSD patients in order to establish a precise diagnosis for better genetic counseling and management.

Methods:
Karyotyping, FISH in blood and gonads and sequencing of SRY, AR, HSD17B3, SRD5A2 and SF1genes were done in all DSD patients. Next generation sequencing was done for idiopathic cases

Results:
Various numerical and structural chromosomal abnormalities were detected. Molecular analysis was done for 46XY DSD patients and revealed reported and novel mutations in AR, NR5A2, HSD17B3 and SRD5A2 gene, G34 R mutation was found in SRD5A2 gene in many patients confirming the gene founder effect. Several novel mutations were reported in genes controlling sexual differentiation which was not previously reported in Egypt.

Conclusion:
Molecular characterization of 46,XY DSD patients is crucial when sex assignment and therapy outcomes are discussed for proper genetic counselling and diagnosis, it is also essential to provide centers of tertiary pediatric care with a consistent and standardized model of care for patients with DSD

PO 23
Increased Expression of ZFPM2 Bypasses SRY to Drive 46,XX Testicular Development: A New Mechanism of 46,XX DSD

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We present a patient with a novel cause of 46,XX Intersex/Differences of Sex Development (IDSD). Genome-wide array from blood showed 46,XX with a chromosome 8q duplication, containing 257 OMIM genes including ZFPM2 and CYP11B1. Congenital adrenal hyperplasia testing was negative, testosterone was elevated, and SRY was absent. The infant had a uterus,

one streak ovary (<5% 8q duplication) and one testicle (75% 8q duplication). We hypothesized that mosaic ZFPM2 duplication resulted in localized ZFPM2 overexpression and testicular development. In typical testicular development, ZFPM2 and its binding partner, GATA4, drive expression of the SRY master regulator.

RNAseq from gonadal tissue containing the duplication showed increased dosage of ZFPM2, and upregulation the early testis development network. SOX9 (FC=39.2, p=1.1x10-121) and NR5A1 (FC=1.4, p=4.8x10-4) interact to produce the functional marker of fetal Sertoli cells AMH (FC=108.4, p=2.3x10-56) and inhibit female sexual differentiation. Several components of the testicular sex development pathway were upregulated in addition to SOX9 and AMH, including the pro-testicular transcription factor MAP3K1 (FC=1.5, p=5.4x10-6), DMRT1 (FC=13.9, p=1.5x10-13), LHX9 (FC=2.5, p=2.2x10-15), DHH (FC=12.0, p=2.5x10-32), PTGDS (FC=2.5, p=8.6x10-20), and SOX8 (FC=10.9, p=6.2x10-11). ZFPM2 may function as a master temporal and spatial regulator of mammalian testicular organogenesis whose increased dosage elicits significant and cascading downstream effects. PTGDS (prostaglandin D2 synthase). Further, components of the ovarian WNT-signaling pathway were repressed, including LEF1 (FC=-3.7, p=2.1x10-23) and FOXL2 (FC=-8.1, p=1.2x10-41).

We have shown that increased ZPFM2 dosage can induce 46,XX testicular development in a manner not dependent on SRY. This contravenes the previous understanding that GATA4/ZFPM2 drives testicular development through SRY. ZFPM2 may modulate numerous critical sex development genes including transcription factors otherwise thought to be downstream of SRY (MAP3K1, SOX9, AMH). Findings from this single high-yield patient demonstrate that the primary role of ZFPM2 in testicular development may be independent of SRY. This adds ZFPM2 to the brief (<10) list of genes capable of directing testicular development in the 46,XX context, absent SRY.

Overall, new understanding of these genes demonstrates that the role of SRY as a “master regulator" of testicular development may be less than previously thought.

PO 24

Homozygosity for a novel INHA mutation in two male siblings with hypospadias, primary hypogonadism, and high normal testicular volume

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Background:

The human INHA gene encodes the inhibin subunit alpha protein, which is common to both inhibin A and B. The functional importance of inhibins in male sex development, sexual function, and reproduction remain largely unknown.

Objective:
We report for the first time two male siblings with homozygous INHA mutations.

Methods:
The medical files were examined for clinical, biochemical, and imaging data. Genetic analysis was performed using next-generation and Sanger sequencing methods.

Results:
Two brothers complained of gynecomastia, testicular pain, and had a history of hypospadias. Biochemistry revealed low serum testosterone, high gonadotropin and anti-Mullerian hormone, and very low/undetectable inhibin concentrations, where available. Both patients had azoospermia in spermiogram. We have identified a homozygous 2bp deletion (c.208_209delAG, R70Gfs*3) variant, which leads to a truncated INHA protein in both patients and confirmed heterozygosity in the parents. The external genital development, pubertal onset and progression, reproductive functions, serum gonadotropins, and sex hormones of mother and father, who were heterozygous carriers of the identified mutation, were normal.

Conclusion:
Homozygosity for INHA mutations causes decreased prenatal and postnatal testosterone production and infertility in males, while the heterozygous female and male carriers of INHA mutations do not have any abnormality in sex development and reproduction

PO 25
Contribution of Next Generation Sequencing to the molecular diagnosis of patients with Disorders/differences of Sex Development

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One aspect in the health care of patients with DSD is the identification of the genetic cause that underlies their conditions, which can help to establish an accurate diagnosis for appropriate clinical management, follow-up, and genetic counseling. The most common methods for genetic diagnosis have been Sanger and/or panel sequencing. However, the etiology of most DSD phenotypes remain elusive. Next Generation Sequencing (NGS) techniques are becoming more affordable and turning into a more efficient tool in the genetic diagnostic. Here we bring

examples of cases from our group which highlight the importance of looking beyond the DSD candidate genes and protein coding regions through genome wide sequencing: 1) pathogenic variants identified in two genes that were not commonly related to DSD at the time of patients' evaluation: a stop codon variant in MYRF gene in a 46,XY PGD patient with Scimitar-syndrome and hyperopia; and one missense variant in DHH in two 46,XY sisters with DSD and polyneuropathy; 2) duplications at chromosome Xp21.2 found in two 46,XY GD patients, upstream a single copy of NR0B1, one originally detected by WGS and the other first detected by q-PCR and then characterized by Whole Genome Sequencing (WGS); 3) three 46,XY DSD patients with variants within the NR5A1 promoter and 5'-noncoding region, which could not be detected by Whole Exome Sequencing (WES), and have been shown to affect gene expression by in-vitro studies. Our results show that WES and WGS could favor faster and precise diagnostics, increasing the overall yield compared to panel or Sanger sequencing. In the same way, other new technologies, such as RNA sequencing or long-read sequencing could help, respectively, in the identification of new molecular pathways involved in sex development and of more complex genetic variants, such as structural or epigenetic changes, involved in the DSD phenotype. A joint effort in a multidisciplinary team is essential to a successful outcome, specially between physicians, geneticists and bioinformaticians, once screening through the immense amount of data generated by these technologies requires a precise clinical description of patients, knowledge about molecular pathways and genetic variation, and finally computational methods to process the data.

PO 26

Overview of the Genetics in Disorders of Sex Development at an Academic Hospital in Pretoria, South Africa: What is going on?

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Introduction:
The incidence of DSD in the general population is estimated at between 1 in 4500-5000, but the frequency of specific types of DSD presenting at birth is unknown. (Lee et al. Horm. Res. Paediatr 2016; 85.3: 158-180.) Klinefelter and Turner Syndromes appear most commonly, while 46 XX DSD conditions such as CAH are rarer and Ovotesticular DSD (OT-DSD) rarest of all. This study evaluated the frequency and genetics of various DSDs presenting to an academic hospital in Pretoria, South Africa.

Methods:
A retrospective case series analysis was conducted on information from patient databases. Data was obtained anonymously, and analysis done.

Findings:
A total of 185 patients were identified, 44 adult and 141 pediatric. The most common diagnosis

in the pediatric group was 46 XX true OT-DSD (33 [90%]), followed by CAH (24 [58%]) and 46XY undervirilized males (15 [25%]). In the OT-DSD group, 61(36%) of patients tested negative for SRY-gene translocation, a finding not typically seen in 46 XX males. (Berglund et al. Hum Reprod 2017; 32(8):1751-60.)

Conclusions:
The spectrum of DSDs presenting in this study is different from what is traditionally seen in the Western world. True OT-DSD occurs significantly more frequently, and the underlying genetics also differ from what is classically seen, with most patients testing negative for SRY-gene translocation. The underlying contributory factors are unknown and need to be explored further.

PO 27

Comprehensive Cytogenetic Study of a Large Cohort of Egyptian Referral Patients with Disorders of Sex Development (DSD)

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Background/Aims:

Genetic abnormalities of sexual differentiation are known as disorders of sex development (DSD). Different numerical and structural abnormalities of sex chromosomes and autosomes were reported in DSD patients with a wide phenotypic variability. This comprehensive 9-year study aimed at improving the diagnostic strategy of Egyptian DSD patients and to detect types and frequencies of different DSD categories.

Methods:
The study was conducted at the National Research Centre on patients referred to the Endocrinology and DSD clinic, Clinical Genetics Department and the Human Cytogenetics Departments, National Research Centre, Egypt. The study included 803 patients who were subjected to detailed clinical evaluation, genital examination and pubertal staging, hormonal profiling and imaging studies. Thorough evaluation of the chromosomal status was performed, using GTG banding and FISH techniques applied on chromosomes prepared from cultured blood lymphocytes. FISH was also performed on gonadal tissues biopsies from selected patients. Chromosomal microarray (CMA) using Genome-Wide Human SNP Array 6.0 (Affymetrix) was conducted for selected patients with associated congenital abnormalities.

Results:

Sex chromosomal abnormalities were found in 37 % of the patients and included a wide array of numerical and structural anomalies, while autosomal abnormalities were detected in 3 %. 34 % of the patients had 46,XY DSD ; while 26 % had 46,XX DSD, of them 20 male patients had XX testicular DSD and 8 patients were diagnosed according to gonadal histopathology to have ovotesticular DSD Gonosomal mosaicism was detected in 5 patients and clinically significant

copy number changes were detected in four patients with congenital anomalies. CMA detected significant copy number abnormalities in 3 patients, which were correlated to the phenotype.

Conclusion:
The study reports a large number of Egyptian DSD patients and the frequency of different DSD groups and the chromosomal abnormalities in relation to different phenotypes. It also illustrates the importance of cytogenetic screening and comprehensive molecular cytogenetic analysis in proper diagnosis of DSD patients, which is mandatory for better counseling, decision making and long-term management of those patients.

PO 28
Spectrum of SF-1/NR5A1 gene variants in the large international SF1next cohort

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Background:
Variations in the NR5A1 gene are frequent causes of 46,XY differences of sex development (DSD). To date, the Human Gene Mutation Database contains 291 NR5A1 variants, most of which are missense (69%). Mouse models demonstrated the effect of loss of SF-1 on sex development, but the interactome of SF-1 is huge and an explanation for the broad phenotype is still missing. Controversies exist as: a) in vitro transactivation assays of NR5A1-regulated genes show contradictive results for several variants, b) in vitro modelling of heterozygous variants does not show a dominant negative effect, c) several variants are present in combination with other DSD-related gene variants of unknown significance. We aimed to describe the genotype in the largest possible international SF-1/NR5A1 cohort to allow future identification of phenotype-genotype clusters.

Methods:
After recruiting cases through the I-DSD registry and through contacting researchers from previous publications on SF-1, collaborators entered genotype data in a REDCap database. Gene variants were identified by single gene analysis, next generation sequencing (NGS) and/or comparative genomic hybridization array. We performed variant classification according to guidelines from the American College of Medical Genetics and Genomics.

Results:
Among 107 individuals (90% 46,XY, 8% 46,XX, 1% 47,XXY, 1% 47,XYY), we found 78 different NR5A1 variants, of which 28 were novel (11/28 missense, 8/28 delins, 3/28 nonsense, 2/28 silent, 2/28 small deletions or insertions). All but 6 were heterozygous (72/78, 92%). Variants were scattered throughout the whole NR5A1 gene, mostly in the DNA-binding (33/78, 42%) and the ligand-binding domain of the protein (28/78, 36%). We classified 59/78 (76%) variants as pathogenic/likely pathogenic and 16/78 (20%) as variants of unknown significance. Additional gene variants (e.g. DHX37) were identified in 26/107 (24%) individuals using various methods (52% single-gene analysis, 33% NGS).

Conclusion:
Novel variants are still identified in the NR5A1 gene. Further studies are required to explain the broad phenotype of SF-1 individuals. Current targeted approaches have limitations as they may not detect additional gene variants. In the future, individuals who have loss-of-function SF-1 variants may have to be re-evaluated with newer methods, e.g. NGS.

PO 29
Said's Procedure, (Modified Fenton's Procedure) as a unique solution for Vaginal Stenosis, as a longterm complication of Vaginoplasty

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Aim:
Evaluate Said's procedure, (Modified Fenton's procedure) as a solution of vaginal Stenosis in Adolescent Congenital Adrenal Hyperplasia (CAH) and other patients with vaginal Stenosis due to other causes.

Patients and methods:
Seven patients; Case1; Post CAH repair, 18 years had feminizing genitoplasty in childhood, who developed vaginal Stenosis affecting her personal life. Her vaginal length was more than 5cm. Classic Fenton's procedure performed which ended by satisfactory functional with unsatisfactory cosmesis. Cases 2-6; all had vaginal stenosis Post CAH repair age average from 11 to 17 years. N.B. A modified Fenton's by Gynaecologist can't be done in CAH patients. All had average vaginal length 5cm+, for whom modified Fenton's procedure (Bilateral Fenton's procedure) was performed. All have a very good functional and cosmetic result. The Last case; twenty-one years old lady had an intact thick flesh labial adhesion, completely covering the vagina. She had a Said's midline procedure; she has an excellent functional and cosmetic result

Results:
All patients except the 1st one have an excellent cosmetic and functional result.

Conclusion:
Unilateral (Classic) Fenton's procedure despite providing optimal functionality, it results less than satisfactory cosmetics. So modified Fenton's procedure (Bilateral one) give a near normal appearance & function of the vaginal introitus in vaginal Stenosis post vaginoplasty repair, also not affecting vaginal length. Regarding non treated adult form of labial adhesion, midline modified Fenton's procedure is the ideal one.

PO 30

Pediatric Adnexal Torsion, Primary and Secondary, Clinical presentation and Single incision Laparoscopic Surgery (SILS) Management

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Aim:
The aim is to recognize the clinical signs and symptoms of adnexal torsion (AT) and/or Ovarian Torsion (OT) and to ripen a simple predictive variable.

Methods:
A retrospective review of the files from June 2017 to June 2021 of total 19 patient aged from 30 months to 14 years. File were screened for demographic and clinical data. These included clinical data, laboratory tests, radiology studies and laparoscopic/Surgical management.

Results:
In this study analyzed 19 files of patients aged from 30 months to 14 years. 3 out of the 19 patients had primary ovarian torsion, 15 had torsion secondary to ovarian cyst and last one had paratubal/paraovarian torsion. Most of the girls presented with leukocytosis, vomiting and right lower abdominal pain. Urine analysis 47% had pyuria without bacteriuria. Ultrasound (US) confirmed ovarian cyst 15 out of the 19, and torsion of 2 out of the 3 primary torsion cases. US missed the diagnosis of the Paratubal/paraovarian torsion, Even the CT. Fourteen out of 15 managed by SILS detorsion with safe cyst excision (4 teratoma and 11 simple/hemorrhagic cyst). Only one case had open ovarian cystectomy (Single ovary and mother refuse laparoscopy) in primary torsion, simple detorsion in one case and detorsion and ovarian suspension in 2 cases.

Conclusion:
Ovarian/adnexal torsion should be well-thought-out/considered in any female in pediatric age with acute onset lower abdominal pain associated with vomiting. Pain is constant, does not typically migrate. Sterile pyuria in about half of the patients. US is the most important initial diagnostic modality, nevertheless the absence of flow in Doppler image is not constantly present. Conservative management with detorsion, cystectomy and/or ovarian suspension (in single ovary and recurrent torsion) is mandatory.

PO 31

International variations in Vaginal Lengthening Treatments among Individuals with Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome

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Background/Aims:
Variations in surgical and non-surgical vaginal lengthening (VL) options used by patients with Mayer-Rokitansky-Küster-Hauser (MRKH) or Müllerian agenesis around the world is unknown. We aimed to identify VL techniques used by individuals with MRKH internationally.

Methods:
Adult individuals with MRKH (n=616) were recruited via support groups to an online, cross-sectional survey assessing VL treatment history.

Results:
Participants, with median age of 29 years, representing forty countries reported their race as Caucasian (81%), Asian (9%), Black (3%), or other (7%); 83% identified as non-Hispanic. 54% (N=332/616) reported undergoing one or more VL treatments starting at a median age of 18 years (range 12-52 years); 72% reported dilator use (238/332), 34% coital dilation (114/332), and 39% surgery (130/332). Africa: 11% (1/9) reported VL treatment (coital dilation, n=1). Asia: 16% (n=8/49) reported VL treatment; 75% (n=6) had VL surgery (McIndoe (n=1), Bowel graft (n=1), other (n=2), unspecified (n=2)). Europe: 64% (82/128) reported VL treatment; 50% (n=41) had VL surgery (McIndoe (n=5), Vecchietti (n=10), Bowel graft (n=8), Davydov (n=5), Williams (n=3), other/unspecified (n=10). North America: 57% (224/392) reported VL treatment: dilation (147/224; 66%), surgery (77/224; 34%). VL surgeries included: McIndoe (n=34), Vecchietti (n=9), Bowel graft (n=12), Davydov (n=13), Williams (n=4), other/unspecified (n=5). Oceania: 41% (n= 11/27) reported VL treatment, with 36% (4/11) reporting surgery (McIndoe (n=1), Vecchietti (n=1), Williams (n=1), other (n=1)). South America: 20% (n= 1/5) reported VL treatment (coital dilation, n=1).

Conclusions:
Most individuals (59%) with MRKH in North America and Europe reported VL, but VL was less common in Africa, Asia and South America (16%). Dilation was the most commonly used method throughout the world. Vaginal surgery was reported in Europe (50%), Asia (75%), North America (34%) and Oceania (36%).

In Europe, the Vecchietti and bowel graft were reported most often, while in North America the McIndoe and Davydov procedures were noted most frequently. 46% of respondents reported

not using any VL treatment; 43% in North America and 36% in Europe. This data suggests that future research should: 1) work towards international consensus on best practice in VL in MRKH and 2) investigate factors that play a role in decisions regarding VL.

PO 32

Vaginal Lengthening Treatment Experiences among Individuals with Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome

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Background/Aims:
MRKH, characterized by absence of the uterus, cervix and vagina, occurs in 1 in 5000 individuals assigned female at birth. Both surgical and non-surgical vaginal lengthening (VL) interventions are available, yet little is known about individuals' experiences of VL in MRKH. We aimed to describe experiences of VL in people with MRKH internationally.

Methods:
616 individuals with MRKH (aged 18+) were recruited to an online cross-sectional study via MRKH support groups. Questions assessed demographics and VL treatment history. Descriptive statistics were used to describe the sample. The focus of this sub-analysis was an open-ended question about challenges, complications or issues experienced during VL. Two researchers independently analyzed qualitative responses using inductive thematic analysis. Codes and themes were discussed amongst the wider research team throughout the analytic process.

Results:
Over half (54%, 331/616) reported undergoing one or more VL treatments, and 50% (n=166) of that group responded to the open-ended question and met inclusion criteria. The median age was 30 (range = 18-66). Respondents were from North America (72%), Europe (21%), Asia (2%), Oceania (4%), Africa (0.6%), and unspecified (0.6%). Participants identified their race as Caucasian (90%), Asian (2%), Black (3 %), or other (5%), and 86% identified their ethnicity as non-Hispanic. Four major themes were identified: (1) Experiencing Difficult Physical Symptoms, which described pain, bladder, and bowel symptoms that participants attributed to VL, (2) Practical and Psychosocial Challenges, including time burden, psychological distress, anxiety, and privacy issues that affected engagement with VL, (3) Intimate Relationships and Sexual Satisfaction, which included positive experiences and challenges with sexual relationships, and (4) Impact of Experiences with Healthcare Providers, which described the ways in which helpful and unhelpful interactions with healthcare providers shaped participants' experiences of VL.

Conclusions:
In this large international MRKH cohort, significant challenges as well as positive experiences related to VL were reported in several domains. This study highlights aspects of care that can be optimized and emphasized in the care of individuals with MRKH, specifically, the importance of

providing psychosocial support, clear discussions of diagnosis, treatment options and expectations, and ongoing care through diagnosis and beyond.

PO 33

Decision-making regarding orchiectomy in patients with 17-beta-hydroxysteroid dehydrogenase type 3 deficiency: Clinical considerations

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Background/Aims:
Individuals with 46,XY differences of sex development (DSD) due to 17β-hydroxysteroid dehydrogenase type 3 (17βHSD3) deficiency are generally assigned female at birth. With known future virilizing puberty, orchiectomy is often discussed with patients and families. Decision-making and factors to consider around orchiectomy are challenging and complex. We report two patients who presented at different ages to highlight the considerations and complexities surrounding gonad management, including malignancy risk, fertility potential and preservation options, and current knowledge of gender identity outcomes.

Cases:
Two patients, assigned female at birth and currently identifying as female, were diagnosed with 17βHSD3 deficiency. The first presented at 16 months with bilateral inguinal herniae and underwent orchiectomy. At age 12 years, she requested pubertal induction with oestrogen. The second patient presented at 13 years with voice deepening and hirsutism at puberty. After reviewing management options, she elected to defer the decision for orchiectomy and proceed with pubertal suppression with a histrelin implant. Due to differing ages of presentation, family preference drove the decision for the first patient, whereas the second patient expressed her preference regarding orchiectomy.

Discussion:
Decisions regarding orchiectomy in patients with 17βHSD3 deficiency should include multidisciplinary shared decision-making around malignancy risk, fertility potential, gender identity and hormone replacement. The published literature suggests low risk of malignancy; early orchiectomy may further decrease malignancy risk but necessitates pubertal induction and limits patient participation in decision-making. Fertility potential is uncertain; current fertility preservation protocols remain experimental for patients with DSD and more data is needed.

Gender identity is challenging to assess at a young age. While preliminary data suggests that orchiectomy may reduce the likelihood of a gender identity discordant with the assigned sex, some argue that decisions about children's gender identity are outside the scope of parental discretion. Delaying or not proceeding with orchiectomy allows patients to participate in decision-making and recognizes the importance of body image and understanding of the

adolescent. Options should be presented and discussed using shared decision-making by a multidisciplinary team with expertise in caring for patients with DSD.

PO 34

The Multidisciplinary team approach importance in the parents' decision-making process

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Introduction:

Disorders of sex development (DSD) is an umbrella term for complex conditions. The most severe clinical presentation for DSD is atypical genitalia. Since the 2006's consensus, concerns on long-term follow up have been highlighted in the context of a multidisciplinary team management. Surgical interventions are an important step; however, it has been the key focus in the recent discussions. Some groups, including support groups, advocate for more parent's/patient's participation in procedure decisions. Data evaluating parents empowering on surgical management are still scarce. The aim of this study was to evaluate parent's experiences regarding their participation in surgery approach decisions.

Method:

Data that were recovered from the chart included specific diagnosis, first contact with the DSD MDT, External Genital Score (EGS), age at first surgery, surgery performed, complications and need for reoperation. Patients and family were then personally interviewed by the DSD MDT Psychologist, and asked questions in order to understand how the patient and/or family felt about the procedure: (1) if explanation provided by the team about the surgery was enough and attended all inquiries and (2) if the family and/or patient felt participating in the decision process of undertaking the surgery.

Results:

56 patients/families were selected for the research. Median age at diagnosis was 14 months. 48.2% had 46,XY DSD. 37.5% of patients had a diagnosis of androgen excess. 78.6% had an EGS classification between 4 and 8 points. Of all sample, 71.4% of patients and/or families felt enlightened for making the decision of undergoing surgery. Patients were divided into two groups: (1) contact with the MDT before diagnosis (39.3%) and (2) contact with the MDT group after diagnosis (60.7%). Analysis showed statistical significance between the feeling of enlightening for surgical procedure and an earlier age of diagnosis with MDT contact prior to the diagnosis. All other variables did not show statistical significance.

Conclusion:

Despite the specific diagnosis or the degree of genitalia virilization the single most relevant characteristics in our sample that showed an impact on the parents and patients' feelings of enlightenment regarding surgical decision-making process was the contact with the MDT before the diagnosis.

PO 35

Feminizing genitoplasty in 46,XX Congenital Adrenal Hyperplasia patients: a tertiary centre experience

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Introduction:
Nowadays there are questions about the timing for feminizing genitoplasty in patients with 46,XX CAH, but patients with a PRADER score between 3 – 5 will probably need some sort of correction in their genitalia. Our objective is to demonstrate the outcomes of these patients after surgery.

Method:
Data analysis obtained through the review of the PADS MDT database, describing the surgical techniques used as well as the reported complication rates.

Results:
38 46,XX CAH patients were included. Regarding clitoroplasty, 91.9% (34/37) patients underwent resection of the corpora cavernosa, with 2 patients requiring a second intervention; 8.1% (3/37) were submitted to the technique of separation of the bodies proposed by Pippi Salle. One of these patients reports discomfort when she presents erection of these bodies. Regarding vaginoplasty and/or introitoplasty, 38 patients underwent surgery, and around 65.7% (25/38) underwent a combination pull-through and skin flaps; 23.6% (9/38) had skin flaps only; 7.8% (3/38) underwent an ASTRA procedure; 2.6% (1/38) had the urogenital sinus only dilated. More than 3/4 of the patients underwent a combined surgery of clitoris and vagina. Regarding complications, 15.7% (6/38) had urinary incontinence after surgery, and only two did not show improvement, a recurrence of the urogenital sinus was identified in both cases. Regarding stenosis of the vaginal introitus, 44.7% of the patients had this complication, similar to that found in the literature. 64.7% of these patients underwent further surgery, 17.6% were treated with dilatations only. One of the patients presented, in addition to the stenosis of the vaginal introitus, stenosis of the urethral meatus associated with UTI.

Conclusion:

Genital surgery in patients with CAH is safe at an early stage and may avoid the need for new approaches in the future. In countries such as in Brazil, where parents have the desire to have genitalia suitable for the sex assigned as soon as possible, this approach may be chosen, provided that the parents are well informed of the possibility of re-intervention in the future. More studies are needed for better analysis of these data.

PO 36

It was supposed to be a boy with hypospadias and unilateral undescended testicle, now what?

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Disorders of sex development (DSD) is an umbrella term for complex conditions. The most severe clinical presentation for DSD is atypical genitalia. It requires prompt identification and evaluation in order to quickly achieve an etiological diagnosis. The chimerism is a rare genetic condition and determines that the individual has two different types of DNA in your body. It is even more rare when associated with atypical genitalia.

We describe a newborn baby who was referred to our DSD MDT from the countryside of our state to evaluate an atypical genitalia case. Genitalia presented a phallus of 3.4 cm, right gonad on labioscrotal fold, without left gonad with a hypoplastic left labioscrotal fold, urethral meatus was place in a proximal position (figures). Laboratory findings are total testosterone: 1,29 ng/ml; DHT: 351,1 pg/ml; SDHEA: 1448,7 ug/dl; progesterone: 0,9 ng/ml; FSH: 15,42 mil/ml; LH: 8,16 mUI/ml; K: 5,5 mEq/l; Na: 140 mEq/l; SRY (molecular): Zfx/Zfy +. Ultrasound identified mullerian structures on left side. So the Team decided for a laparoscopy and genitoscopy that shown a left disgenetic gonad with a hemiuterus and hemivagina. Karyotype was 46,XY/46,XX. The Team with family decided for the male sex to preserve the fertility potential without removing mullerians structures until the patient could decide.

This case highlights the importance to complete evaluate every patient even when it looks like something simple, we could face a very rare condition.

PO 37

Predictors of surgical outcomes in boys with hypospadias

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Introduction:
Complications are frequently reported post hypospadias repair and there is a need to understand the factors that influence their occurrence.

Aim:
The aim of this study was to identify the occurrence of complications in boys with hypospadias that are in the I-DSD Registry.

Methods:
Data from boys born with hypospadias between 2010-2020 were obtained from the I-DSD registry. Results: Of the 469 eligible boys in the I-DSD Registry, data were available on 156 (34%) from 15 centres with an additional 27 patients included from one centre. The median (range) age at the time of the study was 7.5 (3, 12) years. Of this total, 119 (73%) had hypospadias repair and of these 97 (79%) had proximal hypospadias.

Of the 119, 89 (75%) had non-specific XY DSD; 13 (11%) had partial androgen insensitivity syndrome; 9 (8%) had partial gonadal dysgenesis; 5 (4%) had 5 alpha reductase deficiency; 2 (2%) had 17 beta dehydrogenase deficiency and 1 (1%) had P450 oxidoreductase deficiency. The median age at presentation was birth (birth, 5.6 yrs). Thirty-nine (33%) were planned single stage repairs. The median number of hypospadias repair operations including redo was 2 (1, 8) per patient. The median age at time of hypospadias repair was 2 (0.8, 7) years. Median follow up time from 1st hypospadias repair was 5 (1,11) years. Complications were reported in 66

(55%) with a median of 2 (1, 8) reported complications per patient. The most commonly reported complications were fistulae (n=28, 24%) and an abnormal meatal position or shape (n=23, 19%). Genetic testing was performed in 93 (78%). Biochemical testing was performed in 98 (82%). Additional comorbidities were reported in 58 (49%). There were no associations between complications and presence of a genetic variant, abnormal biochemistry or presence of an additional comorbidity.

Conclusion:
The complication rate over the first 5 years in the current cohort was much higher than previously reported and probably reflects the high prevalence of proximal hypospadias within the cohort. Although genetic testing was performed in the majority of cases, the low prevalence of variants identified indicates that the cohort needs to be further extended.

PO 38

Attitudes toward fertility-related care and education of youth and young adults with differences of sex development: informing future care models

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Background/Aims:
Youth and young adults (youth) with differences of sex development (DSD) face many challenging healthcare decisions. Fertility preservation is an emerging but experimental option for youth with DSD. Optimal counselling regarding future fertility options has not yet been defined for this population. We sought to examine the fertility- related attitudes and experiences of youth with DSD to inform care needs.

Methods:
Semi-structured interviews were conducted from 2015-2018 with youth with a DSD diagnosis who were seen in our multidisciplinary clinic. Topics covered included attitudes toward fertility and family building, fertility-related communication, and perspectives on fertility-related education and decision-making. Qualitative content analysis was performed using an inductive and deductive approach.

Results:
Eight youth (median age 17 years, range 14-28) with various DSD diagnoses (Mayer-Rokitansky-Küster-Hauser syndrome, androgen insensitivity, congenital adrenal hyperplasia, 46,XY DSD unspecified) participated. Youth were open to many options related to family building and fertility preservation, desired full disclosure of information, and recognized the importance of an age-related progression to autonomy in decision-making. Spanning all topics, the following were salient: 1) diversity of attitudes and care preferences amongst participants, 2) evolution of these attitudes and preferences over time, and 3) an emphasis on individualization of education and care.

Discussion/Conclusions:
The perspectives on fertility and related healthcare experiences of youth with DSD can be used to guide patient-centered education and informed decision-making surrounding the unique circumstances of each individual. A flexible and individualized approach can optimize fertility-related healthcare experiences for youth with DSD.

PO 39
The DSD Translational Research Network: A platform for discovery and improved clinical care

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Background:
Funded ten years ago by the US National Institute of Child Health and Human Development (NICHD), the DSD Translational Research Network (DSD-TRN) is a network of interdisciplinary pediatric clinics and research centers dedicated to establishing harmonized standards of care for patients and families, based on best evidence.

Methods:
Starting with four centers, the network has now expanded to 14 sites. Scope of work for membership includes commitment to: interdisciplinary, patient/family-centered care and shared decision-making; enhanced clinical practices involving deep phenotyping using harmonized, DSD-focused assessment forms in all specialties designed for capture in electronic medical records; psychosocial screening and support for all families; early genetic diagnosis; pursuing diagnosis before irreversible interventions; and research in contested areas of care.

Results and Conclusions:
Team activity (clinic volume, specialties present, genetic testing, patient enrolment, participation in network activities) is tracked in a REDCap database with metrics regularly reported to teams for quality improvement. A recent analysis showed that 74% of encounters provided psychosocial consult (17% not appropriate at this time, 5% no clinician available, 4% refused by family). Clinical genetic testing was offered in 18% of encounters. With 43% of previously known diagnoses, 9% of exhausted available testing, this left 30% of cases where genetic testing was either not offered or refused by insurance or families. In the clinical setting, diagnosis rates (endocrine + molecular) remain under 50%. Network deliverables include over 50 publications, outreach activities such as Family Days hosted jointly by Accord Alliance and clinical sites, a growing Parent & Family Advocacy Network, as well as training opportunities for providers. The network has organized over 75 monthly, CME-accredited, clinical case

videoconferences attended by patient representatives for discussion of management of complex conditions. A central Registry contains standardized, longitudinal information for (currently over 720) families who have agreed to participate in the research component of network activities. Biological samples (n=582) are collected in a Biobank for genetics research. Systematic exome or genome sequencing of undiagnosed samples, on a research basis, identified a diagnosis in a further 20 families and contributed to the delineation of the new GUBS syndrome.

PO 40

Psychosocial Adjustment in Youth with 17-beta Hydroxysteroid Dehydrogenase 3 Deficiency: A Case Series

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Background:
17-beta hydroxysteroid dehydrogenase 3 deficiency (17BHSD3 deficiency) is an autosomal recessive cause of 46,XY differences of sex development (DSD) that results in atypical external genital development, most commonly appearing as female-typical genitalia. This rare condition is often unrecognized or misdiagnosed as a different 46,XY DSD condition. While psychosocial research on youth with other DSD conditions is growing, little is known about the psychosocial adjustment of those with 17BHSD3 deficiency. The objective of the current case series is to describe the psychosocial clinical presentations of a pediatric sample of patients with 17BHSD3 deficiency.

Methods:
This is a retrospective case series of children, adolescents, and young adults (collectively referred to as "youth") who presented to a network of twelve pediatric academic centers participating in the NIH-sponsored DSD Translational Research Network (DSD-TRN). Youth with documented diagnoses of 17BHSD3 deficiency were identified. Demographic information, medical history, and scores on available youth-, parent-, and parent-proxy reported psychosocial measures (i.e., Patient Health Questionnaire-4, Child Behavior Checklist/Youth Self-Report/Adult-Self-Report, Self-Perception Profile, Body Image Scale, Multidimensional Gender Identity Scale) were abstracted from the medical record.

Results:

Cases included 8 youth (7 non-Hispanic White, 1 Black) ages 8-21 years at their last clinical encounter. Six youth were raised as girls and two youth were raised as boys. One girl and one boy indicated they may be exploring their gender identity. There was variability in psychosocial adjustment across all domains. Low gender typicality, elevated felt pressure to conform to gender of rearing, and positive gender contentedness was self-reported for several patients, consistent with data on youth with DSD generally.
There were few concerns reported in the domains of patient global self-worth, body image, and parental depression/anxiety.

Conclusions:
These young patients with 17BHSD3 deficiency illustrate the diversity of clinical presentations in this population. Additional reports are needed to understand predictors of adjustment and to demonstrate the generalizability of results. The current observations hint at the importance of targeted interventions to ameliorate the apparent burdens of 17BHSD3 deficiency on self- or other perceptions of its implications for the person.

PO 41
Change in newborn registration legislation for individuals with Disorders/Differences of Sex Development

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Disorders/Differences of Sex Development (DSD) are defined, since 2006 consensus, as congenital conditions in which chromosomal, gonadal and/or anatomical sex are atypical. In these cases, the most striking clinical presentation occurs in the neonatal period with atypical genitalia. This condition is considered an emergency as it has medical, psychological and social implications. In this sense, the time spent to establish a precise etiological investigation (and consequent adequate sex designation) in Brazil has always conflicted with the need for speed in the civil registration of the newborn.

For many years, the suggested course of action was that these patients should not be registered until the medical investigation was completed. However, this way management brought several difficulties from a social and legal point of view. In 2019, the state of Rio Grande do Sul pioneered, through the General Internal Affairs Department of the State Justice, by the provision number 016/2019 (of June 3rd, 2019), which allowed the registration of the unborn child as ''Newborn of... (followed by parents name) '' and sex record as ''ignored'' being able after 2 months, free of charge, to make a direct correction in any notary for the name and definitive sex. In 2021, based on Rio Grande do Sul's document, the National Justice Commission of Brazil published the provision number 122 (of August 13th, 2021) which maintained practically the same bases, only deciding that a name useful for both sexes should

be provisionally or in the non-agreement of the parents for this, let their name's suggestion be used.

Although it still lacks some adjustments to better adapt to the cultural reality of DSD management, this document is an unprecedented initiative in Brazil. It is an inclusive measure, as it assists in functional details of the care of these patients.

PO 42

Denys-Drash syndrome with Focal Segmental Glomerulosclerosis and novel WT1 mutation: a case report

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Background:
Denys-Drash syndrome is a rare cause of 46, XY DSD due to mutation on the WT1 gene and usually presents with gonadal dysplasia and renal insufficiency by diffuse mesangial sclerosis.

Case Report:
We describe a 10 months-old girl who was referred from the countryside of Rio Grande do Sul state in Brazil to our DSD team in the state capital (Porto Alegre) due to atypical genitalia and renal insufficiency already needing dialysis. She had a 46,XY karyotype. Genitalia presenting clitoromegaly with female differentiation of urethra and vagina, no gonads were palpable. Renal biopsy showed focal segmental glomerulosclerosis.

Molecular analysis of WT1 gene were executed presenting the undescribed missense variant c.703G>A; p. (Gly235Ser). Patient was submitted to bilateral gonadectomy, which presented bilateral streak gonads with gonadoblastoma histology. The female sex of rearing was maintained, prophylactic bilateral nephrectomy was executed (due the high risk of Wilms' tumor) and then patient was referred to a renal transplant service.
Conclusion:
This is an atypical renal presentation of Denys-Drash syndrome, and to the best of our knowledge, it is the first to present the Gly235Ser mutation in the WT1 gene.

PO 43

Spectrum of DSD disorders at Haukeland University Hospital, Norway from 1998-2018

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Background/Aims:
We wanted to know the distribution of DSD diagnoses, karyotype and prevalence of gonadal tumors in an outpatient clinical setting in a national DSD service serving Western Norway.

Methods:
We collected clinical data from electronic health records over a time period of 20 years (1998-2018) using search queries consistent with the most common DSD diagnoses.

Results:
We identified 131 patients. Of the 31 male patients with available karyotype, 15 patients had 46XY karyotypes, whereas the remaining patients had sex chromosomal mosaicisms. One of the boys, diagnosed with partial 46XY gonadal dysgenesia developed seminoma grade 1. Of the 32 female patients with available karyotype, 20 patients had 46XX-karyotype whereas five patients were 46XY-girls, of which three patients had developed gonadal tumors (one five year old girl with gonadoblastoma in situ, a 15 year old girl with gonadoblastoma in situ and a 15 year old girl with local dysgerminoma). Of the five patients with sex chromosomal mosaicism, one girl had a mosaicism containing Y-material. Five patients had mixed gonadal dysgenesia and one patient had true hermaphroditism.

Conclusion:
We identified gonadal tumors in 6/63 DSD patients in an outpatient clinical setting in Norway.

PO 44
Endocrine and Genetic Evaluation of XY Boys Investigated For A Disorder Of Sex Development

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Introduction:
A diagnosis remains elusive in a considerable number of patients with XY DSD and it remains unclear whether standardised pathways improve diagnostic yield.

Objectives:
To investigate the range of endocrine and molecular genetic variation in a group of boys undergoing investigation for XY DSD.

Methods:
181 boys were evaluated by the Glasgow DSD Diagnostic Board from 2016 to 2021. Sequence variants were classified according to ACMG guidelines and, in addition to pathogenic and likely pathogenic variants, variants of uncertain significance (VUS) were assigned as causative or coincidental, depending on phenotypic concordance or discordance, respectively.

Results:
The median external masculinization score (EMS) was 9 (2,12) at the median age of 0.9 (0, 18) years. Endocrine assessment, performed in 177 (98%) boys, revealed an abnormality in 42 (24%) including a disorder of gonadal development (DGD) in 24 (14%), LH deficiency (LHD) in 13 (7%), disorder of androgen synthesis (DAS) in 3 (2%) and disorder of androgen action (DAA) in 2 (1%). No significant difference in baseline EMS was identified between those with or without endocrine abnormality, family history of DSD and presence of associated condition. Of the 132 boys who had molecular genetic analysis, variants were found in 10/58(17%) by Sanger sequencing of seven genes, 2/7 (29%) by NGS of twenty-one genes, and 39/99(39%) by NGS of fifty-six genes. Of the 36/42 boys with endocrine abnormality who had gene analysis performed, molecular genetic diagnosis was reached in 12/36 (LHD, 6; DAS, 3; DAA, 2; DGD, 1) and 4/36 boys had coincidental VUS only (DGD, 4). Of the 135 boys without endocrine abnormality, 92 had gene analysis results available and 35/92 (38%) had an abnormal genetic finding reported. Of these 35 boys, 19 had a single nucleotide variant (SNV) that was classified as causative and 16 had findings that were considered to be coincidental.

Conclusions:
The likelihood of identifying an endocrine or genetic abnormality is not related to the EMS in boys with XY DSD. Although, a more extensive gene panel is associated with a higher likelihood of a genetic variant, it also introduces challenges in variant interpretation.

PO 45
Immunohistochemical characterization of Leydig cells in gonadal tissues from adolescent and adult patients with complete androgen insensitivity syndrome

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Background:
Testosterone (T) is believed to be synthesized mainly in Leydig cells which proliferate in two (or three) waves during the fetal, (neonatal) and adolescent periods. In a recent case report of a postpubertal patient with CAIS, gonadal tissues with Leydig cell (LC) tumor were shown to express HSD17B3 in Sertoli cells (SCs) and not in LCs. Here, we aimed to study the expression of LC and SC markers in testes from adolescents and adults with CAIS to elucidate a possible divergent localization of T synthesis.

Methods:
We used immunohistochemistry to stain serial sections from formalin-fixed, paraffin-embedded tumour-free gonadal tissues from four adolescents and adults with CAIS (age range at gonadectomy: 13.7-25.6-year-old) as well as one testicular tissue from a 28-year-old adult control for HSD17B3, and examined its colocalization in serial sections with CYP17A1 as LC marker, SOX9 as SC marker and DDX4 as germ cell marker. To further assess the developmental state of LC population, we stained tissue sections for DLK1 as a marker of immature/fetal LCs and INSL3 as a marker of mature LCs.

Results:
Here we show that HSD17B3 is exclusively expressed in SCs in all adolescent and adult CAIS gonads and not in LCs in contrast to adult control testis, where HSD17B3 is mainly expressed in LCs. We have also identified DLK1-expressing LCs as a separate population from INSL3-expressing LCs in the interstitial tissues of gonads from pubertal and adult patients with CAIS.

Discussion:
Our data show that SCs in gonadal tissues from adolescents and adults with CAIS most likely contribute to testicular T production and raise the question whether T is synthesized in these patients mainly by SCs rather than LCs. The pattern of HSD17B3 expression we report in this study is similar to that known for fetal mouse testis und suggests that androgen signalling is required for normal adult LC and SC development in human testis. Separate clusters of DLK1 and INSL3 expressing LCs in gonadal tissues in CAIS s suggests an accompanying developmental defect of ALCs and possible a failure of FLC regression. Taken together, the data suggest that AR mutations are associated with functional and developmental alterations in gonadal tissues in CAIS.

PO 46
Comprehensive Multidisciplinary Digital Pixel Phenotyping of Patients with Hypospadias

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Background:
Hypospadias is an abnormal penile formation of the urethra, ventral skin, and corporeal bodies. Location of the urethral meatus has historically been the phenotypic landmark that defines hypospadias. Classifications following location of urethral meatus fail to predict outcomes and have no correlation with the genotype. Description of urethral plate is very subjective and difficult to reproduce. We hypothesize that use of digital pixel cluster analysis and correlation to histological analysis can provide a novel method to describe the phenotype of patients with hypospadias.

Methods:

A standardized hypospadias phenotyping protocol was developed. 1. Digital images of the anomaly, 2. Anthropometric assessment of penile dimensions (penile length, urethral plate length and width, glans width, ventral curvature), 3. Classification using the GMS score, 4. Tissue sampling (foreskin, glans, urethral plate, periurethral ventral skin) and H&E analysis by a blinded pathologist. A k-means colorimetric pixel cluster analysis was performed following the same anatomical landmark distribution as the histology samples. Analysis was performed using MATLAB v R2021b 9.11.0.1769968

Results:
A total of 24 patients were enrolled using the standard protocol. Mean age at surgery was 16.25 months. Urethral meatus was at the distal shaft in 7 patients, 6 coronal, 4 glanular, 3 midshaft, 2 penoscrotal and 2 urethrocutaneous fistulas. Average GMS score was 7.14. Average glans size was 15.71 mm and urethral plate width 5.57 mm. Nine patients underwent Thiersch-Duplay repair, 7 TIP, 5 MAGPI, 2 urethrocutaneous fistula repair and 1 a first stage preputial flap. Two postoperative complications. Mean follow-up was 2.75 months. Twenty-one had complete histological analysis and 11 (52.3%) had an abnormal pathology report. Of those, 6 had reported chronic inflammation at the urethral plate. Second most common finding was hyperkeratosis. K-means pixel analysis demonstrated a mean of 64.2 for reported urethral plate inflammation vs 53.1 for non-reported urethral plate inflammation (p=0.002). Other differences were noticed comparing GMS scores but did not reach statistical difference.

Conclusions:
Current phenotyping of hypospadias using only anthropometric variables can be expanded including histological analysis and pixel analysis correlation. A larger cohort will allow identification of possible predictive associations that might impact intraoperative decision-making.

PO 47
Central Precocious Puberty in Congenital Adrenal Hyperplasia. Data from a Single Center

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Background:
Chronic hyperandrogenemia may trigger the activation of the hypothalamic-pituitary axis, leading to central precocious puberty (CPP) and hydrocortisone treatment reduces androgen levels and activates gonadotropins. The decrease in sex steroids during treatment of the congenital adrenal hyperplasia (CAH) causes activation of the hypothalamic gonadotropin-releasing hormone (GnRH) pulse generator via feedback mechanisms.

Methods:
The patients (n=11) diagnosed with CPP accounted for 10.4% of the 105 patients who presented with CAH at our clinic during 2015 to 2020. A diagnosis of CPP was confirmed via elevated LH response in a GnRH analog stimulation test with. CPP was defined as peak LH >7 IU/Land bone age at least 1 year greater than chronological age.

Results:
It should also be noted that the majority of patients with CPP had simple virilized form of disease (n=5, 45%), 2 patients with non classic and 4 patients with classic salt wasting form, respectively. The interesting thing is that in the whole group there were 14 patients with simple virilized form of whom 35.7% developed CPP. Its noteworthy that the patients with CPP from salt wasting form group were relatives(2 brothers from one family and sister and brother from second family). The mean chronological age of CAH diagnosis was 7.49±0.81 years, but the mean chronological age at onset of CPP and at start of treatment was 6.0± 0.61 years. In group with CPP the mean age of CAH diagnosis was 4.2 ± 1.08 years. All patients with CPP in this group had an advanced BA (mean 5.0 ± 2.4 years) at diagnosis. Mean basal androgen levels were significantly higher in the CPP-CAH than the CAH without CPP group: androstenedione, 6.01 vs 1.95 nmol/L (P<0.001); basal 17-OHP, 35.4 vs 5.82 nmol/L (P < 0.001); and DHEAS, 32.6 vs 1.72 nmol/L (P <0.001).

Conclusion:
This combination of CPP in patients with CAH is worthy of wider clinical recognition and attention, and better clinical management of patients is needed

PO 48

Development and validation of a short version of the Quality of Life DSD questionnaire (QoL-DSD) for parents of young children with disorders/differences of sex development

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Background:
Disorders/differences of sex development (DSD) may be associated with adverse psychosocial outcomes in adults. There is a paucity of information on health-related quality of life (QoL) outcomes in parents and children with DSD and a lack of instruments available for evaluating these outcomes. Recently, this has led to the development of Parent Self-Report and Proxy-Report QoL questionnaires (QoL-DSD), validated measures for parents of young children with DSD, comprising 63 items within 13 domains and 25 items within 5 domains, respectively. We aimed to develop short forms of the QoL-DSD, optimizing their use in routine clinic settings.

Methods:
Short forms of the DSD-QoL Parent Self-Report (QoL-DSD Short PSR) and Parent Proxy-Report (QoL-DSD Short PPR) questionnaires were developed following exploratory factor analysis, using previous QoL-DSD data from 132 parents. Long and short form questionnaires were completed online by parents of 18 children with DSD, attending endocrine and urology clinics at one tertiary hospital in Scotland.

Results:
Item selection for the short forms — QoL-DSD Short PSR and QoL-DSD Short PPR — based on factor loadings o>0.8, produced questionnaires containing 16 and 7 items, respectively. Eighteen parents completed both long and short forms of the PSR for children aged <7 years, and a subset of these (n=13) also completed long and short forms of the PPR for children aged 2 to 7 years. Of the 18 target children, all were boys with a median age of 3.6 years (range 0.4, 6.6); 10 (59%) had proximal hypospadias. Agreement was achieved between the short and long questionnaires in 9 out of 12 (75%) and 4 out of 5 (80%) domains on the PSR and PPR, respectively.

Parental feedback (n=18) regarding acceptability of the short versus long forms was evaluated using a 5-point Likert score: 83% (versus 66%) of parents agreed the length of time (less than 3 minutes) taken to complete short forms was acceptable, 39% preferred the short forms compared with 11% whom preferred the longer version, 45% (versus 22%) stated a preference to complete the short forms should they be implemented routinely at clinic visits in the future.

Conclusions:
Short forms of the QoL-DSD for parents of young children with DSD may be more acceptable for use in a routine outpatient setting to evaluate psychosocial distress experienced by young children with DSD and their caregivers. Further psychometric validation in a larger cohort is warranted.

PO 49
Sexually dimorphic visual perception of sex characteristics: an eye-tracking study

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Background:
For most people gender identity is consistent with assigned sex given at birth and primary and secondary sex characteristics. However, some individuals may experience feeling of discomfort (gender dysphoria) between their sex and gender identity, which is more common in people with differences or disorders of sex development (DSD). Currently, there is no biomarker that could predict one's gender identity. We hypothesized that individuals with gender dysphoria

and/or DSD condition may present a different visual perception pattern of sex characteristics, which differs from typical female and male pattern.

Methods:
We conducted a pilot study using eye-tracking among individuals (n: 22, 11 females) with no gender dysphoria or a DSD condition to define female and male visual perception patterns of sex characteristics. A series of 12 faces stimuli (6 females and 6 males) was displayed during (1) free-viewing, (2) sex discrimination and (3) rating attractiveness tasks. After defining areas of interest of internal (iAOI) and external (eAOI) facial features, standard visual scanning parameters were assessed.

Results:
Women spent more time in iAOI in comparison to men ($p<0.0001$). The first fixation in iAOI was made faster and it lasted for a shorter time ($p<0.0001$). They made more fixations in iAOI and when both AOIs were analyzed ($p<0.0001$). Irrespective of the AOI, the average fixation duration was shorter ($p<0.001$). Men spent more time in eAOI in comparison to females ($p<0.0001$). They tended to make more shifts to eAOI, especially during rating attractiveness task ($p<0.0001$), where they made more fixations ($p<0.001$).

Conclusions:
There is a sexual dimorphism in visual perception of sex characteristics. Further studies in individuals with gender dysphoria and/or DSD are required to define their pattern, that could give some insight into gender identity indicators.

PO 50
DSD clinical coordinator role: Impact on clinical care

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Background:
The Differences of sex development (DSD) Intersex variations clinical coordinator (CC) role began in 2016 to facilitate clinical coordination and psychosocial support of individuals living with DSD and their families at the Royal Children's Hospital, Melbourne. Here, we report the impact of the role on service delivery and its current key components.

The DSD multidisciplinary team (MDT):
Formal coordination of the DSD MDT meetings by the CC has resulted in numerous benefits. The joint monthly meeting across two paediatric centres in Melbourne has increased clinical participation which now includes over 35 specialists and further encompasses clinicians from regional Australian and international centres. The DSD MDT forum ensures all case discussions including individual/parent perspectives and care pathways are discussed within an ethical framework.

Clinical coordination:
The CC supports families through paediatric and adolescent care, transitioning into adulthood, and increasingly in the prenatal setting. Common CC support includes appointment coordination (multiple specialists), translation of complex health information, and referral for general psychosocial services including accessing peer support. The CC has a 410+ patient load and provides psychosocial support for 4-15 patients and their families per day.

Stakeholders:
The CC is a central liaison point for a broad range of stakeholders. This includes the provision of expert advice for government intersex advisory groups and other organisations, developing relationships with peer support and advocacy groups, and membership in clinical and academic organisations. The CC position enables different sectors to connect with the MDT for support, information, and education.

Research and education:
To promote evidence-based care, the CC has led projects and collaborated with multiple research teams to identify the health gaps and priorities for this community. As a member of a Reproductive Development Research Laboratory, the CC liaises with participants and encourages connections between clinical groups and researchers. Informed by individuals lived experiences of DSD/ intersex variations the CC has developed online resources available in different formats and has provided DSD education for external organisations such as schoolteachers, book authors, and midwives.

The CC raises awareness of DSD/intersex variations in the community, promoting better outcomes for individuals and their families.

PO 51

Case series of 16 patients with 17β-hydroxysteroid dehydrogenase type 3 deficiency at five children's hospitals in the United States

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Background:
The 17β-hydroxysteroid dehydrogenase type 3 (17βHSD3) enzyme converts androstenedione to testosterone in the testes. 17βHSD3 deficiency causes a 46,XY difference of sex development (DSD). To date, 12 cases of 17βHSD3 deficiency have been reported in the literature in the United States. We report a series of 16 patients diagnosed at five children's hospitals in the United States.

Methods:
Multi-center chart review of patients with 17βHSD3 deficiency.

Results:
Sixteen patients were identified, ranging in age at diagnosis from birth to 22.3 years. One patient, assigned female at birth, was diagnosed due to a positive family history. Three patients were diagnosed after discordance was noted between sex predicted by prenatal cell-free DNA testing and external genital appearance (two assigned female, one assigned male). An additional four patients had non-binary (atypical) genitalia at birth (two assigned female, two assigned male). Two children assigned female were diagnosed in childhood after undescended testes were identified during hernia repair. Six patients who were assigned female were diagnosed peri-pubertally due to excess androgen effects and/or primary amenorrhea. Data on gender identity is limited by patients' current ages, but as of most recent follow-up, one patient assigned male and one assigned female have reported exploring their gender identities.
Four patients had an earlier inaccurate diagnosis of complete or partial androgen insensitivity syndrome. Eleven patients had genetic testing confirming pathogenic or likely pathogenic variants in the HSD17B3 gene (two identified on whole exome, one on a DSD multi-gene panel, and 8 on single gene testing). One had a clinical diagnosis due to their sibling's genetically-confirmed diagnosis. Four declined or have not completed genetic testing, but had hormonal evaluation consistent with the diagnosis.

Conclusions:
17βHSD3 deficiency is likely much more common in the US than previously appreciated, and can present at any age with a range of physical findings. Accurate diagnosis is important, as the broad category of 46,XY DSD encompasses a wide spectrum of gonadal malignancy risk, potential for pubertal hormone function and fertility, and gender identity outcomes. We suggest evaluating for this potential diagnosis with genetic and/or hormonal testing in cases of 46,XY DSD with absent uterus.

PO 52

Leukocyte telomere length in children with congenital adrenal hyperplasia

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Background:

Exposure to chronic stress and hypercortisolism is associated with decreased leukocyte telomere length (LTL), a marker for biological aging and cardiovascular disease. Children with congenital adrenal hyperplasia (CAH) are treated with glucocorticoids. The aim of this study was to investigate LTL in children with CAH and its relation with treatment characteristics.

Methods:
This prospective observational cohort study included children aged 0-18 years with genetically confirmed CAH. Patients were followed-up at two consecutive outpatient clinic visits (mean 4.1 ± 0.7 months apart). At each visit, LTL was determined by monochrome multiplex quantitative real-time polymerase chain reaction. All subjects underwent detailed clinical and endocrinologic evaluation, and were classified as undertreated, optimally treated or overtreated, accordingly. The influence of clinical factors on LTL was investigated using linear mixed models adjusted for age, sex, and BMI z-score (BMI-z).

Results:
We studied 76 patients [31 (41%) girls; 63 (83%) with classic CAH; 67 (88%) received hydrocortisone and 8 (11%) prednisolone]. Their median age at first visit was 12.0 years (IQR 6.3–15.1) and median BMI-z was 0.51 (IQR -0.12–1.43). At first visit, 46 (61%) patients were optimally treated, 22 (29%) were undertreated and 7 (9%) were overtreated. At second visit, 41 (55%) patients were optimally treated, 31 (42%) were undertreated and 2 (3%) were overtreated. Median LTL at first visit was 1.18 (IQR 1.04–1.39); mean ΔLTL was 0.017 ± 0.083. LTL was shorter in patients with classic than non-classic CAH (coefficient -0.25, 95% CI -0.47 to -0.03, p=0.02), in those overtreated than optimally treated (coefficient -0.07, 95% CI -0.12 to -0.03, p=0.002), and in those treated with prednisolone than hydrocortisone (coefficient -0.31, 95% CI -0.47 to -0.14, p<0.001). LTL was not associated with undertreatment or daily hydrocortisone-equivalent dose (p>0.05).

Conclusion:
In patients with CAH, LTL is shorter in the classic than non-classic form of the disease, as well as in patients overtreated or treated with long-acting glucocorticoids. This may be attributed to chronic exposure to supraphysiologic glucocorticoid concentrations, indicating that LTL may be used as biomarker for monitoring glucocorticoid treatment in CAH.

Author Index

Number refers to abstract number