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11th I-DSD Symposium

Stockholm, Sweden, 26 – 28 June, 2024

Abstracts

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Programme

I-DSD Symposium

Symposium Day 1 (Wednesday, June 26th 2024)

Sune Bergström Aula, Karolinska University Hospital, Stockholm

I-DSD Workshops *Wednesday, June 26th 2024* (08:45-12:30) Karolinska University Hospital Choice of 3 workshops out of 4, lasting 45 mins each			
The I-DSD/I-CAH/I-TS registries *(SDMregistries)* **Malika Alimussina Glasgow, UK**	DSD Diagnostics **Sabine Hannema Amsterdam, Netherlands**	Communication with patients and parents **Anna Strandqvist, Stockholm, Sweden**	Hormone replacement **Aneta Gawlik, Katowice, Poland**
Lunch for workshop 12:00 – 12:30			

Registration & Coffee from 11:30 – Sune Bergström Aula
13:00: Opening
Session 1 – Setting the Scene (13:00-13:35) Chair: Anna Nordenström
13:00 – 13:05 Introduction - Anna Nordenström, Stockholm, Sweden 13:05 – 13:20 Lived experience – Chris Breen, UK 13:20 – 13:35 Patient support & advocacy – Giorgio Dal Maso, Italy
Session 2 –Update on I-DSD Activities (13:40-14:10) Chair: Christa Flück
- Recent Developments – Faisal Ahmed, Glasgow UK - Research & Data Access – Jeremy Tomlinson, Oxford UK - Care Quality Improvement – Justin Davies, Southampton UK - Learning & Training – Sabine Hannema, Amsterdam, Netherlands 5 mins each and then Discussion

Oral Communications 1 (OC1) (14:20-15:30) Chairs: Stefan Wudy, Giessen, Germany	
14:20 – 14:30	OC1.1 A tiered approach to exome sequencing analysis in Primary Ovarian Insufficiency: results from a large, early-onset cohort – Sinead McGlacken-Byrne, London, UK
14:30 – 14:40	OC1.2 Increased Blood Pressure SDS and Oxidative Stress in Boys With Early Onset Hypogonadism – Angela Lucas-Herald, Glasgow, UK
14:40 – 14:50	OC1.3 Health related quality of life in children, adolescents and young adults with differences of sex development (DSD) and their relatives after participating in a modular DSD-specific education programme (Empower-DSD) – Uta Neumann, Berlin, Germany
14:50 – 15:00	OC1.4 Turner Syndrome: Genomic Unity and Inflammation Across Karyotypes – Claus Gravholt, Aarhus, Denmark
15:00 – 15:10	OC1.5 Gonadectomy in individuals with Differences of Sex Development – A prospective I-DSD Registry Study – Michele O'Connell, Melbourne, Australia
15:10 – 15:20	OC1.6 "There was so much shame and embarrassment wrapped up in my decision making": The experience of making decisions for adolescents and young adults with differences of sex development – Kristina Suorsa-Johnson, Salt Lake City, Utah, USA
15:20 – 15:30	OC1.7 Long Term Outcomes In 21 Hydroxylase Deficiency Congenital Adrenal Hyperplasia: Patient Identification And Initial Results From A Single UK Centre – Joseph McElvaney, Glasgow, UK
Coffee Break 15:30 – 16:00	
Session 3 – Androgen Insensitivity Syndrome (16:00-17:30) Chair: Olaf Hiort, Luebeck, Germany	
16:00 – 16:25	The epidemiology and genetics of AIS – Rafael Batista, Sao Paulo, Brazil
16:25 – 16:50	Looking beyond *AR* – Nadine Hornig, Kiel, Germany
16:50 – 17:15	Long-term outcomes in women with AIS – Giovanna Mantovani, Milan, Italy
17:15 – 17:30	Discussion
Free Evening	

Symposium Day 2 (Thursday, June 27th 2024)

Session 4 –Real World Solutions for Supporting Patients & Services (08:15-09:45) Chair: Erin Sharwood, Brisbane, Australia	
08:15 – 08:40	Supporting and developing the workforce – Arianne Dessens, Rotterdam, Netherlands
08:40 – 09:05	Shared decision making in clinical practice – David Sandberg, AnnArbor, US
09:05 – 09:30	Supporting patients and people in resource restricted settings – Annastasia Ediati, Jakarta, Indonesia
09:30 – 09:45	Discussion
Oral Communications 2 (OC2) (09:45-11:05) Chair: Claus Gravholt, Aarhus, Denmark	
09:45 – 09:55	OC2.1 Towards an experimental proof of oligogenicity explaining a severe 46,XY DSD phenotype associated with heterozygote NR5A1/SF-1 variation – Rawda Naamneh-Elzenaty, Bern, Switzerland
09:55 – 10:05	OC2.2 Evaluation of quality of care for people with differences of sex development (DSD) – results of an annual benchmarking of DSD centres in Germany – Ulla Doehnert, Luebeck, Germany
10:05 – 10:15	OC2.3 Family Planning and Preimplantation Testing: family experiences in Congenital Adrenal Hyperplasia – Kristen Neville, Sydney, Australia
10:15 – 10:25	OC2.4 A conserved NR5A1-responsive enhancer regulates SRY in human testis-determination: A new cause of 46,XY DSD – Anu Bashamboo, Paris, France
10:25 – 10:35	OC2.5 SGPL1 deficiency, a cause of 46XY DSD and adrenal insufficiency, impairs lipid metabolism and steroidogenesis in Leydig cells – Ruth Ming Wai Kwong, London, UK
10:35 – 10:45	OC2.6 Validation Of A New Short Parent Reported Outcomes (PRO) Questionnaire For Boys With A Condition Associated With A Difference or Disorder of Sex Development (DSD) – PRO-DSD Short – Xanthippi Tseretopoulou, Glasgow, UK
10:45 – 10:55	OC2.7 Long-read sequencing resolves CYP21A2 alleles in Congenital Adrenal Hyperplasia – Emmanuèle Délot, Washington DC, USA
10:55 – 11:05	OC2.8 High throughput screening of VSD candidate genes with the help of powerful model Drosophila melanogaster – Isabel von der Decken, Freiburg, Germany
Coffee Break 11:05 – 11:30	

Session 5–Data Driven Approach To DSD Care (11:30-13:00) Chair: Justin Davies, Southampton, UK	
11:30 – 12:00	Evidence Driven Care in CAH – Nils Krone, Sheffield, UK
12:00 – 12:30	Advances in improving the genetic diagnosis in DSD – Eric Vilain, Irvine, CA, US
12:30 – 13:00	The use of metabolomics for personalised care in steroid deficient states – Stefan Wudy, Germany
12:50 – 13:00	Discussion
Lunch 13:00 – 14:00	
Session 6 – Debate (14:00–15:15) 'This house believes that the clinical need for a genetic diagnosis in DSD has been exaggerated' Chair: Anna Nordenström, Stockholm, Sweden	
14:00 – 14:05	Introduction and poll – Anna Nordenström
14:05 – 14:25	For – Christa Flück, Bern, Switzerland
14:25 – 14:45	Against – David Zangen, Jerusalem, Israel
14:45 – 15:15	Discussion & poll
Coffee and Posters 15:15 – 17:30	
15:30 – 17:30	Guided poster rounds
19:30 – Social Evening	

Symposium Day 3 (Friday June 28th 2024)

Session 7 – Delayed Genitoplasty & Its Implications (09.00–10.30) Chair: David Sandberg, Ann Arbor, USA	
09.00 – 09.25	Surgical solutions – Gundela Holmdahl, Stockholm, Sweden
09.25 – 09.50	Psychosocial support- Anna Strandqvist, Stockholm, Sweden
09.50 – 10.15	Legal & Ethical aspects – Martine de Vries, Leiden, the Netherlands
10.15 – 10.30	Discussion
Coffee Break 10.30 – 11.15	
Session 8 – The Ovaries (11:15–12:45) Chair: Giovanna Mantovani, Milan, Italy	
11.15 – 11.40	Ovarian Development – Vince Harley, Melbourne, Australia
11.40 – 12:05	The genetics and outcome of ovarian insufficiency – Anne Bachelot, Paris, France
12:05 – 12.30	Assisted reproduction in women – Kenny Rodriguez-Wallberg, Stockholm, Sweden
12:30 – 12:45	Discussion
12:45 – Close (Faisal Ahmed)	

CME (CPD) – accreditation by UEMS EACCME®

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Invited Speaker Abstracts

Lived experience

Chris Breen[1, 2, 3]

[1] *Senior Lecturer, School of Health and Social Care, University of Lincoln, UK*
[2] *Trustee Klinefelter's Syndrome Association, UK*
[3] *EPAG Endo-ERN*

I didn't find out I had Klinefelter's Syndrome until I was 50 and then it was an incidental finding, initially it was a surprise despite at the time having worked for over 20 years in Health Care I had never heard of it or most of the other DSDs I now know about. However, the more I learnt about it the more I could relate features of it to myself, how I had felt, challenges I faced and in some cases still do.

In the last 9 years since getting diagnosed I have interacted with many healthcare professionals both personally and professionally, some have been excellent, but most like me have never heard of the various DSD conditions. Now I explain it to all my colleagues and students to raise awareness and acceptance.

Some interaction with medical colleagues has not been great and some seem obsessed with fixing something which isn't necessarily broken, giving hormones which do not necessarily align with a person's gender identity. Think everyone wants to be able to reproduce and are deeply concerned about our mental health, the quality of our sex lives and size of our genitalia. I have had some embarrassing intimate examinations, some without explanation and thus informed consent, and have been told that measuring an anogenital distance is as non-invasive as measure someone height. However, the associated comorbidities associated with these conditions are largely ignored especially in primary care who are particularly poor at routine investigations we should be having such as blood test and dexa scans.

What we can do better is treat people with dignity and to educate those colleagues that lack the knowledge to recognise and effectively support individuals with these conditions and comorbidities. And not encourage secrecy and marginalisation of intersex individuals.

I use the term "Intersex" not "DSD" in the title as I do not consider it a disorder but a variation that in some ways I found extremely validating and knowing has made my life richer and more interesting.

This is particularly poignant as the United Nations in April 2024 made a historic move to protect the human rights of intersex persons, 35 civil society organisations said today, as the Human Rights Council adopted its first-ever resolution specifically addressing discrimination, violence, and harmful practices against persons with innate variations in sex characteristics.

The role of patient and family associations in the management of CAH at the national and European level

Giorgio Dal Maso [1]

[1] *Associazione Regionale Famiglie Sindrome Adreno-Genitale ODV, CAH Italy, Bologna, Italy*

A rare patient affected by CAH cannot be left alone and move autonomously within the national health system. In a complex environment such as hospitals, always attentive to resources and personnel, with complex administrative rules that tend to compress patient space and entrap them within a practice and a management mechanism, living with CAH is not simple.
How to assess the level of care provided? How to understand the quality of the care? How to evaluate whether the center truly offers an adequate level of service?
The role of the association is not only to aggregate patients to share daily experiences but also to gather information and monitor the uniform application of the right to care in all facilities at the national level, to act as a spokesperson for the needs and essential levels of care, and to guide patients through the bureaucratic folds of managing the disease.
This is especially true in Italy, where the bureaucratic component is very intricate and burdensome.

But an association for a single rare disease seldom gathers a large number of members. Hence, there is a need to extend its commitment and collaboration towards other associative structures: national, European, and international.

A brief explanation of the Italian association, the UNIAMO Federation for Rare Diseases, the experience in ENDO-ERN, and the activities of the association within CAH-International.

The epidemiology and genetics of AIS

Rafael Loch Batista [1]

[1] *Developmental Endocrinology Unit, Hormone and Molecular Genetics Laboratory (LIM/42), Endocrinology Division, Internal Medicine Department, Medical School, University of São Paulo (USP), São Paulo, SP, 05403-000, Brazil.*

Androgen Insensitivity Syndrome (AIS) is a rare genetic condition that affects sexual development. It is clinically characterized by androgen resistance. The epidemiology of AIS suggests that it occurs in approximately 1 in 20,000 live births. However, this figure may vary depending on the population studied and the criteria used for diagnosis.
AIS can present in three phenotypes: complete androgen insensitivity syndrome (CAIS), partial androgen insensitivity syndrome (PAIS), and mild androgen insensitivity syndrome (MAIS). In CAIS, individuals typically have a completely female appearance externally, including typically-female external genitalia. PAIS encompasses a spectrum of clinical presentations, where individuals may have atypical genitalia or varying degrees of undermasculinization largely depending on the remaining activity of the AR. MAIS, on the other hand, is the mildest form of AIS, where affected individuals may have subtle signs of androgen insensitivity, such as infertility, gynecomastia, or reduced facial hair growth.

The genetics of AIS primarily involve allelic variants in the androgen receptor gene (AR) located on the X chromosome. As for CAIS, most mutations leading to PAIS affect the ligand binding domain (LBD) while those causing MAIS are more distributed with recurrent variants covering TAU-5 region of the N-terminal domain (NTD). As AIS follows an X-linked recessive pattern of inheritance, the condition typically affects XY individuals. In recent years, advancements in genetic testing have facilitated the identification of AR variants in AIS, allowing for more accurate diagnosis and genetic counselling. Additionally, other genes and other unusual genetic mechanisms of androgen resistance has been revealed.
In conclusion, AIS is a complex genetic condition that affects sexual development and manifests in various degrees of androgen insensitivity. Understanding the epidemiology and genetics of AIS is crucial for accurate diagnosis, management, and genetic counselling to support affected individuals and their families.

Looking beyond AR

Nadine Hornig[1]

[1]*Institute of Human Genetics, University Hospital Schleswig-Holstein, Kiel, Germany*

Androgen insensitivity syndrome (AIS) is a common cause of 46,XY differences of sex development (DSD) characterized by reduced or absent cellular responses to androgens. AIS is classically explained by mutations in the androgen receptor (AR) gene. Nevertheless, the majority of individuals with the clinical diagnosis AIS do not harbour mutations in the *AR*. This significantly complicates the counselling and clinical care of these individuals.
This talk will give an overview of current research approaches trying to explain the aetiology of *AR*-mutation negative AIS by looking beyond the AR.

Long-term outcomes in women with androgen insensitivity syndrome

Giovanna Mantovani[1]

[1]*Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Endocrinology Unit; University of Milan, Department of Clinical Sciences and Community Health, Milan, Italy.*

Androgen insensitivity syndrome (AIS) is a disorder characterized by peripheral androgen resistance due to androgen receptor mutations in subjects with 46 XY karyotype. It represents one of the most frequent disorders of sexual development (DSD) and the severity of hormone resistance determines the wide spectrum of phenotypes.

The clinical phenotype and especially the decision on sex assignment of the patient, if the diagnosis is made at birth or in the neonatal period, will guide the following medical, surgical and psychological management. After paediatric care, one of the main challenges is the transition of patients to expert care in adulthood. Patients frequently experience difficulties in accessing specialised medical care in adulthood, resulting in loss to follow-up affecting the patients' physical and psychological health as well as quality of life.

Overall, little is known about long-term outcomes in AIS but some evidence suggests that osteoporosis and impairment of quality of life are frequent, regardless of hormone replacement therapy regimen and compliance. Similarly, preservation of gonads does not seem to guarantee optimal hormone levels. The talk will especially focus on bone and sexual health.

Shared decision making in clinical practice

David E. Sandberg, PhD[1]

[1]*Susan B. Meister Child Health Evaluation and Research Center and Department of Pediatrics, University of Michigan Medical School, Ann Arbor, Michigan, USA*

Few topics are as controversial as the clinical management of disorders/differences of sex development (DSD). Decisions involve genetic testing, gender assignment, and deliberation regarding genital and/or gonadal surgery, among others. Evidence of dispute appear in the medical literature, social media, legislatures, and courts of law. Activists claim that clinicians bias parents' healthcare decisions in directions preferred by the provider. This circumstance fuels the argument that proxy decisions made by parents are a violation of the child's human rights. To address concerns that parents are making poorly informed decisions, we developed decision aids to engage parents/caregivers as partners in shared decision making (SDM).

SDM is a collaborative process allowing patients and clinicians to make healthcare decisions together. Patient decision aids (PtDAs) support SDM by making decisions explicit, providing information about options and associated benefits/harms, and helping clarify congruence between the chosen option and patient/family values. PtDA development followed a co-design process, guided by the *Ottawa Decision Support Framework* and the *International Patient Decision Aids Standards* (IPDAS). A survey of clinicians delivering pediatric DSD care (n=28) identified priority needs for decisional support. Four PtDAs were created – diagnostic exome sequencing; gender of rearing; and surgery (gonadal and genital). This presentation focuses on the 2 surgical decision aids.

Information on the condition, options, benefits and harms are presented in a format facilitating comparison between the positive and negative features of available options with linkages to evidence sources, including expert opinion or consensus. The PtDAs provide an interactive exercise to clarify parents' values for features of options.

Although not directly responding to the charge that elective genital surgery violates the child's bodily autonomy, PtDAs operationalize the ethical standard of informed decision making. Next steps include evaluating factors influencing implementation of all 4 PtDAs in routine clinical practice and assessment of parents' decisional experiences.

Supporting patients and people in resource restricted settings

Annastasia Ediati, Jakarta, Indonesia

No abstract available

Evidence Driven Care in CAH

Nils Krone[1]

[1]Division of Clinical Medicine, School of Medicine and Population Health, University of Sheffield, Sheffield, United Kingdom

Congenital adrenal hyperplasia (CAH) is one of the commonest forms of primary adrenal insufficiency with an incidence of about 1 in 15,000. Several studies highlighted the suboptimal health status and care provision in adults with CAH that were associated with significant co-morbidities in relatively young adults. The onset and progression of problems and their interrelation with clinical management remain unclear. However, it appears of paramount importance to prevent and reduce co-morbidities from an early age. Clinical practice guidelines for the management of CAH exist since over 20 years. However, significant differences in the approach to CAH can still be observed. This even includes the treatment with glucocorticoids and mineralocorticoids as well as the ongoing debate about therapy control. Despite the huge variability of patients' care, the long-term consequences of different approaches have never been systematically compared. Furthermore, current studies reporting health data have a significant risk of selection bias and the overall situation of care provision in specific countries and at international level remains unclear. Clinicians' perception of services and that of patients, parents and career seem to vary in parts illustrating the need to further develop services according to patients' needs. Ongoing data collection and analysis, as well as service evaluation and bench marking, should become a mandatory cornerstone of service provision similar to other conditions such as type 1 diabetes where such an approach has resulted in major improvements of care provision.

The use of urinary steroid metabolomics for personalized care in steroid deficient states

Stefan A. Wudy [1]

[1] *Paediatric Endocrinology & Diabetology, Justus Liebig University, Giessen, Germany*

Already around mid of last century it was believed that most problems in steroid metabolism had already been solved. After the short interplay of molecular genetics dominating research in the 80s and 90s of last century, studies investigating the metabolome are currently facing a renaissance. Particularly in the field of steroid metabolism, exciting rediscoveries and new observations have taken place. Besides studies in human beings, essential for these revolutionary findings were also investigations in animals, as well as the use of new steroid analytical techniques based on mass spectrometry.

This talk will first introduce the audience to the principles of mass spectrometry based analytical techniques most commonly used in clinical care or research. Thereafter it will focus on the use of these techniques in the metabolic diagnosis or monitoring of the various forms of DSD putting particular emphasis on the enormous potential of urinary steroid metabolomics. The talk will also touch on the aspect how traditional concepts of human steroid metabolism became shattered by new insights into alternative androgen synthetic pathways and "newly" discovered highly potent androgens.

Surgical solutions

Gundela Holmdahl[1]

Ass Prof, Senior Consultant Pediatric Urology
[1]*Astrid Lindgren´s Childrens Hospital, Karolinska University Hospital, Stockholm, Sweden*

During the last decades the indications and timing for genitoplasty in patients with DSD have been discussed and practice has changed. Especially in Europe and North America there is more than a trend today to postpone clitoris reduction until the patient can give informed consent. This is also true concerning both timing and indications for vaginal reconstruction. Self-dilatation to create a neovagina is today the standard procedure whenever it is possible and should always be performed after puberty when the patient is prepared and asks for it herself. On the other hand, there are arguments that male genitoplasty, read hypospadias repair, should be done early due to less complications compared to reconstruction in puberty, that it possibly is a reversible surgery and that some self-reported outcome studies have shown that few patients regret the surgery. However, evidence that the new surgical strategies will improve patient self-reported outcome are, to a large extent, missing. New knowledge on the functional and cosmetic results when postponing surgeries such as female genitoplasty and hypospadias repair in DSD patients is warranted.

Psychosocial support in DSD

Anna Strandqvist[1]*, PhD*

[1]*Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden*

Psychosocial support is recommended to be an integral part of clinical management for individuals with DSD and a cornerstone in an interdisciplinary approach. The timing, type of and reasons for psychosocial support differ between individuals with different conditions and over the lifespan. Typically, it relates to getting to know about and living with differences in anatomy, fertility, somatic sex development, gender expression/behaviour and identity development. An important aspect of psychosocial support in DSD is to facilitate information, promote shared decision making between the patient, or parent of the patient, and healthcare representatives. Challenges emerge around different perceptions of normality, and divergent cultural and religious values. Present recommendations call for a preventive approach, meeting parents and patients to promote good coping and build resilience for the future.

Few studies have examined the perceived need for, utilization of and the opinions of individuals with DSD regarding psychological support. New knowledge is emerging regarding the need for support from a patient perspective.

The need for psychosocial support has hitherto been explored from the perspective of parents to children with a DSD and for adults in retrospective quantitative self-report studies.

Some but not all parents of children with DSD experience a need for support. The perceived need for support is more pronounced among individuals with 46,XY DSD and androgen effects. The prospect of or, experience of surgery neither increases nor decreases perceived need.

Emerging results from outcome studies shows that many individuals with a DSD condition experience a need for psychological support at some point in their life. In addition, an increasing number of people with DSD receive psychological support from their healthcare provider which in the majority is perceived as a positive intervention. Individuals with DSD agree with the notion that psychological support should be an integral part of DSD healthcare, still largely an unmet need.

Legal & Ethical aspects
Martine de Vries, Leiden, the Netherlands
No abstract available

Ovarian and testicular development

Vincent Harley [1]

[1] *Hudson Institute of medical Research, Melbourne Australia*

Identification of causative genes in DSD has helped our understanding of the molecular events that occur during the differentiation of the bipotential gonads into ovaries and testes during embryonic development. Conversely, DSD-causing genes have been identified through molecular studies of ovarian or testicular differentiation, through either omic approaches or evolutionary conservation or through serendipity in for example gene knockout studies in mice. Ovarian genes either promote ovarian development directly and/or repress testicular developmental programs, whereas testicular genes either promote testes development directly and/or repress ovarian developmental programs. Examples of these scenarios will be outlined.

The genetics and outcome of ovarian insufficiency
Anne Bachelot, Paris, France
No abstract available

Assisted reproduction in women

Kenny A. Rodriguez-Wallberg [1,2]

[1] *Department of Reproductive Medicine, Karolinska University Hospital, Stockholm, Sweden*
[2] *Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden*

It is estimated that infertility affects around 186 million people and that more than 10 million children have been conceived using assisted reproductive technology (ART) worldwide, overcoming several infertility causes. For women, the typical ART treatment involves ovarian stimulation, follicle aspiration for oocyte retrieval, and thereafter in vitro fertilization, embryo culture and embryo transfer. Over the years, additional procedures have been developed, including the cryopreservation of embryos since the 1980's and the cryopreservation of oocytes,

which has achieved a clinical level under the 2010's. These methods have been applied also for fertility preservation of women during several decades.

At the end of the 1990's also methods for human ovarian tissue cryopreservation were developed, with the objective to preserve reproductive potential for the future. The ovarian tissue has demonstrated to resume functionality again after being retransplanted and several programs for fertility preservation, including ours at Karolinska University Hospital in Stockholm, are currently offering this type of treatment to women and girls in several clinical situations including cancer, chronic benign chronic and genetic conditions.

OC 1.1

A tiered approach to exome sequencing analysis in Primary Ovarian Insufficiency: results from a large, early-onset cohort

Sinéad M. McGlacken-Byrne[1,2,3], Jenifer P. Suntharalingham[1], Miho Ishida[1], Federica Buonocore[1], Ignacio del Valle[1], Antoinette Cameron-Pimblett[2], UCL Genomics[4], Mehul T. Dattani[1,3], John C. Achermann[1], Gerard S. Conway[2]

[1] Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, University College London, London, UK
[2] Institute for Women's Health, University College London, WC1E 6AU, London, UK
[3] Department of Paediatric Endocrinology, Great Ormond Street Hospital, London, UK
[4] UCL Genomics, Zayed Centre for Research, University College London, London, UK

Background: Sequencing of Primary Ovarian Insufficiency (POI) cohorts have identified variants in >100 "POI genes" in up to 50% of women, with different degrees of evidence supporting their pathogenicity. Whether early-onset POI (EO-POI; POI with adolescent onset) has a unique genetic profile remains unknown.

Methods: We performed exome sequencing (Nonacus) in an EO-POI cohort, sporadic and familial, and their unaffected family members. Filtering (QCI (Qiagen)) retained variants which were 1) rare/novel (minor allele frequency <0.01%), 2) predicted pathogenic *in silico*, 3) enriched in the cohort compared to controls (gnomAD v4.0); and 4) pathogenic/likely pathogenic (ACMG criteria). Three categories of variants were considered: 1) variants in genes included on the Genomics England Primary Ovarian Insufficiency PanelApp (Jan 2024); 2) variants in genes included on the POI PanelApp but following unexpected inheritance patterns *or* variants in genes not on the POI PanelApp but previously associated with POI; and 3) homozygous variants in novel candidate POI genes.

Results: A total of 149 women with EO-POI were recruited (31 familial POI from 17 kindreds (8 consanguineous); 118 sporadic POI). Of these, 81.2% (n=121) had primary amenorrhea. Of 17 kindred with familial POI, 13 (76.5%) had a Category 1, 2, or 3 variant identified (n=6 homozygous Category 1 variants in *STAG3, MCM9, PSCM3IP, POLR2C, YTHDC2,* and *ZSWIM7* and n=5 Category 2 variants in *NLRP11* and *PRKD1* (heterozygous), *PLEC, IGSF10,* and *KMT2A* (homozygous), *PDE3A, POLR2H, MSH6,* and *CLPP* (polygenic)). A total of 65.3% (n=77) women with sporadic POI had a variant identified (20.3% (n=24) Category 1 and 42.4% (n=50) Category 2). Within the entire POI cohort, heterozygous, homozygous, and polygenic variants in genes previously associated with POI were found in 30.9%, 9.4%, and 21.8% of women respectively. Most heterozygous variants were present in gnomAD controls, albeit enriched in our cohort. The cohort was then screened for Category 3 variants, revealing 10 novel POI candidate genes in 8 women. These included genes with convincing animal gonadal insufficiency models (*PCIF1, DND1, MEF2A, TGFBR1*), DNA repair genes (*XRCC1, MMS22L*, *RXFP3*), mitochondrial genes (*PPAN, CLUH, COQ10B, MRPS14*), and others (*C4orf33, ARRB1*).

Discussion: Using a tiered evidence-based approach, we characterise genetic variants in POI-associated genes in, to our knowledge, the largest EO-POI cohort described. Our findings suggest that POI may often represent a multigenic disorder and that pathogenicity of single heterozygote

variants in POI-associated genes is uncertain. We also describe a higher proportion of women with autosomal recessively inherited, monogenic POI in EO-POI compared to previously reported in mixed POI cohorts. Lastly, we identify convincing novel candidate genes for POI.

OC 1.2
Increased Blood Pressure SDS and Oxidative Stress in Boys With Early Onset Hypogonadism

Angela K Lucas-Herald[1], Jane McNeilly[2], S Faisal Ahmed[1]

[1] Developmental Endocrinology Research Group, University of Glasgow, Glasgow, UK
[2] Department of Clinical Biochemistry, Royal Hospital for Children, Glasgow, UK

Introduction: Androgens are essential for normal vascular function. As such, early onset hypogonadism may be associated with an increased risk of accelerated vascular ageing and early vascular dysfunction.

Methods: Boys aged 12-18 years were recruited for vascular phenotyping including blood pressure (BP), pulse wave velocity (PWV), carotid artery intima media thickness (CIMT) and brachial artery flow mediated dilatation (FMD). Cases were boys with proximal hypospadias or genetically confirmed Klinefelter Syndrome (KS). Controls were healthy volunteers. Urine samples were tested for markers of oxidative stress, including 8-hydroxy-deguanosine (8OHdG) and Total Antioxidant Capacity. Where appropriate, standard deviation scores (SDS) were used for comparisons adjusting for sex, age and height. Comparisons between groups were via Mann-Whitney U tests.

Results: Twenty-two boys with conditions that may have been associated with a period of intra-uterine hypogonadism (hypospadias (n=11), Klinefelter Syndrome (n=11) (median age (range) 14.3 yrs (6.2, 16.9) and 11 healthy controls were recruited (median age 15.5 (6.8, 16.5)). There were no differences between the groups in terms of birthweight SDS, gestation at birth or presence of co-existing conditions. Systolic BP SDS was higher in boys with early onset hypogonadism (median (range) 1.25 *vs.* 0.5, p=0.01) compared to controls. There was no difference in SBP SDS between those with Klinefelter Syndrome and those with hypospadias (median (range) 1.0 *vs.* 1.5, p=0.6). CIMT SDS (1.75 *vs.* 0.0, p=0.02) and pulse pressure (34 *vs.* 30 mmHg, p=0.03) were increased in boys with early onset hypogonadism compared to controls but there were no differences in body mass index SDS, pulse wave velocity, FMD or mean arterial pressure. Boys with early onset hypogonadism had increased urinary 8OHdG (0.13 *vs.* 0.12, p=0.001) and total antioxidant capacity (356.8 vs. 272.6, p=0.004).

Conclusions: Adolescents with early onset hypogonadism have higher systolic BP SDS, CIMT SDS and pulse pressure, which may be secondary to oxidative stress. There is a need to consider regular monitoring and early intervention in boys with early onset hypogonadism for risk stratification to prevent the development of cardiovascular disease later in life.

OC 1.3

Health related quality of life in children, adolescents and young adults with differences of sex development (DSD) and their relatives after participating in a modular DSD-specific education programme *(Empower-DSD)*

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Background: Treatment in DSD requires informed decision-making of the individuals. There are no standardised information and training concepts for DSD in childhood available. Within the government-funded project Empower-DSD, modular structured two-day education programs for children and young adults aged 6-24 years diagnosed with CAH, Turner syndrome, Klinefelter syndrome or XX-/XY-DSD (including MRKH) and their relatives were developed, implemented and evaluated.

Methods: 105 trainings were offered between 08/2020 and 09/2022 in 5 German centres with DSD expertise. All participants answered questionnaires to evaluate health related quality of life (HRQoL) (WHO-5, KINDL), life-satisfaction (Cantril ladder), coping (CODI), satisfaction with the program (adapted ZUF-8), and self-constructed questionnaires for diagnosis-specific knowledge before (t0), immediately after (t1, only adapted ZUF-8), three (t2) and six months after the 2-day education programme (t3). Descriptive data analysis was conducted based on the ITT population for children (6-13 years), adolescents (14-17 years) as well as young adults (18-24 years) and relatives separately. Qualitative interviews were conducted with participants, peers and professionals.

Results: A total of 102 children, 95 adolescents, 56 young adults and 380 relatives took part. The overall completion rate of questionnaires was 96% at t0, 91% at t1, 73% at t2 and 60% at t3. Satisfaction with the program was high. The HRQoL score remained unchanged after 3 and 6 months (mean±SD) in children (t0: 74,3±9,9; t2: 73,4±10,1; t3: 73,6±9,0), adolescents (t0: 56,2±9,0; t2: 56,0±9,3; t3: 57,8±10,6), young adults (t0: 57,2±19,2; t2: 60,4±19,9; t3: 55,4±18,3) and relatives (t0: 59,2±19,1; t2: 61,3±20,0; t3: 61,62±19,8). However, life-satisfaction increased in adolescents and young adults, as well as diagnosis-specific knowledge in all groups. Qualitative analysis revealed the importance of time and space for discussing diagnosis-specific questions, thoughts and fears with other affected individuals.

Conclusion: Participation in the structured, age and diagnosis adapted training programme Empower-DSD did not improve HRQoL, but seems to increase life satisfaction in participants, most affecting adolescents and young adults. Contributing factors are the implementation of coping strategies, psychological support, peer counselling and gain of knowledge. Increased satisfaction and knowledge might potentially increase the individual ability for informed decision-making and therapy adherence already childhood.

OC 1.4
Turner Syndrome: Genomic Unity and Inflammation Across Karyotypes

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Background: Turner syndrome (TS) is associated with short stature, hypergonadotropic hypogonadism and metabolic conditions. Genome-wide changes in TS affect both transcriptome and methylome. Genomic studies have primarily focused on 45,X, but only 35-45% of the TS population has 45,X, while the remaining TS have other karyotypes.

Methods: We used 3 study cohorts. A "genomic cohort" of TS with 45,X karyotype (*TS 45,X*) (n = 32) and alternative karyotypic forms (*TS other karyotypes*) (n = 24), alongside age-matched *46,XX controls* (n = 33) and a "45,X; 46,XX; 46,XY; 47,XXY cohort". We analysed DNA methylation and gene expression profiles from blood and genetic and clinical similarities between groups. Leucocytes were studied with flow cytometry. The "Registry cohort" with routinely sampled biochemistry data from TS (n=135) and Klinefelter syndrome (KS)(n=139) from the outpatient clinic.

Results: We show a shared phenotype in the "genomic cohort" and an identical autosomal transcriptome and methylome between *TS 45,X* and *TS other karyotypes*, with shared expression profile for pseudoautosomal 1 (*PAR1*) and X/Y homologues on X, validated in the "45,X; 46,XX; 46,XY; 47,XXY cohort". Combining DNA methylation, gene expression and white blood cell counts, we observed higher neutrophil count ($p < 0.01$), and increased neutrophil activation among TS, with increased gene expression of neutrophil activation markers (myeloperoxidase, neutrophil elastase, *S100A8/9*, $p < 0.01$), suggested a pathological activation of neutrophils with concomitant release of pro-inflammatory mediators, and further validated the increase of neutrophils in TS in an independent cohort using flow cytometry ($p < 0.01$). In the Registry cohort we show consistently higher neutrophil count already present during childhood.

Conclusions: The X chromosomal p-arm, and perhaps in particular PAR1, appear to be a main driver influencing the genome-wide transcriptome and methylome in all TS. The presence of neutrophil-driven chronic inflammatory stress adds a new layer to the understanding of the

molecular pathophysiology associated with TS and creates new links to the TS phenotype. We suggest that chronic inflammatory stress to be a forerunner of metabolic syndrome, type 2 diabetes and hypertension, and could also be involved in the greatly increased risk of any autoimmune conditions in TS.

OC 1.5

Gonadectomy in individuals with Differences of Sex Development – A prospective I-DSD Registry Study

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Introduction: Gonadectomy may be indicated in people with differences of sex development (DSD), but variation in practice is reported. This study aims to determine, through prospective surveillance, the frequency of gonadectomy and associated care pathways in individuals with DSD internationally.

Methods: The study commenced in December 2022. Participating centres receive a monthly email asking whether a gonadectomy has been performed in an individual with DSD. Where individuals have provided consent for inclusion in the I-DSD Registry, a secondary survey captures additional clinical information.

Results: Of 208 centres invited, 74 have responded to monthly email surveys. Over the first 15 months of surveillance, gonadectomies were reported in 94 individuals from 36 centres across 21 countries and 6 continents (median [range]: 1[1, 5]). Secondary survey data are available for 42/94 (45%) cases to date. Thirty-three (79%) individuals are female; median (range) age at gonadectomy was 9.2 (2.1,20.0) years. All had specialist multidisciplinary team involvement before gonadectomy. Gonads were intra-abdominal in 34/42 (81%). Differences of gonadal development (18/42 [43%]) and Turner syndrome (10/42 [24%]) were the most frequent underlying DSD. Pre-gonadectomy investigations included: hormonal testing (40/42 [95%]), imaging (33/42 [79%] - US alone n=24; US + MRI n=7; MRI alone n=2), direct visualisation at laparoscopy (12/42 [29%]) and gonadal biopsy (4/42 [10%]). Bilateral gonadectomy was undertaken in 33/42 (79%). Mitigation of future malignancy risk in the context of gonadal insufficiency (27/42, [64%]) and hormone production incongruent with sex assigned (7/42 [17%]) were the most common primary indications for gonadectomy. Histopathology confirmed neoplastic change in 8 individuals (19%). Gonadectomy was intentionally deferred in 8/42 (19%) individuals, most commonly to allow their involvement in decision-making. Eighteen individuals (43%) were 12yrs or older at gonadectomy; all were involved in the pre-operative decision-making process.

Conclusions: This study offers important contemporary insights into the practice of gonadectomy in individuals with DSD internationally. Multidisciplinary care provision prior to gonadectomy is standard; however, management pathways vary, likely reflecting diversity of clinical presentations and lack of consensus regarding optimal approach. The I-DSD platform shows clear utility for performing prospective surveillance of rare procedures; such studies are essential for care quality improvement.

OC 1.6

"There was so much shame and embarrassment wrapped up in my decision making": The experience of making decisions for adolescents and young adults with differences of sex development

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Background/Aims: Adolescents and young adults (AYAs) with differences of sex development (DSD) face complex clinical management decisions. Chief among these are decisions regarding elective urogenital/gonadal surgeries. AYAs must balance the uncertain benefits and harms of a variety of treatment options for which high quality outcome data are scarce. Should ongoing legislative efforts to ban elective genital and gonadal surgery during infancy or childhood be successful, surgical decision making will increasingly fall to AYAs. Beyond surgery, there are other decisions facing youth with a DSD for which the responsibility to make the decision shifts from parents/caregivers (together with the child's healthcare provider) to the patient. Expectations that AYAs will make informed, values-sensitive decisions is predicated on our understanding of the specific decision-making needs and experiences of this population. This qualitative study aimed to examine the experiences of AYAs making important decisions about their DSD.

Methods: AYAs with DSD (n=20; mean age=16.0 years; range=11-24 years) from one US children's hospital were recruited to complete an hour-long interview focused on decision making related to their DSD. Interviews were recorded, transcribed, and emerging themes identified.

Results: Decisions discussed included gender identity, sexual health, surgical removal of the gonads, phalloplasty, method of delivery for hormone replacement therapy, puberty blockers, wearing a medical alert bracelet, obtaining peer support, and sharing information with family members, friends, or romantic partners. Factors impacting the decision-making process included internalized DSD-related stigma, concerns for enacted stigma if condition-specific information was shared with peers, wanting more support/guidance from parents/caregivers and healthcare providers, fear of surgery, and difficulty understanding medical information or decision options.

Conclusion: AYAs with DSD noted involvement in a range of decisions related to their condition and identified numerous challenges. Of particular concern is that fear of stigmatization can influence medical decision-making. The use of decision aids is one evidence-based approach to support decision making, but their effectiveness with AYAs is unclear. Future directions include developing interventions (i.e., decision aids) to address the decisional needs of AYAs with DSD.

OC 1.7

Long Term Outcomes In 21 Hydroxylase Deficiency Congenital Adrenal Hyperplasia: Patient Identification And Initial Results From A Single UK Centre

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Background: Long term outcomes in 21 Hydroxylase Deficiency Congenital Adrenal Hyperplasia (CAH) are lacking and subject to selection bias. This study aimed to develop a methodology for identifying historical CAH cases at a single centre and begin to characterise the cohort.

Methods: Serum 17-OHP requested by a Glasgow health care provider between 2014 - 2022 were analysed. Clinical records were reviewed of patients with 3 or more 17-OHP measurements, where at least one was ≥6nmoll. For confirmed CAH cases age, sex, age at diagnosis (≤16 or >16 years old), mortality status and most recent available blood pressure were collected. For all patients most recent height weight and blood pressure (BP) were also collected. Identified cases were cross-referenced against those where a genetic diagnosis had also been confirmed.

Results: Analysis included 8,253 17-OHP results ≥6 nmolL from 5,516 cases. Clinical records were reviewed for 176 cases, of which 105 were confirmed; all genetically diagnosed cases were identified in the biochemistry search. The CAH cohort age range was 2 to 75 years old with 102 being currently alive, with 85 (81%) >16 years old, 20 (19%) ≤16 years old. Maximum 17-OHP level for a given patient ranged from 7.3 nmolL to >151.6 nmolL. In adults, 36 (42%) were diagnosed at ≤16 years old. The overall CAH cohort were 70% female and 30% male (*n*=105). Adult patients (*n*=85) were 74% female while for adults diagnosed at ≤16 years old (*n*=44), 59% were female. Of those diagnosed in adulthood (*n*=36), only 1 was male. Adult patients had a median BMI of 27.99 (range, 15.05, 56.09, *n*=77). Median adult systolic/diastolic blood pressure was 120/80 (systolic 95, 153; diastolic 56, 101, *n*=82). In children, median weight SDS was 0.95 (-1.78, 3.42), height SDS was 0.71 (-1.80, 2.79), and BMI SDS was 0.75 (-2.26, 3.96) (*n*=20).

Conclusion: In summary, in collaboration with the diagnostic labs, a reliable method has been developed to identify cases of CAH. Preliminary analysis suggests that adults with CAH are normotensive but overweight. The identification of this large cohort of cases will facilitate more detailed analysis of long-term outcomes in CAH.

OC 2.1

Towards an experimental proof of oligogenicity explaining a severe 46,XY DSD phenotype associated with heterozygote *NR5A1*/SF-1 variation

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Background: Oligogenic inheritance has been suggested as explanation for the broad phenotype across individuals with a disorder of sex development (DSD). However, to test for the impact of specific gene variants involved in such a network on overall disease, remains difficult. We therefore studied a severely under virilized individual with an *NR5A1*/SF-1 [c.58G>C, p.Val20Leu] variant and its healthy carrier father.

Methods: We reanalysed the WES data of the index patient and its father by an in-house algorithm focussing on SF-1 and DSD-related genes to find candidate genes. Candidates were tested *in vitro* for functional impact on transcriptional regulation by wild-type (WT) or mutant *NR5A1*/SF-1 including promoter-Luc-reporter constructs of *INHA*, *GnRHR* and *AR*. The *AR* promoter was additionally tested for regulation by WT or mutant *NR1H2*/LXRβ. Experiments were all performed in NCI-H295R and/or HEK293T cells.

Results: Additional variants were found in *INHA* [c.675T>G, p.Ser225Arg], *NR1H2* [c.515_516insCAA, p.Arg171_Lys172insAsn], *TCF7L2* [c.1535C>G, p.Pro512Arg], *NIBAN1* [c.929G>A, p.Arg310His] and *SCUBE2* [c.692C>T, p.Thr231Ile] in the index patient, but not its father.
INHA and *NR1H2* genes have been previously associated with DSD. Two wild-type (WT) *INHA* reporter constructs were significantly activated by transfected WT or endogenous *NR5A1*/SF-1 in non-steroidogenic HEK293T or adrenal NCI-H295T cells, respectively. By contrast, mutant *NR5A1*/SF-1 revealed impaired activation on the WT *INHA* and a *GnRHR* promoter constructs in HEK293T cells. Regulation of the *AR* promoter seems more complex: while the *NR1H2*/LXRβ mutant showed decreased *AR* activation compared to WT, *NR5A1*/SF-1 WT and mutant behaved opposite way.

Conclusions: The exact role of *INHA* in human sex development is largely unknown although biallelic variants have been recently described in individuals with 46,XY DSD. Similarly, the role of *NR5A1*/SF-1 in the regulation of the *AR* is not established. Here, we show that *NR5A1*/SF-1 regulates *INHA* transcription and that this regulation is decreased by a *NR5A1*/SF-1 mutation. In

addition, a *NR1H2*/LXRβ variant activates the *AR* receptor less than WT. Our functional studies show that multiple genetic variants identified in a DSD patient may all contribute to the phenotype. Oligogenicity is therefore a real mechanism of DSD.

OC 2.2

Evaluation of quality of care for people with differences of sex development (DSD) – results of an annual benchmarking of DSD centres in Germany

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Background: International guidelines recommend specialised medical and psychosocial care for people with DSD by multidisciplinary teams at designated centres. The DSD Care project, funded by the German Federal Ministry of Health from 05/20-08/23, aimed to evaluate and improve care for children, adolescents and adults with DSD in 10 centres in Germany.

Methods: Structural quality of care was assessed through annual surveys in the participating centres, starting in 2019 before the beginning of the project. Indicators were scored as "met"/ "unmet" and summed up to a final score. Process and outcome quality were assessed from a newly developed patient registry and standardised patient questionnaires on satisfaction with treatment, quality of life (qol), acceptance of one's own body, and transition competence (age 13-21). The percentage of people who received certain services or were extremely/ very satisfied with care and the deviation from the median were presented for all centres. Results of qol questionnaires were scored and compared with the standard population. All results were summarised in annual benchmarking reports for all participating centres.

Results: From 05/21-12/23, 624 children, adolescents and adults with DSD were enrolled into the registry. Questionnaires were returned by 63% of the participants or their guardians.
From 2019 to 2023 an improvement in structural quality was observed in all centres due to the implementation of standards developed in the project. While almost all centres offered psychological, peer and fertility counselling and participated in external registries, only four centres had implemented a structured transition programme by the end of the project, and two others had transition clinics. There was room for improvement in the transition competence of young adolescents. Satisfaction with treatment was generally high. Specific items such as satisfaction with the team dealing with feelings at the time of diagnosis or information about medication showed lower scores. With the exception of physical health, scores of qol questionnaires showed similar results to those in the general population.

Conclusion: Initial results of a national benchmarking exercise suggest that implementation of guideline recommendations improves care for people with DSD. At the same time, participating centres can identify specific aspects of care that can be improved.

OC 2.3

Family Planning and Preimplantation Testing: family experiences in Congenital Adrenal Hyperplasia

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Background/Aims: Pre-implantation testing (PGT) is often suggested by healthcare professionals (HCP) to parents of children with congenital adrenal hyperplasia (CAH) considering subsequent children. Despite this, some families choose to conceive naturally without genetic intervention. Our aims were to document fertility choices of families and explore parents' perceptions and their reasoning behind these choices.

Methods: All parents of current children of our service in 2020 with 21-hydroxylase deficient CAH who had made an active decision regarding family planning after the diagnosis of an index child were invited to participate in a semi-structured interview. Thematic analysis was performed using an inductive, semantic approach.

Results: Thirty families (34 children) were identified. Fourteen had considered subsequent children and offered directed genetic counselling. Eight made an active decision to have subsequent children, 7 agreed to interview.
Thematic analysis identified six key domains. Psychological impact surrounding index child's diagnosis was long-lasting, causing symptoms of trauma such as depression and anxiety. This often influenced a family's choice to pursue PGT to avoid having another affected child.
The perception of the index child having a mild phenotype (regardless of actual severity), and fear of a worse phenotype, often supported this decision. Conversely, lived experience of CAH and low day-to-day impact shifted the balance towards choosing natural conception. Negative experience with unsuccessful PGT, and a greater financial, physical and emotional toll than expected also led some families to consider natural conception.
The role of the healthcare professional (HCP) was important in both CAH and family planning journey. A perceived poor understanding of CAH, overstating its potential life-threatening nature, contributed to trauma. Parents reported feeling judged and/or pressured to undergo PGT and the HCP did not understand/support their decision to conceive naturally. Peer-support had an almost universally positive impact with fertility choices and managing CAH.

Conclusions: This study highlights the complex and dynamic nature of fertility decision making often influenced by the journey itself, and the importance of HCP empathy and withholding judgment. Education of non-specialist HCP may help reduce the trauma of the CAH journey for families. Encouraging peer-support may help families come to terms with the CAH diagnosis.

OC 2.4

A conserved NR5A1-responsive enhancer regulates *SRY* in human testis-determination: A new cause of 46,XY DSD

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Background: The Y-linked *SRY* gene initiates mammalian testis-determination. However, the mechanism for regulation of the expression of *SRY* remains elusive. We hypothesized that the variants involving regulatory elements in testis-determining genes, such as *SRY,* may be a cause 46,XY gonadal dysgenesis. Here, using a combination of evolutionary computational analysis, human genomics, and *in vitro* assays we define a SF-1/NR5A1-binding motif that when mutated causes 46,XY DSD.

Methods: Comparative sequence analysis was used to defined conserved potential regulatory elements in 83 mammalian species at the *SRY* locus. Genomic sequencing and targeted Sanger sequencing of 46,XY DSD cases was used to identify genomic variants in candidate regulatory elements. Pathogenicity was demonstrated using a combination of *in silico* computational analysis, *in vitro* functional analysis and our novel *in vitro* 3D organoid model, where human induced Pluripotent Stem Cells (hiPSCs) are induced to form Sertoli-like cells capable of forming tubular structures (Science Advances 2023 PMID 36598988).

Results: Comparative sequence analysis of regions 5' to *SRY* in mammals identified a conserved SF-1/NR5A1-binding motif within a 250 bp region (E250) of open chromatin located 5 kilobases upstream of the *SRY* transcription start site. Genomic analysis of 46,XY individuals with DSD, including a large six generation family with multiple cases of unexplained 46,XY DSD, identified unique single-base substitutions of highly conserved residues within the SF-1/NR5A1-binding element. *In silico* modelling and *in vitro* assays demonstrate enhancer properties of the E250 motif. Deletion of this hemizygous element by genome-editing resulted in a significant reduction in expression of *SRY* in our novel *in vitro* cellular model recapitulating human Sertoli cell formation.

Conclusions: NR5A1 acts as a regulatory switch between testis and ovary development by upregulating *SRY* expression. We show that disruption of an enhancer can phenocopy variants in the coding regions of *SRY* that cause human testis dysgenesis. Since disease causing variants in enhancers are currently rare, the regulation of gene expression in testis-determination offers a paradigm to define enhancer activity in a key developmental process. Many cases of 46,XY DSD are currently unexplained despite large scale exome sequencing approaches. Many of these unsolved cases may be due to discrete pathogenic variants in gene regulatory elements such as the NR5A1-binding motif in enhancer of *SRY*.

OC 2.5

SGPL1 deficiency, a cause of 46XY DSD and adrenal insufficiency, impairs lipid metabolism and steroidogenesis in Leydig cells

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Background: Loss of function mutations in *SGPL1* (sphingosine-1-phosphate lyase) give rise to a multisystemic syndrome with predominating features of primary adrenal insufficiency (PAI) and steroid resistant nephrotic syndrome. Furthermore, primary gonadal insufficiency is present in a third of male patients, all of whom had concomitant adrenal insufficiency and died in infancy. Pubertal delay is yet to be reported in surviving male patients. SGPL1 carries out irreversible breakdown of sphingosine-1-phosphate (S1P) and deficiency leads to accumulation of S1P and upstream sphingolipid intermediates, that are bioactive signalling molecules with roles in various cellular processes.

Methods: To study the impact of SGPL1 deficiency on gonadal steroidogenesis we generated CRISPR-engineered knock-out (KO) of *Sgpl1* in the MA10 immortalised Leydig cell line, on which we conducted steroid profiling and RNA sequencing.

Results: In response to forskolin stimulation, KO cell lines produced significantly reduced levels of progesterone when compared to wild type (WT). This was associated with decreased steroidogenic enzyme STAR and CYP11A1 protein expression. In addition, transcriptomic analysis highlighted dysregulation of genes involved in cholesterol and glutathione metabolism, with a reduction of protein expression in enzymes involved in these pathways in SGPL1 deficient cells,

providing further insight into possible underlying mechanisms of disease and the role SGPL1 plays in steroid biosynthesis.

Conclusion: Given current findings, SGPL1 deficiency should be considered in the differential diagnosis of 46XY infants with DSD and PAI. SGPL1 deficiency impairs lipid metabolism, cellular antioxidant and detoxification processes and ultimately steroidogenesis in Leydig cells and clinicians need to consider evolving gonadal disease in affected patients.

OC 2.6

Validation Of A New Short Parent Reported Outcomes (PRO) Questionnaire For Boys With A Condition Associated With A Difference or Disorder of Sex Development (DSD) – PRO-DSD Short

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Background: To aid routine assessment of parent reported quality of life outcomes (PRO) in young children with DSD, a short questionnaire (PRO-DSD Short) that includes a parent-proxy report (PPR) and a parent-self-report measure (PSR) have been recently developed and require further validation.

Methods: Parents of 98 boys with a median age of 2.9 yrs (range, 0.2,6.5) and a median external masculinisation score (EMS) of 11 (4,12) were recruited. Group-construct validity factors included surgical status, age, an integrated measure of multiple deprivation in Scotland (SIMD), EMS, reporting parent (mother vs father) and parental education. All comparisons were adjusted for multiple comparisons. In a subset of 41 parents, test/re-test validity was also assessed by calculating intra-class coefficients (ICC).

Results: On the PSR measure, the parents of boys with a lower EMS were more concerned about the appearance of their child's genitalia compared to those with a score above 10.5 ($p= 0.01$). A relationship with EMS was also observed in the questions that related to future social concerns ($p<0.01$), future relationships ($p<0.01$) and stress on receiving the diagnosis ($p=0.03$). A lower proportion of parents who had completed tertiary education 14/56 (25%) reported feeling stress fitting their child's condition into the usual routines and 4/56 (7%) reported that the condition affected how often they go out socially compared to the non-tertiary educated parents, with 20/42 (48%), $p=0.03$ and 11/42 (26%), $p=0.02$, respectively. Amongst parents of boys below 2 yrs old, 11/33 (33%) reported feeling stressed managing the child's behaviour during the clinic visit compared to 43/65 (66%) parents of boys older than 2 yrs ($p<0.01$). In the group comparison according to SIMD, surgery and reporting parent, no statistically significant differences were noted. No statistically significant differences were observed on the PPR measure. The median

(range) ICC for all 28 questions was 0.7 (0.4, 0.9) with only one question in the domain of 'gender concerns' having an ICC below 0.5.

Conclusion: The current validation study of the PRO-DSD-Short questionnaire shows that it may be a useful tool to detect DSD specific health-related quality of life outcomes in parents of young boys with DSD.

OC 2.7
Long-read sequencing resolves *CYP21A2* alleles in Congenital Adrenal Hyperplasia

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Background/Aims: We evaluated utility of long-read sequencing (LRS) and optical genome mapping (OGM) in regions of the genome of critical importance for Differences of Sex Development (DSD) conditions. *CYP21A2*, the gene associated with Congenital Adrenal Hyperplasia (CAH), sits in the middle of the segmentally duplicated RCCX module. Modules include either *CYP21A2* or its pseudogene *CYP21A1P*, and because of high homology, short-read sequencing is insufficient for full resolution of the region.

Methods: High-molecular-weight DNA extracted from blood of participants in the DSD-Translational Research Network (DSD-TRN) was subjected to OGM (Bionano platform) and/or LRS using average parameters to mimic likely clinical testing conditions. LRS was performed on both the ONT Nanopore platform and the PacBio Revio instrument.

Results: With limited numbers of fluorescent markers in the region, OGM was not able to resolve the gene/pseudogene conversions and deletions responsible for most pathogenic alleles in CAH. Analysis of the HiFi sequence for 6 samples using PacBio's Paraphase tool, designed to resolve regions with clinically relevant segmental duplications, accurately identified all the alleles, including *CYP21A1/CYP21A2* fusions (aka the 30 kb deletion), single nucleotide variants in the active gene, trimodular alleles with two pseudogenes and one mutated *CYP21A2*, or monomodular alleles with deletion of the entire active gene.
On the Nanopore dataset, reads of average of 24 kb were often too short to span the entire region. We developed a tool, ParaKit, using three different approaches to confidently call the various variants: read coverage, fraction of reads supporting variants between copies, and putative junctions from long reads. We used the existing alleles in the Pangenome dataset (HPRC) to create an enriched local pangenome specifically for this region. This also allowed accurate calling of all alleles in the 6 samples.

Conclusion: Both LRS technologies were able to identify the various complex alleles in the *CYP21A2* region. Thus LRS could replace the current cumbersome clinical test (which requires 4 long-range PCRs, bidirectional Sanger sequencing, and MLPA) for CAH. The Paraphase tool is available to call the various alleles in PacBio HiFi datasets. Taking advantage of Pangenome data, we developed ParaKit to do the same in Nanopore datasets.

OC 2.8

High throughput screening of VSD candidate genes with the help of powerful model *Drosophila melanogaster*

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Background: Drosophila melanogaster has significantly contributed to understanding the mechanisms of many human diseases, yet it has been underutilized as a model for human sex development. Nanda et al. (2009) demonstrated the essential role of Sox100B, the Drosophila orthologue of SOX9, in testis development. Similarly, we found that cv-c, the fly homolog of STARD8, implicated in sex reversal in two 46 XY sisters, shares similar location and function with its mammalian counterpart. Mutant cv-c male flies exhibited defects in embryonic gonad and germ cell formation, suggesting conserved molecular mechanisms in gonad development across phyla. Establishing the fruit fly as a new alternative model offers insights into the general consequences of mutations identified by Whole Exome Sequencing (WES) in individuals with Disorders of Sex Development (DSD).

Methods: Employing the Gal4-UAS system, we conducted high-throughput screening for novel VSD-causing genes. Initially, we predicted human orthologues of fly sterility genes, excluding known VSD genes. Filtering for orthologs with a "high" ranking and reproductive tissue expression yielded 443 genes for knockdown in fly germ cells or somatic gonadal tissue. Subsequently, we evaluated fertility after 10 days and examined variants within candidate genes in an international VSD cohort.

Results: The initial screening identified 42 UAS X Gal4 crossings resulting in infertility. Subsequent analysis with the patient cohort revealed 20 patients harbouring a variant in one of the genes associated with sterility.

Conclusion: Further evaluation of the consequences on sex development will provide insights into the roles of these genes in sex determination and differentiation. The establishment of these fly strains as models offers opportunities to study sex development mechanisms comprehensively and understand defects associated with further evaluation of the consequences on sex development will provide insights into the roles of these genes in sex determination and differentiation. The establishment of these fly strains as models offers opportunities to study sex development mechanisms comprehensively and understand defects associated with VSD.

PO 1

Certified online course covering Differences of Sex Development (DSD) – an example for digital transfer of knowledge

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Background: International guidelines recommend holistic care for DSD in specialized centres with multidisciplinary teams. Outside of these centres people with DSD risk to encounter uncertainty or ignorance even of medical staff. Training offers and availability are limited. In order to disseminate knowledge of DSD conditions, a certified online course has been developed within the Project "DSDCare" sponsored by the German Ministry of Health.

Methods: An interdisciplinary curriculum was defined for external health care providers. Experts of different medical centres and disciplines (endocrinology, surgery, gynaecology, urology, andrology, psychology) as well as patient representatives created short educational videos. A comprehensive internal review process ensured harmonisation of attitude and language. The videos were both produced in a professional studio and locally with innovative technical support. Patient representatives were actively enrolled in curriculum development, video production and internal review process.

Results: Voices of people with DSD mark the start of the 7 ½-hour self-study course, continuing with the presentation of basic principles of sex development and a description of DSD conditions. Eight case reports illustrate diagnostic investigations. The subject "management" includes surgical interventions, hormone replacement therapy, and patient support. Finally, the role of psychosocial support and relevant aspects of communication with patients and relatives are explained. The videos are complemented by interactive tasks. Participants have up to six months to complete the course. Completion of the course including a short exam will result in accreditation of 20 CME points by the German medical association. Additionally, the course is accessible for health care professionals, psychosocial professionals and teachers.

Conclusion: A certified online course covering rare conditions is a low-threshold service for medical staff outside centres of expertise. Utilisation and influence on care have to be evaluated in the future. Implementation of a course requires human, technical and financial resources that are only available in the framework of a research project. Means of accreditation by the Austrian and Swiss medical association are currently considered.

PO 2

Case report: Gender fluidity and a complicated social background in an adolescent with PAIS

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Background: In September 2023 a 15 y/o adolescent presented themself to our DSD clinic. They were born with ambiguous genitalia and raised in Ukraine as male and had surgical corrections of perineal hypospadias, micropenis, bipartite scrotum and undescended testes. During puberty no virilization but instead bilateral gynecomastia was observed. Masculinizing surgeries were recommended by Ukrainian surgeons without knowledge of genetic diagnosis and without psychological evaluation of gender. At age 14, a bilateral mastectomy was performed and later, genetic testing followed. Results showed a hemizygous AR-mutation (c.2515C>A in exon 7) compatible with PAIS. The patient came to Germany as war refugee few months prior to first presentation.

Methods: The patient was evaluated clinically (including laboratory analysis) and psychologically shortly after first presentation. Psychological counselling is currently ongoing.

Results: Clinically, the patient had hypertrophic scars from their mastectomy, a penoscrotal fistula without functional impairment and labio-scrotal hypersensitivity. Phallus size corresponded to clitoromegaly/micropenis. They had absence of male-pattern body hair and reduced pubic and axillary hair. Their voice was high-pitched compared to typical male range. Laboratory results were typical for AIS (T>15µg/l, E2 66ng/l, LH 30.9IU/l). They showed signs of conflict about their gender identity and were now asking for a surgical transition to female.
They presented androgynous in their outward appearance and reported to try out more feminine expressions recently while feeling comfortable among friends. However, they felt rejected due to their androgynous nature in neighbourhood and school. In addition, the patient felt conflicted due to the forced relocation, a difficult family situation, the war in their home country and linguistic/cultural differences. They wished to understand their physical variation. The patient did not express regret concerning surgeries during evaluation.

Conclusion: The adolescent is showing a fluid gender identity and needs time for further exploration. We, therefore, initiated psychological counselling and recommended support groups. Androgynous phenotypes and a high variability in gender identity are typical for PAIS. The prior surgeries performed without consent, psychological evaluation or genetic diagnosis will likely present a challenge for the future. This demonstrates the importance of exact diagnosis before performing irreversible interventions prior to the age of consent.

PO 3

Case report: 46,XY DSD with partial gonadal dysgenesis and a frameshift mutation in *MAMLD1*

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Background: The patient (currently 22 years old) was born with ambiguous genitalia. His phenotype included perineal hypospadias, micropenis, bilateral undescended testes and bipartite scrotum. Karyotype was 46,XY. Bilateral orchidopexy, hypospadias repair and urethral reconstruction were performed. Left gonadal biopsy showed testicular tissue. A rudimentary vagina and uterus were initially present. Genetic testing did not reveal abnormalities in several genes including AR. During puberty the patient showed gynecomastia and reduced virilization with normal levels of testosterone typical for AIS. Reduced testicular volume, low inhibin B levels, testicular microlithiasis and persistent Müllerian duct structures, however, were more typical for partial gonadal dysgenesis. To understand the specific pathophysiology, we aimed to perform functional testing on androgen receptor action and further evaluate genetic causes by Whole-Exome-Sequencing.

Methods: Genital fibroblasts (GFs) from scrotal biopsy were cultured and APOD-induction assays were performed using DHT at UKSH in Kiel, Germany. Whole-Exome-Sequencing was performed using the Agilent sureselect V6_r2 kit. For data analysis Varbank Programm of the Cologne Center for Genomics was used.

Results: Patient derived GFs showed normal androgen receptor expression and -activity. Whole-Exome-Sequencing revealed a hemizygous frameshift variant in the *MAMLD-1* gene (c.1502dup; p.Gln502Alafs*7, not previously reported). His mother was heterozygous for the variant. No other familial cases are known. *MAMLD-1* is associated with Leydig cell differentiation and androgen production. Reported phenotypes range from hypospadias to female genitalia including gonadal dysgenesis [Miyado et al, 2022]. Müllerian duct derivatives are, however, rare. Patients often develop deteriorating testicular function and microlithiasis. Oligogenicity is discussed as an etiological factor. Our patient later spontaneously developed more masculine characteristics and his gynecomastia regressed partially. Sertoli cell function, however, decreased over time and both LH and FSH became elevated. PAIS can be ruled out in vitro and clinically.

Conclusion: It remains unclear how exactly the here described MAMLD-1-variant influences the complex phenotype of our patient. Yet, in the absence of other variants we conclude it to be the major cause of XY-DSD and gonadal dysgenesis in this case.

References:

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PO 4

The process of self-reflection and transformation – gender transition in an individual with 5α-reductase deficiency: a follow-up over 13 years

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Background: Reporting a 13-year follow-up of a child with 5α-reductase-2 deficiency (5α-RD-2), we address the challenges of gender identity, sex reassignment, and the significance of psychosocial care. 5α-RD-2 is a rare autosomal recessive 46,XY difference of sexual development (DSD), presenting a spectrum from male phenotype with hypospadias to female phenotype with wolffian structures. Though frequently raised as girls, individuals are likely to virilize during puberty. Gender identity and assignment are complex in DSD, especially in 5α-RD-2 due to multifactorial influences.

Methods: 5α-reductase deficiency was confirmed at the age of 1 year by high T/DHT ratio (29.5), absence of visible uterus on ultrasound and laparoscopy, 46,XY-Karyotype, and homozygous mutation in *SRD5A2* exon 1 (c.176C>G). Non-consanguine parents were heterozygous carriers. Gonads were relocated to the labioscrotal region for sonographic monitoring, showing no abnormalities. Female sex of rearing was maintained by the parents after diagnosis due to mainly typically female genitalia.

Results: Psychosocial care was initially infrequent but intensified, particularly in prepubertal stages. Monthly an individual psychological assessment, including peer counselling and self-help group interaction, focused on identity, understanding of the condition and coping with the diagnosis burden. Blocking puberty with GnRH-analogues provided a timeframe for gender identity reflection. Triptorelin 3.75 mg i.m./28 days was administered at age 11 due to rising gonadotropins and testosterone. A transition from female to male identity occurred, evaluated with self-assessment scales. This also shows that the patient effectively used the period of puberty-blocking for the decision process and eventually decided to stop GnRH-analogues at 13 8/12 years, allowing biologically male puberty to proceed. So far, this resulted in an increase of the gonadal volume corresponding to Tanner G2 after 5 months.

Conclusion: Individuals with 5α-RD-2 may be raised as girls but often develop male gender identity after puberty, prompting a gender role change. Deciding on irreversible therapy strategies for prepubertal children and their parents poses challenges. Our experience highlights the importance of patient involvement, peer-counselling, and self-help-group interactions. Integrated psychosocial care should address diagnosis coping, body acceptance, identity, psychosocial health, sexuality, and fertility. In conclusion, personalized care, with focus on psychosocial support, is crucial for those with DSD like 5α-RD-2.

PO 5

Two interesting cases of congenital adrenal hyperplasia with dual genetic association- Duchenne muscular dystrophy and distal myopathy-4

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Background: Congenial adrenal hyperplasia (CAH) is a rare autosomal recessive disorder of the adrenal cortex caused by deficiency of steroidogenic enzymes. Dual genetic disorders present with pathogenic variants at two distinctly segregated loci and would be disease-causing when occurring in isolation. Although contiguous gene deletion syndrome has been reported the exact incidence of dual genetic disorder with CAH is not known. Here we report two cases with novel dual genetic mutations associated with CAH that presented to a tertiary referral hospital in South India.

Case reports: Case 1- A 1 year 10 month old boy, born to second degree consanguineous parents, with uneventful perinatal period, presented with one episode of generalized tonic-clonic seizure. He had genital hyperpigmentation and post axial polydactyly. He was hypertensive and his Tanner stage was 2. Biochemical analysis showed hypokalaemia, low cortisol(0.697mcg/dl), increased adrenocorticotropic hormone(1167pg/ml), increased basal 17-hydroxyprogesterone(9.86ng/ml) with an advanced bone age(4.2years). Genetic analysis revealed homozygous deletion in exon 2 of CYP11B1 gene and hemizygous deletion of exon 45 to 51 in the dystrophin gene. Further evaluation for Duchenne muscular dystrophy (DMD) showed mildly elevated creatinine phosphokinase. 2D Echocardiography showed concentric left ventricular hypertrophy. He was managed with oral hydrocortisone and antihypertensives. Oral prednisolone was added in view of advancing bone age in spite of higher dose of hydrocortisone. Case 2 - An 8 month old girl, born to second degree consanguineous parents, with atypical genitalia and salt losing crisis at birth for which she was on medications, was noticed to have increased flexibility of joints. Connective tissue disorder was suspected and genetics revealed homozygous mutation in CYP21A2 gene and heterozygous mutation in exon 40 of FLNC gene causing distal myopathy-4. She was managed with oral hydrocortisone and fludrocortisone.

Conclusions: The possibility of being affected by two rare inherited genetic conditions needs to be suspected when signs and symptoms are incoherent with the primary diagnosis. Identifying the unique associations led to better management in terms of monitoring the features of DMD and myopathy in both patients. This further helped us in better genetic counselling, prognosis and long –term follow-up.

PO 6

Sexual health in adult women with complete androgen insensivity syndrome: a single centre experience

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Background: Reduced sexual satisfaction is reported in complete androgen insensitivity syndrome (CAIS), yet in small and heterogeneous cohorts. We aimed to assess sexual health and body uneasiness in CAIS through validated questionnaires.

Methods: single-center, cross-sectional study on 34 adult CAIS patients (age 34±8.6 years), 29 with gonadectomy at mean age of 12.2±8.8 years and 5 with intact gonads. All gonadectomized patients but 3 were receiving hormonal replacement therapy (HRT) (14 transdermal estradiol, 10 oral estradiol, 2 testosterone). We measured hormonal levels (testosterone, estradiol, FSH, LH) and adherence to HRT through self-reporting, resulting intermittent in 5 subjects. Sexual function and body uneasiness were evaluated through: Female Sexual Function Index (FSFI; not applicable if sexually inactive) Female Sexual Distress Scale-Revised (FSDS-R) and Body Uneasiness Test (BUT) questionnaires.

Results: FSFI was applicable to 22 patients and 17 (77%) reported sexual dysfunction (FSFI score<26.55). At FSDS-R scale, 18/34 women (52.9%) resulted to have a hypoactive sexual desire disorder (HSDD; score>11). Finally, 17/34 patients (50%) reported body uneasiness with a BUT-Global Severity Index (GSI) >1.2 When focusing on the subgroup with intact gonads, body uneasiness and sexual distress remained very high, with 4/5 patients reporting a pathological score at FSFI and GSI-BUT, and 2/5 also at FSDS-R scale. In gonadectomized patients, no significant differences among different HRT regimes and questionnaires' results were registered. Among the two patients with testosterone therapy, one had normal scores. Despite receiving standard HRT-dose and mostly referring optimal compliance, most patients (69%) still had suboptimal serum oestradiol concentration (<50 ng/L). A trend between oestradiol levels and better sexual function was observed, although it did not reach statistical significance. Overall, vaginal hypoplasia was present in 10/34 patients (29%) but only 9 accepted vaginal dilation treatment. No correlation between vaginal dilation treatment and sexual scores was found.

Conclusion: Sexual dysfunction, HSDD and body uneasiness are worryingly common in adults with CAIS. Preservation of gonads and standard-dose HRT does not guarantee adequate sexual function nor optimal hormone levels. Psychological and sexual aspects must be taken into consideration in the management and therapeutic choices for these patients, as they highly impact quality of life.

PO 7

Evaluation of outcomes for Multidisciplinary team (MDT) clinics for Differences in Sex Development (DSD)

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Background: Differences in Sex Development (DSD) is a complex condition, presenting the patient, their caregivers and health care professionals with important but difficult decisions about multiple aspects of their well-being. In Manchester, we have established patient-centred DSD MDT clinics to enable to such decisions to be made jointly, efficiently and in a timely manner. We have aimed to report outcomes-based clinical utility of these clinics.

Methods: Structured proformas from the DSD MDT clinics from 2019 to 2023 were reviewed retrospectively to evaluate the consensus process in achieving definitive diagnosis, gender, gonad preservation/removal and reconstructive genital surgery.

Results: In total, 64 patients attended 95 in-person visits for the DSD MDT clinics from 2019 to 2023. Median (range) age at clinical presentation and first clinical attendance was 1 day (1 day to 16.7 years) and 5.0 (0.1 to 17.9) years respectively. Of the 64 patients, 34 (53%) had 46,XY DSD, 25 (39%) had 46,XX DSD and 5 (8%) had other complex/combination karyotypes.
A definitive genetic diagnosis was achieved in 39 (60%) patients, the commonest being 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) 21 (33%), androgen insensitivity 16 (25%) and 5 alpha reductase deficiency 8 (13%).
Of the patients who had gender assigned before the clinic (22 male, 42 female), gender was reassigned female to male in 3 patients (25 male, 39 female). In 23 patients with XY gonadal dysgenesis, gonads were preserved in 14 and resected in 9 patients owing to risk of malignancy. In 14 patients with androgen insensitivity, gonads were preserved in 8 and resected in 6.
Reconstructive genital surgery was discussed in 57 patients, with 27 having had previous genital surgery. During the period of the DSD MDT, additional genital surgery was recommended in 17 (30%) patients with the majority being under age 3 years (59%).

Conclusion: Discussions among professionals, patients and caregivers in DSD MDT clinics contributed to a common understanding and shared decision-making guiding consensus in achieving diagnosis, gender assignment, and gonad preservation/resection.

PO 8

Reproductive and Sexual Health Concerns in Adolescents and Young Adults with Complete Androgen Insensitivity Syndrome

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Background: Patients with complete androgen insensitivity syndrome (CAIS) have been reported to have increased mental distress, feelings of inadequacy, and fear of sexual contact. They may experience dyspareunia and penetration challenges due to their decreased vaginal length. Gonadectomy, regardless of hormone replacement (HRT), may also decrease sexual experience. CAIS is commonly diagnosed in the teenage years by pediatric and adolescent gynaecologists (PAG) during the work-up for primary amenorrhea, however, studies on sexual health are lacking and focus mainly on adults. Since sexual and reproductive health assessment and counselling is part of the standard PAG visit, we sought to evaluate these concerns in adolescents and young adults (AYA) with CAIS.

Methods: Patients over 10 years old with the ICD-10 diagnosis of CAIS between 2008-2024 were collected from a single children's institution. Electronic medical records were reviewed for presentation at diagnosis, gonadal management, use hormone replacement (HRT), vaginal length/dilation, sexual experience, and mental health concerns.

Results: 30 patient met inclusion criteria. PAG saw 24 (80%) patients and 14 (46.7%) were diagnosed with CAIS during work-up for primary amenorrhea. 11 (36.7%) patients had gonadectomies; HRT was administered via oral estrogen (36.4%), transdermal estrogen (27.3%), and the vaginal ring (9.1%). One non-binary patient chose testosterone HRT. Vaginal length was not assessed in 17 (56.7%) patients. When documented, vaginal length ranged from 3.5 to 10cm with an average of 5.73cm. 4 (13.3%) patients initiated vaginal dilation. 14 (46.7%) were sexually active; all were sexually active with men and 3 (21.4%) expressed sexual dysfunction including anorgasmia, dyspareunia, and penetration challenges. Psychology was involved in half the cohort's care and addressed adjusting to the CAIS diagnosis, anxiety, depression, gender identity, anorexia, and alcohol abuse.

Conclusion: AYA with CAIS have varying psychosocial and medical needs. Our cohort echoes adult studies demonstrating concerns of sexual dysfunction, which are important to address early as to not affect their adult quality of life. Obtaining a baseline assessment of vaginal length can help provide anticipatory guidance about need for vaginal dilation. Fostering an open discussion about sexual experience and perspectives, perhaps by utilizing a clinical psychologist, can also facilitate comprehensive patient care.

PO 9

Prevalence of Raised Blood Pressure in Individuals With 46,XY DSD: an I-DSD Registry study

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Introduction: Males with XY Differences of Sex Development (DSD) may have an increased risk of high blood pressure and accelerated vascular ageing. It is not clear which individuals are most at risk of this.

Methods: Data were obtained from centres using the International Disorders of Sex Development (I-DSD) Registry on boys and men with 46,XY DSD. Blood pressure (BP) readings were requested as well as information on risk factors for hypertension (birthweight, obesity, family history, associated malformations) as well as ongoing management of any high BP readings.

Results: In total BP readings from 208 individuals with 46,XY DSD were available from 22 centres worldwide. Of these, the median (range) age at the time of the BP reading was 13 years (1, 54). In total 97 (47%) had a non-specific XY DSD; 37 (18%) had a disorder of gonadal development; 34 (16%) had a disorder of androgen synthesis; 23 (11%) had a disorder of androgen action; 14 (7%) had hypogonadotrophic hypogonadism; and 3 (1%) had a disorder of Müllerian development. There were 77 (37%) cases ≥16 years of age, of whom 7 (10%) were classified as hypertensive. Of the 131 (63%) individuals <16 years of age, 25 (19%) had a BP > 95th centile for age and height. Of the 25 children with a raised BP, 6 (24%) had a BP >99.8th centile and 19 (76%) had a BP >98th centile. There were no differences in BP SDS at the time of the study according to gestation at birth, birthweight, type of underlying condition or presence of a co-existing anomaly. However, BP SDS was significantly associated with age. Of the 32 with hypertension, 3 (9%) were treated with antihypertensives; 2 (6%) had an echocardiogram and none (0%) were reported to have had ambulatory blood pressure monitoring.

Conclusions: Up to 20% of young people with XY DSD may have a BP in the hypertensive range during childhood compared to approximately 5% reported global prevalence in children. Management of these individuals requires adherence to international guidelines to prevent future cardiovascular damage. More research into the underlying cause of this phenomenon is required.

PO 10

A systematic review of core reported outcomes in studies of boys and men with Klinefelter syndrome

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Background: Klinefelter syndrome (XXY) can have a wide range of presentations, health consequences and outcomes. The aim of this systematic review was to identify the relevant core outcomes in males with XXY.

Methods: Systematic literature searches of PubMed, Science Direct, and Cochrane were performed by 2 independent reviewers to source studies published in the English language up until October 2023. The following key terms were searched: Klinefelter syndrome OR Klinefelter's syndrome OR 47, XXY OR Klinefelter OR Klinefelter's. The inclusion criteria were studies involving KS males with any intervention, comparison, or outcome, with separate searches for studies reporting on children <16 years of age and for adults ≥ years of age.

Results: For children <16 years of age, 43 studies met the eligibility criteria. Behavioural, cognitive developmental and psychiatric outcomes were reported in the majority (25, 58%) followed by biochemical results in 16 (37%) studies. Of these, the most common were serum testosterone (12, 75%) and FSH (12, 75%). Sixteen (37%) studies reported anthropometric measurements, most commonly penile length (9, 56%). Other outcomes included fertility outcomes (4, 9%) side effects to testosterone treatment (4, 9%), bone health (2, 5%) and neonatal outcomes (1, 2%). In the studies focusing on individuals ≥16 years of age, 182 studies met the eligibility criteria. Outcomes

were inconsistently reported and only 7 were reported in >25% of studies. The biochemical parameters testosterone, FSH, LH and oestradiol were reported in 62%, 52%, 49% and 28% of studies respectively. Outcomes relating to fertility, occurrence of co-morbidities, and testicular size were reported in 36%, 33% and 29% of studies respectively. Quality of life was reported least frequently in 2% of adult studies.

Conclusions: Klinefelter syndrome has a wide range of presentations and health outcomes. As well as demonstrating an imbalance in the number of research studies in children compared to adults, the present study highlights the variety of outcomes studied in boys and men with KS. These results can support the development of age-specific core outcome sets for clinical research to promote homogeneity and to aid standardised data collection.

PO 11

Trends in glucocorticoid prescribing practice in CAH over the last 6 years (2017-2023)

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Background and Aims: In 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) several glucocorticoid (GC) medications (Acecort®, Alkindi®, Efmody®, Plenadren®) have recently been developed to improve health outcomes. This study explores the range of GC preparations being prescribed, barriers to prescribing novel GC medications and the geographical and temporal trends in GC prescriptions.

Methods: There are 2 arms to the study: a retrospective data analysis of treatment regimens, identified through the I-CAH Registry, for patients (n = 790, mean age 16 (SD 12.8)) in 46 CAH centres from 19 countries from 4 continents between 2017-2023; and a qualitative survey of 39 centres exploring barriers to prescribing novel medications. Of the 46 centres, 33 were from high-income countries and 13 from middle-income countries.

Results: From 2017-2023, 44/790 (5%) patients changed from traditional to novel GC therapy. Western Europe showed the highest use of novel medications. 100% of patients precribed Alkindi® were <7 years-old (mean age 4 (range 0-7)), whereas 97% of Efmody® adopters were aged ≥7 years-old (mean age 13 (range 0-24)).
In 2018, among 39 centres, 5% had Alkindi®, 26% Plenadren®, and none had Acecort® or Efmody®. By 2023, Alkindi® was available in 54% centres, Efmody® in 46%, Plenadren® in 33%, and Acecort®

in 15%. The most commonly reported barriers to prescribing novel medications were; insufficient legislative approval (Efmody®: 16/21, Plenadren®: 17/26, Alkindi®: 11/18, Acecort®: 23/33), underdeveloped supply chains (Efmody®: 6/21, Plenadren®: 8/26, Alkindi®: 6/18, Acecort®: 9/33), and perceived high costs (Efmody®: 5/21, Plenadren®: 3/26, Alkindi®: 4/18, Acecort®: 3/33). Some centres faced multiple barriers (Efmody®: 9/21, Plenadren®: 7/26, Alkindi®: 4/18, and Acecort®: 8/33), with the commonest combination being lack of legislative approval with supply chain issues (Plenadren®, Alkindi® and Acecort®) and lack of legislative approval with high costs (Efmody®).

Conclusion: This study revealed limited adoption of novel GC medications, with approximately 5% of patients transitioning from traditional treatments from 2017 to 2023. Novel medications are primarily being offered in the paediatric setting. Barriers to adoption include lack of legislative approval, supply chain issues, and perceived high costs, highlighting the need for a continued focus on facilitating access to novel drugs in CAH.

PO 12

Management of 46,XX Disorders of Sex Development: A Two-Decade Experience from a National Referral Hospital in Indonesia

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Background: Disorders of sex development (DSD) is defined as congenital condition associated with atypical development of chromosomal, gonadal, and phenotypic sex abnormalities. The 46,XX DSD is one of the most common DSD types in Indonesia. This study aims to describe the classification, sex of rearing, diagnosis, and management in patients with 46,XX DSD who visited Cipto Mangunkusumo National Referral Hospital in Indonesia.

Methods: We retrospectively reviewed medical records of all patients with 46,XX DSD who were referred to Cipto Mangunkusumo National Hospital from January 2002 to December 2023. Patients were classified into gonadal (ovarian) development disorders, disorders in androgen synthesis or action (fetal, fetoplacental, or maternal), and other disorders (cloacal exstrophy, labial adhesion, ambiguous genitalia, and other rare syndromes). Treatment and gender assignment were given to each patient according to the protocol and preferences of patients and parents/spouses.

Results: There were 57 46,XX DSD patients, with the most prevalent diagnosis was congenital adrenal hyperplasia (CAH, 42.2%), followed by ambiguous genitalia (22.8%). Patients with more prominent external genitalia abnormalities or more severe clinical symptoms tended to be diagnosed earlier. Most of the patients or their guardians chose to undergo gender assignment surgery within 5 years of diagnosis.

Conclusions: The most prevalent presentation of 46,XX DSD cases in dr. Cipto Mangunkusumo National Referral Hospital were congenital adrenal hyperplasia, followed by ambiguous genitalia. Most of the patients or their guardians chose to take surgical treatment.

PO 13
46,XX DSD secondary to Maternal Adrenocortical Tumor

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Background: Exposure to intrauterine adrenocortical tumors (IATs) is an exceedingly rare of virilization in females. We present the case of a virilized female infant, born after diagnosis of a maternal adrenocortical tumour, diagnosed in pregnancy. To the best of our knowledge, this is the first such case to be reported.

Case Presentation: The mother conceived a dichorionic diamniotic twin pregnancy following clomiphene induction due to a history of infertility. During routine first-trimester pregnancy, a large abdominal mass was discovered. Termination of pregnancy was advised, but the mother chose to continue the pregnancy. She proceeded to tumour excision, which confirmed a large adrenocortical carcinoma. Mother underwent planned emergency caesarean section at 31 weeks' gestation. The female twin had DSD (Prader Stage 4), with a single urethral opening,rudimentary sac, and no palpable gonads. Her male sibling was healthy.

Results: A comprehensive diagnostic evaluation, including laboratory investigations and imaging studies, were performed on the infant to determine the underlying cause of DSD. Karyotype confirmed XX. Abdominal ultrasound showed normal female internal organs with cloacal abnormality and an enlarged left adrenal gland with an irregular nodule. She had elevated testosterone, DHEAS, and 17-hydroxypregnenolone levels. This prompted concern regarding transplacental metastasis, however a skeletal survey and other imaging did not show evidence of this. The hyperandrogenism persisted until 9 months of age, when normalization of adrenal androgens was observed. Repeat ultrasound and MRI confirmed resolution of the nodular adrenal enlargement**.**

Conclusion: This case highlights the importance of careful and rigorous evaluation in a very complexcase, rendered more challenging due to persistent hyperandrogenism, coupled with the finding of a possible adrenal mass in the infant, raising the question of transplacental metastasis.

PO 14
Aromatase deficiency: 46,XX difference of sex development caused by a unique variant in the *CYP19A1* gene (c.146-2A>G) identified with direct-to-consumer genetic testing

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Background: Aromatase deficiency is an autosomal recessive condition that can lead to a 46,XX virilized female difference of sex development. Aromatase is expressed in placental, gonadal, and other tissues and converts androstenedione and testosterone to estrone and estradiol, respectively. The androgen excess causes variable degrees of virilization in the fetus and mother. Abnormal phenotypes result from pathogenic variants in the *CYP19A1* gene (Chr15q21.1).

Methods: In this case report, we discuss a novel homozygous, likely pathogenic variant in *CYP19A1* (c.146-2A>G) detected on a direct-to-consumer genetic test (Nebula Genomics). Additionally, we discuss the potential implications of this testing option.

Results: The patient was born in South America with ambiguous genitalia. After adoption, diagnostic tests confirmed the presence of a uterus and 2 pelvic gonads consistent with pre-pubertal ovaries. Exam showed clitoromegaly with rugation and posterior fusion of the labioscrotal folds, a single perineal opening at base of clitoris, and no palpable gonads. Given that the patient did not require the same amount of steroid replacement as a typical CAH patient, the aetiology of the patient's condition was unknown. The patient's adopted mother did not believe that their commercial health insurance would cover clinical genetic testing, and, as a result, performed an internet search and found Nebula Genomics. This relatively affordable ($US 600) direct-to-consumer test produced raw data rather than a standard genetic test report; there was also no formal genetic counselling provided with the results. Therefore, the mother actually had to perform her own research to understand the data. This revealed that the patient has a homozygous, likely pathogenic variant, c.146-2A>G, in *CYP19A1*—consistent with a diagnosis of aromatase deficiency. Medical genetics recommended the CLIA-certified Invitae DSD gene panel which identified the identical variant. This variant is not present in population databases (gromAD no frequency) and has not been previously reported in the literature.

Conclusions: This case highlights a novel *CYP19A1* variant revealed through direct-to-consumer genetic testing. This particular test provided an affordable option for the family to seek answers regarding their child's condition but highlights the drawbacks of such a method as it required the family to do their own research.

PO 15
New Educational Materials: a Brochure for Parents and a Box with Cards for Adolescents

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Background: A DSD diagnosis can be difficult to understand and to accept. The societal taboo on variations in genital appearance, fertility, sexuality and gender make patients vulnerable for stigmatization. Patients and parents may face many challenges. Coping with these challenges will be facilitated in case patients and parents understand their diagnosis well and are able to communicate about the diagnosis and their needs with their health care provider and their nearest and dearest. We hypothesize that educational materials that stimulate to take an active role, will reinforce coping abilities.

Aim of our project: In this project we translated and adapted an educational brochure focusing on parents, and a set of "Questions young people have" developed by Denise Steers (New-Zealand) and DSD families (UK) respectively, for Dutch-speaking parents and adolescents.

Methods: In collaboration with the Intersex Trust Aotearoa/New Zealand and the Wellington Hospital Department of Paediatric and Child Health, Denise Steers developed an educational guide for parents explaining the basics of variations of sex characteristics, gender and shared decision making. Parents are stimulated to inform themselves and to use different sources of information, to seek support from their nearest and from parents and patients with lived experience. Professionals experience difficulties in educating adolescents and to discuss coping with challenges, whereas (young) adults report their loneliness and difficulties in puberty. 'Questions young people have' aims to open up a conversation on the DSD condition with the adolescent. In our version, we provide single questions in a box. The adolescent is asked to select a question. By taking the initiative to offer the educational material in a playful way, we aim to reduce barriers for getting informed and asking questions.
Health care professionals working in the field of DSD will be asked to review the translated questions and extend the collection with new questions. All translated and produced materials will then be tested in a small patient group in order to evaluate and refine these materials.

Results: The original and translated educational materials will be presented at the conference where we also hope to receive further input from the audience.

PO 16
Biallelic variant at 5' UTR DMRT1: A novel 46,XY DSD syndrome?

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Background: 46,XY Differences of Sexual Development (DSD) is a condition in which an individual has a male karyotype but exhibits atypical development of their external genitalia, internal

reproductive organs, or both. The risk of gonadal germ cell tumours is increased over the lifetime of patients with 46,XY-DSD.

Methods: The DSD panel analysis with next-generation sequencing was performed on two unrelated 46,XY DSD patients with female external genitalia and germ cell tumour.

Results: Patient 1, presented to the hospital with amenorrhea and abdominal pain at 15 years old leading to surgical intervention for an adnexal mass. The pathology report identified the tumour as a mixed germ cell tumour (yolk sac, teratoma, seminoma, gonadoblastoma) and patient's karyotype result was reported as 46,XY. Patient 2, raised as a girl, presented with pain in the left inguinal region. After detection of the mass, she underwent surgery and was diagnosed with a mixed germ cell tumour of the ovary (choriocarcinoma and yolk sac tumour). Subsequent karyotyping revealed 46,XY.
The second patient, raised as a girl until the age of 13, presented with pain in the left inguinal region. Upon detection of a mass, she underwent surgery and was diagnosed with a mixed germ cell tumour of the ovary (choriocarcinoma yolk sac). Subsequent karyotyping revealed 46,XY
The DSD panel analysis from both patients revealed a homozygous c.-63C>G variant in the 5' UTR region of *DMRT1* gene. Segregation analysis was performed and both parents were found to be heterozygous carriers.

Conclusions: To date, only few heterozygous deletions or mutations in the DMRT1 gene have been reported in association with 46,XY DSD phenotype. This is the first report of a biallelic variant in the 5' UTR region of the DMRT1 gene associated with germ cell tumour and 46,XY DSD phenotype. Considering the strikingly similar and specific clinical presentations of the two patients, if variant supported by functional studies, it may be possible to consider evaluating this as a novel 46,XY DSD syndrome.

PO 17
A case report of rare 46,XY DSD in female adolescent with SRY gene

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Background: This study aimed to present a rare clinical case of 46 XY DSD and difficulties of its further management.

Methods: The study was performed as a clinical case report. 13 year old patient with complaints on an ambiguous genitalia, clitoris enlargement, masculinization was hospitalized to the urology department UMC in 2023. DSD was defined at 4 yrs. They had consultations in the local clinics, dynamic observation until the age of 12 years was recommended. In August 2022 patient was hospitalized into the UMC urology department.

Results: Patient with female gender has 46,XY DSD, urogenital sinus, bilateral cryptorchidism, inguinal form. Genetic examination revealed SRY gene. Duplication was detected in the AZFc factor,BPY2 gene.
Hormonal profile:Testosterone 2.50 (0.10 - 0.30),Estradiol 35.87(5.00 - 115.00),FSH 52.04(0.68 - 6.70), LH 9.50(0.10 - 4.10),17-OH progesterone 13,67.
46 XY Karyotype. Tanner MA0,PB1-2,ME0,Ax1, mixed external genitalia, hypertrophied clitoris in the form of a penis, the foreskin is distributed in the form of a hood with an underdevelopment of the penis and labia majora. There is no entrance to the vagina. The meatus is located on the perineum. Masculinazation.Prader III.
US investigation of pelvis 26/05/2023: inguinal retention of testicles on both sides. MRI of pelvis 27/11/2022: bilateral cryptorchidism, penile hypoplasia, aplasia of the corpus spongiosum of the penis, uterine hypoplasia, aplasia of the vagina, and ovaries.
X-ray of the left hand 28/11/2022: bone age 12 years.

Conclusion: During master class at the UMC in august 2023, multidisciplinary concilium was held with the head of the department of minimally invasive surgery of Children's Hospital of Philadelphia (USA) prof. Aseem R. Shukla, ass. prof. department of urology Katherine Fischer and our team. It is recommended to refrain from surgical correction until the age of 18 years and observe by an endocrinologist, urologist, gynaecologist once every 6 months.

PO 18

Longitudinal Change in External Masculinization Score in Boys with XY Disorders of Sex Development (DSD)

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Background: The External Masculinization Score (EMS) is an objective tool for quantifying external genitalia in undermasculinised individuals with DSD. However, information regarding EMS changes over time in routine clinical practice is lacking.

Objectives: To determine longitudinal changes in EMS and their determinants in a cohort of boys with XY DSD in Glasgow.

Methods: 205 boys with XY DSD evaluated by the DSD Diagnostic Board from 2010 to 2020 were included. Hormonal and genetic assessment data, as well as initial (EMS1) and most recent EMS (EMS2) data were obtained from clinical records. EMS-changing interventions, such as testosterone therapy (TRT) and surgeries, were also recorded.

Results: Median EMS1 was 8 (range: 2-12) and increased to 11 (1.5-12) ($p<0.001$) over a median follow-up of 3.5 years (0.2-17.3). EMS improved in 79% of subjects and decreased in 5%. Full

masculinization (EMS2=12) was achieved in 36% of boys. EMS1 did not differ between boys with (n=45) and without endocrine abnormalities (n=155). However, boys with endocrine diagnoses had significantly lower EMS2 (median: 9 vs. 11, p=0.0062). Boys with gene variants (n=54) had lower EMS1 than those without (n=94) (6 vs. 8, p=0.039). Causative gene variants were associated with micropenis at baseline (p=0.014). Among 172/205 patients who underwent EMS-changing surgery, 29% had more than two operations, and their EMS2 was lower than those who required two or fewer operations (9 vs. 12, p<0.001). EMS1 and EMS2 were no different between boys with and without TRT history. The probability of achieving EMS2=12 was 20% by age 5, 38% by age 10, 59% by age 15, and 100% by age 19.3 years.

Conclusions: EMS improves during childhood and adolescence. Baseline EMS is lower in boys with definitive genetic XY DSD diagnoses. Changes in EMS are less favourable in those with endocrine abnormalities and those who require multiple surgeries. This study is the first to evaluate longitudinal outcomes using EMS in XY DSD boys.

PO 19

The Phenotypic Spectrum of The External Genitalia In Males In The I-DSD Registry

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Background: To understand the quality of information that is available in the I-DSD Registry, this study aimed to describe the phenotype of the external genitalia in males who have been included in the Registry with a condition that may be associated with a DSD.

Methods: A total of 3,188 male cases with a median current age of 16.8yrs (range, 0.3, 85.1) from 104 centres from 39 countries, excluding those that had androgen excess, were analysed.

Results: Within this cohort, 1,973 (62%) had a 46,XY karyotype, 719 (23%) had 47XXY or related variants, 203 (6%) had 45,X or related variants, 124 (4%) had 46,XX, and 155 (5%) had another karyotype. Of the 1,973 cases with 46,XY, 860 (44%) had non-specific XY DSD (NS-DSD), 340 (17%) had disorder of androgen action (DAA), 304 (15%) disorder of gonadal development (DGD), 227 (12%) disorder of androgen synthesis (DAS), 48 (2%) had Persistent Müllerian duct syndrome, 42 (2%) had hypogonadotrophic hypogonadism (HH), and 152 (8%) other disorders. Of the 124 cases that were 46,XX, 110 (89%) had DGD, 2 (2%) had DAS, and the remaining 12 (10%) had another disorder. The genital appearance was described in 1,226 cases out of 3,188 (38%) cases. Information on the location of the meatus was available in 1152 out of 1,226 (94%) cases, of which 853 (74%) had hypospadias, with 196 (23%) being isolated and in 657 (77%) combined with other external genitalia anomalies. The location of the gonads was available for 1,118 out of 1,226 (92%) cases, with 597 (53%) having undescended testes. The appearance of labioscrotal folds was described in 1,131 (92%) cases, with a bifid scrotum evident in 327 (29%). The phallus size was described in 1,170 (95%) cases, with a record of micropenis in 610 (52%).

Conclusion: Even though the proportion of cases with detailed information of external genital phenotype in males with suspected DSD is about a third, the actual numbers of cases are over a

1,000. However, given the aetiological heterogeneity in males with DSD, there is a need to increase the overall proportion of cases with that have detailed phenotypic information.

PO 20

Clinical characteristics of patients who underwent gonadectomy from a low middle income country

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Introduction: Gonadectomy in children and adolescents with disorders of sex differentiation is influenced by the genetics, risk of gonadoblastoma, prevent hormone production discordant to the gender, and socio-cultural concerns. The aim of this study was to determine the clinical characteristics of patients who underwent gonadectomy from a low middle income country.

Method: Retrospective data was obtained from children who are followed up in a single centre since 2013.

Results: There were nine patients who underwent bilateral gonadectomy. Age at presentation varied from 8 years to 15 years. Seven patients (77%) underwent surgery due to risk of malignancy. Age at surgery varied from 11-15 years. All of them had turner phenotype who presented with short stature. They had mosaic karyotype with Y chromosome. One patient had ambiguous genitalia. Two patients who presented late had gonadoblastoma in situ.
Two patients underwent surgery to prevent hormone production discordant to the gender. One of them underwent surgery before presenting to endocrinology unit, at the age of 1 year. She is well adjusted to the current gender and has no regret over the decision taken in the past without her consent. Other patient received appropriate counselling prior to surgery at 16 years. She presented at 14 years with virilization and wished to continue as a female. She is awaiting genital reconstruction surgery. Gonadectomy was delayed till she was competent to give consent. Until such time she received GnRH analogues and oestrogen therapy.
Only two patients were old enough to give consent. Five patients received age-appropriate explanation prior to surgery. There were no post-surgical complications. All patients had started hormone replacement therapy.

Conclusion: The commonest reason for the gonadectomy in this cohort was tumour risk who presented with karyotype consistent with tuner mosaic. The decision to do surgery was late compared to published data as they presented to the unit after the age of eight.
The number of patients who underwent surgery to prevent hormone production discordant to the gender were relatively low. Further prospective studies are needed to understand reasons and long-term effects of gonadectomy in adolescents.

PO 21

Surgical interventions in girls with congenital adrenal hyperplasia – Experience from a low middle income country – A preliminary report

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Background: Virilizing congenital adrenal hyperplasia (CAH) is a complex disorder which requires a multidisciplinary approach. Exact timing of genitoplasty in children with virilization varies on the available resources, patients' perspectives, and cultural influences. This study is aimed to assess surgical interventions based on the degree of virilization in girls with congenital adrenal hyperplasia from a single centre.

Methods: Nineteen patients attending routine endocrine and surgical clinics were analysed retrospectively using medical records. The indications, timing, anatomy, surgical interventions, early and late complications, and parental satisfactions were studied.

Results: There were 16 patients with classic CAH. 12 had salt wasting and 04 were simple virilizing CAH. One had non-classic CAH. The degree of external virilization was assessed using Prader scale. There were 11 (57%) patients with Prader stage III while 5 (26%) had stage IV and 3 were stage II (16%). The preoperative anatomical assessment was performed in all patients using ultrasonography, examination under anaesthesia and lower genito-urinary endoscopy. One patient had high vaginal- urethral confluence. 18 patients underwent feminizing genitoplasty while surgery was deferred in one patient due to male gender identity at 3-years of age. Age at surgery ranged from 14 months to 13 years. 17 patients had surgery at the mean age of 40 months. All Prader scale IV patients needed clitoroplasty, vaginoplasty and labioplasty. Out of the Prader stage III patients one did not need clitoroplasty, others underwent all 3 components. Stage II patients underwent selective components of the procedure depending on the anatomy.
No postoperative complications like urinary tract infections, vaginal strictures, or bleeding were noted. All patients underwent subsequent EUA and vaginal calibration. No vaginal scarring was noted. None needed additional major revision of anatomy or re-do surgery. The parental satisfaction on the cosmetic and the functional outcome of the surgery assessed verbally revealed satisfactory outcome.

Conclusion: Early surgical intervention for girls with severe degree of virilization due to congenital adrenal hyperplasia has resulted in good anatomical outcomes without significant increase in the complication rates. Assessment of patients' perspective on the outcome will be studied comparing the cohort who did not undergo surgical intervention.

PO 22

Supporting parents of children with differences in sex development and genital variations

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Background: Psychosocial support is a key element in the multidisciplinary care of people with DSD/Intersex. There are many barriers that limit how and what psychosocial supports are made available to families. Significant legislative proposals are currently underway across Australia and internationally to potentially drastically changing clinical care. These changes aim to include the de-pathologisation of intersex variations, positive affirmation of variations, cessation of non-essential genital surgeries until the child can consent. Despite this, there are many areas of contention including even the terminology, but also issues around the different human rights.
Victoria has a culturally and linguistically diverse (CALD) population, with 49% of Victorian's either being born overseas or born to parents who were. Societal expectations of sex and gender have a different meaning for each of us as individuals. How families manage a diagnosis depends on factors such as their biomedical healthcare beliefs and their socio-cultural beliefs. This study explores parents' experiences and desired support and resources for raising children with DSD/intersex from a diverse range of backgrounds.

Methods: This is a qualitative study exploring the experiences and resource needs of parents who are raising a child born with a genital variation. Participants were recruited from the Royal Children's Hospital, Melbourne. Semi-structured interviews were conducted via telephone or a video-conferencing platform, audio recorded and transcribed. We applied Inductive Content Analysis (ICA) to identity themes.

Results: Purposeful sampling reflective of the population was used. From the 24 families invited, we interviewed 13 parents whose children ranged from 1 to 20 years old. Seven families where one or both parents were from CALD backgrounds. Participants lived in metro, regional and rural areas.
The preliminary themes identified: recognising their own mental health needs; what will the future look like?; finding ways to normalise differences and build resilience; and lastly, cultural identity and family-centred care.

Conclusions: Parents' experiences and insight can inform the development of support structures and resources. Finding the right balance between the evolving legislation and the ongoing needs of families is crucial. The next step will be incorporate recommendations for supports outlined in this study and to evaluate their effectiveness.

PO 23

Perceptions and practices of Australasian clinicians regarding genetic testing in Differences of Sex Development

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Background/Aims: To identify perceived gaps/strengths/barriers in current practice and investigate the diagnostic approach of clinicians involved in the diagnosis and management of individuals with DSD (Differences of Sex Development)/VSC (Variations in Sex Characteristics), particularly in regard to genetic testing.

Methods: An anonymous online survey was developed, with questions exploring demographics, perceptions of genetic testing, availability of genetics and opinions on the role and utility of genetic testing in DSD/VSC. The survey was open for 4 months from July 2022 to October 2022. Clinicians involved in the diagnosis and management of individuals with DSD/VSC, recruited from relevant societies and clinical departments across Australia and New Zealand.

Results: 79 eligible clinicians commenced the survey, with 63 complete and 16 partial responses to the survey, from all states and territories of Australia/New Zealand. The perceived benefit in having a genetic diagnosis in DSD/VSC was almost unanimous (n=66/68, 97%). Almost half (n=26/54, 48%) of respondents reported barriers in genetic testing. An associated downside with having a genetic diagnosis for individuals with DSD/VSC was reported by 47% (n=32/68). 81% (n=55/68) of respondents reported they order genetic tests for individuals with DSD/VSC currently. Approaches to genetic testing when faced with four different clinical scenarios varied across respondents. Clinicians perceived genetic testing to be underutilised (median 36 on sliding scale from 0-100).

Conclusion: Despite 97% of respondents reporting benefit in a genetic diagnosis for individuals with DSD/VSC, this was not reflected throughout the survey in regard to clinical implementation. When faced with clinical scenarios, the recommendations for genetic testing from respondents was much lower, again indicating the discrepancy between perception and clinical practice. Genetics in the context of DSD/VSC seems to be seen as both beneficial and desired, yet there are multiple barriers impacting its integration into standard clinical care. As genomic testing by non-genomics specialists becomes more common practice, this needs to be the focus of more targeted education programs.

PO 24

Current care provision models in Differences of Sex Development (DSD): a survey of Australasian clinicians

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Background/Aims: There are limited evidence-based guidelines for DSD/VSC and the multidisciplinary team (MDT) has been recommended as an optimal model of care. This study aimed to explore current care models for individuals with DSD/VSC in Australasia and to identify perceived gaps and barriers in current practice.

Methods: An anonymous online survey was conducted between July 2022 and October 2022, recruiting clinicians involved in the diagnosis and management of individuals with DSD/VSC in Australia and New Zealand. Participants were approached through secretariat newsletters of relevant medical societies as well as through heads of relevant units across Australia and New Zealand.

Results: 79 eligible participants commenced the survey from all states and territories of Australia and New Zealand, with 63 complete responses. 76% (n=52/68) of respondents identified changes to DSD/VSC care over the past 5 years and 75% (n=51/68) identified barriers to care. 69% (n=47/68) of participants are currently part of an MDT meeting for DSD/VSC at their centre. For those who are holding regular MDT meetings, the consensus is that the frequency of these meetings is appropriate Current availability of team members is below international recommendations, with 93% having endocrinology, 91% urology, 70% clinical genetics and 20% psychology. 57% (n=26/46) feel that psychology is a missing part of their team.

Conclusions: Responses to the survey identify gaps and barriers to DSD/VSC care across Australasia, in particular the lack of psychosocial supports, which is an internationally recognised standard of care. Further work to interrogate the specific gaps in clinical expertise, funding and education will hopefully lead to improved implementation of nationwide services consistent with international recommendations.

PO 25

Evaluating clinical pathways and outcomes in individuals with Differences of Sex Development (DSD)

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Background/Aims: Data pertaining to clinical outcomes and the natural history of different DSD are lacking for many reasons, including the high rates of individuals without a specific genetic cause for their variation. Evidence-based guidelines regarding management of DSD remain limited. This study aimed to evaluate clinical presentations, diagnostic approaches and clinical outcomes for a large cohort of individuals with DSD, as well as assess changes in management over time.

Methods: A retrospective analysis was undertaken for all individuals with DSD at the Royal Children's Hospital, Melbourne over 20 years (first presentation between 2001-2021). Data was collected for those with 46,XY DSD or 46,XX DSD (excluding Turner/Klinefelter syndrome, congenital adrenal hyperplasia, premature ovarian insufficiency and MRKH syndrome) from a thorough review of medical records.

Results: 254 individuals with DSD were identified. 85/254(33%) had a specific DSD diagnosis (either genetically or clinically confirmed), while 87/254(34%) were classified as "46,XY DSD" and 82/254(32%) were classified as "hypospadias" despite meeting clinical criteria for DSD (complex

hypospadias +/- additional genital variation). The median [IQR] external genitalia score (EGS, out of maximal score 12) for the cohort was 7.5[4.5]. 60/254(23%) of the cohort never had a karyotype and 156/254(61%) hadn't had genomic testing. Of those with genomic testing, 39% resulted in a genetic diagnosis and 5% had a variant of uncertain significance. 86/254(34%) of the cohort had hormonal therapy as part of their clinical management and 235/254(93%) had surgical intervention, including biopsies. Additionally, data has been analysed regarding the frequency of subspecialty reviews, psychosocial supports, discussion at MDT meetings, gender identity, growth, puberty, bone health, fertility, histopathology and transition to adult care (where available).

Conclusion: This study describes a large single-centre cohort of 254 individuals with DSD over a 20 year period, leading to expanded knowledge about our utilisation of clinical pathways. More identification of phenotypic severity through the EGS is recommended to guide diagnostic pathways, including multidisciplinary team review and assess to genetic testing The data informs the need for prospective data collection for our DSD cohorts, together with the need for national/international collaboration to improve knowledge in relation to clinical outcomes and optimal management pathways.

PO 26

Impact of a Comprehensive Model of Care for Individuals Diagnosed with Mayer-Rokitansky-Küster-Hauser (MRKH) Syndrome and their Families

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Background: While many difference of sex development (DSD) conditions are treated through multidisciplinary care, the care of individuals diagnosed with MRKH is often managed by gynaecologists with a focus on gynaecologic concerns. Like other DSD conditions, MRKH -- defined by underdevelopment of the mullerian tract – impacts both fertility and the genitals/reproductive structures, and individuals with the diagnosis may be hesitant to share their experience and access support, leading to a sense of isolation.

Methods: We developed an interdisciplinary care approach designed to provide comprehensive care to patients and their families by promoting knowledge, empowerment, body positivity, self-determination, adjustment, and information sharing/relationship building. We strive to incorporate these values into the longitudinal care provided - from diagnosis and beyond. Our model includes clinical psychology in the direct care of the individual as well as social work in the direct support of family members. This fosters resilient adjustment to the diagnosis and treatment. Our model also includes a pelvic health physical therapist who addresses multiple functional challenges (e.g., stress incontinence, prolapse, pelvic pain) while also supporting and empowering patients who pursue vaginal lengthening through dilation by providing techniques

to increase comfort and success. Our care timeline includes pre-clinic support, interdisciplinary care in clinic, and timely, longitudinal follow-up visits. Our focus on growing social media presence is another mechanism of information sharing that enables our team to enact our core values and offer support to affected individuals and families using a broader platform.

Results: By providing multidisciplinary care, patients and families are afforded care that supports them holistically. Since the inception of this interdisciplinary care model, patient and family experience surveys show positive impact of the comprehensive care model, with 9 and 10 out of 10 ratings. Moreover, our social media presence grew by 140 followers within the first 90 days of launch.

Conclusion: Early patient and family experience data suggest that the interdisciplinary model our Center has adopted – focused on empowerment, information sharing, self-determination, and body positivity – helps to support comprehensive care including the psychosocial, medical, surgical, and anatomical concerns experienced by individuals with MRKH.

PO 27

Exploring oligogenic inheritance through whole exome sequencing in individuals with *NR5A1*/SF-1 variants: Findings from the International SF1 Next Study

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Background: Individuals with *NR5A1*/SF-1 variants encompass a wide spectrum of phenotypes, ranging from healthy carriers to severe forms of differences of sex development (DSD). The mechanisms contributing to this wide variability of observed phenotypes remains elusive. Oligogenic inheritance has been suggested as a potential mechanism. We aimed to investigate the oligogenic inheritance patterns in individuals with *NR5A1*/SF-1 variants from the international SF1next study cohort, shedding light on how multiple genetic variants collectively influence DSD phenotypes.

Methods: DNA samples and DSD phenotype data from individuals carrying *NR5A1*/SF-1 variants, and available family members, were collected from 11 collaborating centres. Whole exome sequencing (WES) data of 23 individuals/families were utilised. WES data were analysed using a tailored filtering algorithm to identify rare variants in SF-1- and DSD-related genes. Identified variants were assessed for potential pathogenicity based on American College of Medical

Genetics and Genomics (ACMG) and clinical disease associations in related databases. Oligogenic combinations between the additional variants and the specific *NR5A1*/SF-1 variants were tested using Oligogenic Resource for Variant Analysis (ORVAL). Genotype-phenotype correlations were explored by integrating these findings with the phenotype data.

Results: Novel genetic workup of 23 individuals detected rare, additional variants in SF-1- and DSD-related genes. The phenotype of these individuals, all with 46,XY karyotype, ranged from severe to opposite-sex DSD. Using ORVAL, oligogenic pathogenic combinations were found in 18 (78%) individuals, with one to four additional variants in different genes per individual. Certain genes were frequently involved in the oligogenic networks of several 46,XY DSD individuals with *NR5A1*/SF-1 variants , but in different combinations. *ZFPM2, FLNB, GLI3*, and *PDGFRA* were among the DSD-related genes identified more frequently (11/18, 61%). In 5/23 (22%) individuals, no oligogenic combinations were identified through ORVAL analysis in relation to *NR5A1*/SF-1.

Conclusion: Our study shows that in 3 out of 4 individuals with a *NR5A1*/SF-1 variant and a 46,XY DSD, additional genetic variants may explain the broad variability of the DSD phenotype, indicating oligogenic inheritance. Thus, the genetics explaining the DSD phenotype in many individuals and their families might be more complex than previously thought.

PO 28

Impact of oral contraceptives on the metabolic profile of young women with “classic” 21 hydroxylase deficiency

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Background: Managing androgen excess in 21-hydroxylase deficiency (21OHD) remains challenging in congenital adrenal hyperplasia (CAH). Oral contraceptives (OC) containing ethinylestradiol are known to influence ovarian and adrenal androgen status. In a retrospective pilot study, we observed a positive impact of OC on the androgen status of women with "classic" CAH. Therefore, we aimed to prospectively investigate the OC’s influence on the plasma steroid metabolome in young women with “classic” 21OHD.

Methods: Collaborating with seven centres, we enrolled young women aged 13-25 years diagnosed with classic 21OHD who had already planned to start OC. The study comprised three visits: baseline (Visit-1, prior to OC), three months post-OC-initiation (Visit-2), and six months post-initiation (Visit-3). Liquid chromatography-mass spectrometry (LC-MS) was utilized for steroid analysis of plasma samples. Differences in steroid metabolite levels across the three visits were assessed using the Friedman-Test.

Results: The median age of the 15 young women participating in the study was 20 years (range: 15-26 years). We observed a significant reduction in plasma androgen levels and an increase in cortisol levels (Table 1). Seven out of fifteen (47%) women experienced a reduction in their hydrocortisone doses between visit-2 and visit-3.

Table 1: Plasma metabolites (nmol/L).

	Median (P25 -P75)			
Plasma metabolites	**Visit-1**	**Visit-2**	**Visit-3**	**p-value**
Cortisol	224.0 (97.0 - 292.2)	776.5 (287.4 - 1027.4)	558.6 (313.5 - 894.5)	<0.001
21-Deoxycortisol	4.4 (1.7 - 10.6)	1.4 (0.2 - 12.6)	3.9 (1.5 - 8.8)	0.07
Dehydroepiandrosterone sulfate	298.2 (83.7 - 3559.5)	145.7 (21.8 - 2389.7)	146.8 (34.9 - 2240.2)	0.040
Androstenedione	9 (2.7 - 12.7)	1.4 (0.4 - 4.3)	1.9 (0.4 - 4.6)	0.002
Testosterone	1.2 (0.8 - 1.8)	0.3 (0.1 - 0.8)	0.4 (0.1 - 1.1)	0.001
Dehydroepiandrosterone	41.8 (18.7 - 104.2)	15.2 (1.0 - 34.9)	12.4 (1.3 - 56.5)	0.001
17α-Hydroxyprogesterone	61.3 (8.2 - 78.5)	1.6 (0.3 - 31.6)	2.7 (0.6 - 28.7)	<0.001

Conclusion: These findings suggest an improvement in the steroid metabolome of women with classic 21OHD under OC treatment. OC could become a viable standard additional therapy especially in women with 21OHD and with an unsatisfactory steroid profile.

PO 29

Rights-based resources developed from research with those with lived experience in Aotearoa/New Zealand -Decision making navigation tool for parents with children born with a VSC

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Background: There has been and continues to be much controversary around the treatment and care of individuals born with a Variation in Sex Characteristics (VSC)/Differences in Sex Development (DSD). There is little support for parents who have a child born with a VSC here in Aotearoa/New Zealand. Parent peer supports are not established in Aotearoa and it is often difficult to develop capacity so parents feel able to connect and provide support in an ongoing way in addition to managing their own situation and lives.

Methods: Using data gathered from my PhD Research that was collected from clinicians working in the DSD field of expertise (22), parents of children with a VSC (17) and young people with a VSC (10, aged 14-26 yrs) looking at the influences on health care decision making for those born with a VSC. A resource was developed and evaluated by those from the initial research. Feedback from participants was collated and the resource was re-developed accordingly.

Results: The resource was developed into a booklet with illustrations to help clinicians and parents have conversations to broaden their thinking and increase self-reflection about issues such as gender stereotyping bias, bodily autonomy and future implications. Parents were keen to have an online resource.

Conclusions: Using research findings can translate into practical tools to help both parents and clinicians navigate the at times challenging areas of decision making for children born with a VSC. Using research findings alongside a rights-based framework, parents and clinicians can gain better insight to the issues that children with a VSC as adults may present and therefore make better health care choices.

PO 30

The pathogenic variant in *CYP11A1* gene in a child with early onset primary adrenal failure and 46XY sex reversal -a clinical follow-up

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Background: P450 side-chain cleavage enzyme coded by *CYP11A1* gene converts cholesterol to pregnenolone, the first step in the biosynthesis of all steroid hormones. P450scc deficiency is an autosomal recessive disorder caused by pathogenic variants in the *CYP11A1 gene*. Depending on the severity of the enzyme dysfunction, patients present with mild to severe early-onset adrenal failure. A disorder of sex development is prevalent in 46XY patients from hypospadias to complete female phenotype.

Methods: In molecular analyses whole exome sequencing was performed.

Results: A 7/365 female newborn was referred to NICU due to suspicion of adrenal insufficiency. The baby was from P&D 1, prenatally abnormal nuchal translucency was noted (without further diagnosis), 38 Hbd, bw-3400g, bl-56 cm. The baby was born in primary apnoea, hypotonic, areactive, placed on NeoPuff, iv glucose and saline. On following day episodes of apnoea and bradycardia were noted, hyperbilirubinemia and skin and mucose hyperpigmentation. Lab analyses revealed hyponatremia, hyperkalemia and hypoglycaemia, ACTH>1380pg/ml, cortisol <5 ng/ml, aldosterone<7.6 pg/ml, plasma renin activity> 32.1 ng/ml/h. Steroid profile in urine revealed low levels of metabolites of androgens, mineral- and glucocorticosteroids. Karyotype

was assessed and was 46, XY. Ultrasound of adrenal glands revealed abnormal small adrenal glands with microcalcifications. The therapy with hydrocortisone and fludrocortisone was started. At the age of 7 years the patient is developing well, however due to short stature (-2.1 SDS) with delayed bone age we started evaluation of growth hormone secretion before growth hormone therapy. The patient presents also facial dysmorphic features.
Whole exome sequencing revealed two pathogenic variants c.358del (p.Arg120AspfsTer18) and c.835del (p.Ile279TyrfsTer10) in *CYP11A1* gene as a cause of the patient`s disorder.

Conclusions: Pathogenic variants in CYP11A1 gene can cause early onset adrenal insufficiency with life-threatening failure to thrive**. The question arises whether or not gonadectomy should be performed in this patient.**

PO 31
Children with variations in sex characteristics: youth and parent reports of gender identity/preferences and depression and anxiety

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Background: Parents of youth with variations in sex characteristics (VSC) frequently look to healthcare providers for information about the likely course of their child's gender and emotional development. To better inform parents and providers, this project utilized updated measures to evaluate gender-typed preferences, gender identity and mental health status in children with and without VSCs.

Methods: 78 participants aged 3-12 (M = 7.14, SD = 2.85) with variations in sex characteristics were recruited from 3 children's hospitals in the USA; and 78 community comparison participants (ages 3-13; M = 7.15 ± 2.88 yrs.) were recruited through two university databases of families willing to participate in child development research. Child participants completed assessments of gender-typed toy, clothing and peer preferences, gender identity, and perceived similarity to boys and to girls. Parents reported on their child's gender identity and related history. Children and parents completed measures of anxiety and depression.

Results: Overall children with and without VSCs did not show many significant differences in their gender development. Children with VSCs raised male selected more masculine toys ($t(56.85) = 2.274$; $p = 0.027$; $d = 0.587$) and responded in a more-masculine way on the continuous gender identity measure ($t(38.48) = 2.484$; $p = 0.018$; $d = 0.652$), than did comparison controls. The two groups did not differ on their clothing preference, peer preference, similarity to boys, similarity to girls, or likelihood of picking "boy" in response to the categorical gender identity

question. Children with VSCs raised female had more masculine toy preferences (t(84.89) = 3.421; p = 0.001; d = 0.698) and felt more similar to boys (t(67.43) = 2.994; p = 0.002; d = 0.648), than comparison controls. They did not differ on the continuous gender identity measure, clothing preference, peer preference, similarity to girls, or likelihood of picking "girl" in response to the categorical gender identity question. The groups did not differ on depression and anxiety scores and scores indicated minimal or mild anxiety.

Conclusions:
The data suggest that overall, children with VSCs are similar to their peers on indices of gender development and mental health. Follow-up during adolescence is needed.

PO 32
Diagnosis and management of Complete Androgen Insensitivity Syndrome (CAIS)
Is gonadectomy necessary?

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Background: Complete Androgen Insensitivity Syndrome (CAIS) is a frequent cause of primary amenorrhea, though in paediatric population it should be suspected among girls with inguinal hernias. This study aimed to evaluate clinical presentation, hormonal evaluation and genetics in a series of patients with CAIS with emphasis on pros and cons of maintaining gonads.

Methods: 14 patients who visited Department of Endocrinology and Diabetology, The Children's Memorial Health Institute in Warsaw, Poland between 2005 and 2024, with confirmed mutation in androgen receptor gene were retrospectively reviewed. Age at the time of medical consultation ranged between 5 days old and 18 years. Most of the patients were diagnosed in prepubertal age. There were three affected families among studied cohort.

Results: In 3 cases, during inguinal hernia surgery, due to gonadal appearance inconsistent with female phenotype, gonadal biopsy with immunohistochemistry was performed.
5 patients from studied cohort underwent gonadectomy and received oestrogen treatment. The majority of patients (9 cases) were advised and consented to the preservation of their gonads. Based on follow up, we noted better psychical functioning in patients who have retained their gonads compared to those who underwent gonadectomy and received oestrogen replacement treatment. Systematic ultrasound assessment of the testes was performed in all the patients.

Conclusions: In the described patients, leaving the gonads until puberty gives an opportunity for spontaneous maturation, development of secondary sexual characteristics, growth spurt and

decreasing psychological stress related to surgery. Taken into consideration low risk of malignancy as well as benefits of keeping gonads intact, gonadectomy may be delayed or even abandoned. Additionally, postponing the decision about surgery makes an opportunity for the patients to decide themselves about their medical management.

PO 33
Complexity of genetic diagnosis.
Unexpected virilization in Turner Syndrome leading to diagnosis of gonadoblastoma

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Background: Turner Syndrome often manifests with various chromosomal abnormalities, such as 45,X/46,XX, 45,X/47,XXX, and 45,X/46,XY. Presence of Y chromosome in the mosaicism is linked to the higher risk of developing gonadal tumours. The proportion of mosaicism varies across different tissues, with notable differences observed between blood and gonadal tissue.

Methods: Retrospective analysis of a 45,X patient who was found to have mosaic karyotype 45,X and 46,X,der(Y)t(Y,7)(p11.32;q22) in gonads.

Results: A girl with a patent foramen ovale, psychomotor delay, diagnosed with Turner syndrome in her first year of life, karyotype 45,X confirmed twice by conventional GTG-banding technique and array comparative genomic hybridization (array-CGH) and skin fibroblast analysis using array-CGH. Girl was treated with rhGH from the age of 6 to 12 years. Around the age of 12, clitoromegaly, increasing pubic hair without breast development, voice deepening, and intensified autoaggressive behaviours were observed. After excluding congenital adrenal hyperplasia, laboratory tests showed elevated testosterone at 133.9 ng/dl, increasing up to 220 ng/dl during hCG stimulation test. AFP and BhCG markers were negative. Indications for bilateral gonadectomy were established, which was performed laparoscopically. Histopathological examination revealed Intratubular germ cell neoplasia in the right gonad and a small focus of gonadoblastoma. Immunohistochemical reactions were positive: IHC: CD117 (+), PLAP (+), p53 (-/+). Cytogenetic analysis of the gonads revealed two abnormal cell lines, one with monosomy X, the other with an unbalanced translocation between chromosome Y and 7. The altered Y chromosome resulted from a deletion of Yp11.2 and duplication of 7q22. The translocation was confirmed by FISH technique: using painting probes and an SRY probe. The result explains the abnormal gonadal development and significantly delayed mental development. Postoperative control observed normalization of testosterone levels: < 13 ng/dl.

Conclusions: Individuals with Turner syndrome who carry Y chromosome material are at an enhanced risk for germ cell malignancies, such as gonadoblastoma and dysgerminoma. Key signs that necessitate a comprehensive and rapid evaluation include rapid onset of virilization, an

upward trend in testosterone levels. It is advisable to perform molecular analysis for the presence of Y-chromosome sequences not only in blood but even in gonadal tissue.

PO 34

Reprograming skin fibroblasts into Sertoli cells: a patient-specific tool to understand effects of genetic variants on gonadal development

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Background: A limitation in the field is that the relevant cell types that would be needed to study the molecular events occurring at the time of onset of many DSD, are found in the embryonic gonad. This of course, is not accessible for research or diagnostic purposes. We set out to develop a method for directly transforming more accessible cells, from adult skin, into Sertoli cells (SC).

Methods: The computational predictive algorithm Mogrify was used to predict the transcription factors (TFs) required for direct reprogramming of human dermal fibroblasts into SCs. We established trans-differentiation culture conditions where stable transgenic expression of these TFs was achieved in 46, XY adult dermal fibroblasts using lentiviral vectors. The resulting Sertoli like cells (SLCs) were validated for SC phenotype using several approaches.

Results: SLCs exhibited Sertoli-like morphological and cellular properties as revealed by morphometry and xCelligence cell behaviour assays. They also showed Sertoli-specific expression of molecular markers such as SOX9, PTGDS, BMP4, or DMRT1 as revealed by IF imaging, RNAseq and qPCR. The SLC transcriptome shared about two thirds of its differentially expressed genes with a human adult SC transcriptome and expressed markers typical of embryonic SCs. Notably, SLCs lacked expression of most markers of other gonadal cell types such as Leydig, germ, peritubular myoid or granulosa cells.
The trans-differentiation method was also applied to a variety of commercially available 46, XY fibroblasts derived from patients with DSD and to a 46, XX cell line. The DSD SLCs displayed altered levels of trans-differentiation in comparison to control 46, XY-derived SLCs, with condition-specific gene expression, adhesion to substrate, or division rate.

Conclusions: This method provides a new tool to study molecular events occurring at the time of onset of DSD in the embryonic gonad, and the impact of patient-specific mutations on those. It could allow identification of new developmental pathways (and, thus, new candidate genes for DSD), as well as provide models to validate the impact of variants of unknown significance found during clinical genetic testing, or to test approaches to correct the genetic anomaly in patient cells.

PO 35

Bone health in a monocentric cohort of adult patients with complete androgen insensitivity syndrome

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Background: Low bone mineral density (BMD) is reported in complete androgen insensitivity syndrome (CAIS), particularly in the lumbar spine (LS), yet with limited and heterogeneous data. We aimed to assess bone health in a cohort of adults with CAIS.

Methods: Single-center, cross-sectional study of 36 adults with CAIS (age 34±8.7 years), 31 with removed gonads and 5 with intact gonads. All gonadectomized patients but 3 were receiving hormonal replacement therapy (HRT; 14 transdermal estradiol, 12 oral estradiol, 2 testosterone). Bone health was assessed through DEXA, morphometric vertebral fractures and serum and urinary bone turnover markers. Hormonal levels and other risk factors (celiac disease, monoclonal gammopathy) were evaluated. Calcium and vitamin D intake and adherence to HRT were assessed through self-reporting.

Results: BMD resulted impaired in LS (mean Z-score=-1.79±0.9), both in patients with and without gonadectomy (Z-score -1.8±0.9 and -1.65±0.9, respectively), while femoral BMD was less affected (FT-Z-score -0.5±1.1, FN-Z-score -0.7±1.1). In particular, 17 patients (47.2%) had pathologically reduced LS-BMD (15/17 with gonadectomy, p=0.05). No significant differences were found between different HRT regimes. Overall, 2 cases (5.5%) of spontaneous vertebral fractures, both in the gonadectomy cohort, were recorded.
Despite receiving standard HRT-dose and mostly referring optimal compliance, only 9 (32%) had sufficient serum estradiol concentration (E>50 ng/L). Interestingly, all patients with intact gonads had insufficient estradiol concentration. We also registered high gonadotropin levels (LH=37.7±14 mU/L, FSH=54.3±28 mU/L) in patients with and without gonads. Mean ALP, bone-ALP and osteocalcin were overall in range (68.6±28 U/L, 14.2±8 U/L, and 23±8.7 ng/mL, respectively) whereas CTX levels resulted increased (585.2±288 ng/L).
We found 9 patients (25%) with vitamin D deficiency, 4 (11%) with hypercalciuria and 15 (41.6%) insufficient dietary calcium intake. No other risk factors were found. No significant association was found among BMD and all parameters evaluated.

Conclusion: we confirmed the reduction of BMD in CAIS with and without gonadectomy, regardless of HRT regimen and compliance. Similarly, preservation of gonads doesn't guarantee optimal hormone levels and adequate BMD. Treatment should be optimized considering hormonal levels and BMD. Our results reinforce the need of defined guidelines on the most appropriate management of CAIS.

PO 36

A new GATA4 mutation in a child with disorder of sex development and central precocious puberty

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Background: GATA4 gene (8p23.1) is essential for cardiac and gonadal development and sexual differentiation. We report the case of an 8-year-old child with a DSD, central precocious puberty and GATA4 mutation without congenital heart disease (CHD).

Methods: A literature review was conducted to evaluate the correlations between GATA4 mutations and clinical phenotypes.

Results: Second-born child of healthy non-consanguineous parents, born at term by CT after a normal pregnancy. Birth weight 3900 g, length 54 cm. In the second month of life testosterone therapy was administered for 3 months because of micropenis (1,5x1 cm). At 2 years old, orchidopexy was performed for bilateral cryptorchidism. After 6 years he came back under our observation for increase of sexual pubic hair (pubarche). Auxological parameters: height 147 cm (+2,95 SDS), weight 42 kg (+2,21 SDS), bone age 11.25 yrs vs 8 yrs of chronological age. The laboratory parameters and the GnRH test suggested a central precocious puberty (CPP), even if the elevation of gonadotrophins to GnRH test could suggest a future diagnosis of hypergonadotropic hypogonadism. Testicular volumes were 1 ml at ultrasonography. Pituitary MRI was normal. No organ pathology was detected in echocardiography and thyroid ultrasonography. Treatment with GnRH analogues was started. Genetic tests detected a 46,XY DSD due to heterozygous variant c.671CG (p.Ser224Cys) in GATA4 gene. In the literature, 26 cases with 46,XY DSD due to the GATA4 gene were reported. Clinical manifestations range from isolated hypospadias to female-sex genitalia and varying degrees of virilization. Hypospadias is the most frequent clinical manifestation. The p.P407Q variant was found in eight patients. The p.G221R variant caused DSD in three patients, one of whom suffered from CHD. Septal defects are the CHD most associated with the GATA4 mutation. GATA4 mutations result in different clinical manifestations and there is not specific genotype-phenotype correlation.

Conclusions: The novel missense variant of our case (c.671CG) was not already described. This is the first patient in which CPP, despite the lack of increased testicular volume, is associated with DSD due to a GATA4 mutation.

PO 37
Misdiagnosis of pseudo-hypertriglyceridaemia in glycerol kinase deficiency

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Background: Mutation on NROB1 (DAX1) gene can present as adrenal insufficiency in infancy. It can manifest as part of contiguous gene syndrome together with Duchenne muscular dystrophy and glycerol kinase deficiency.

Method: Informed written consent was obtained from the legal guardian for this case report. Whole exome sequencing was performed to delineate the genetic aetiology of this patient.

Results: Herein, we report a Malaysian patient with contiguous gene syndrome of Xp21.2 resulting in NROB1 related X-linked adrenal hypoplasia congenita, glycerol kinase deficiency and X-linked intellectual developmental disorder. A 2-month-old boy from the consanguineous parents presented with salt wasting crisis (his serum sodium of 120 mmol/L, serum potassium of 6.3 mmol/L) with generalized skin hyperpigmentation. The diagnosis of primary adrenal insufficiency was confirmed by poor adrenal response in ACTH stimulation test and elevated ACTH level (34.4 pmol/L). Hydrocortisone and mineralocorticoid replacement were promptly initiated. His blood sample was noted to be lipaemic and his fasting serum lipid showed hypertriglyceridaemia (total cholesterol 3.38 mmol/L, triglyceride 12.52 mmol/L, HDL 1.5 mmol/L, LDL 3.81 mmol/L). Following this, he was initiated on milk protein-based powder with medium chain triglycerides (Portagen). His whole exome sequencing revealed hemizygous deletion at Xp21.2. As pseudo-hypertriglyceridaemia can be seen in individuals with glycerol kinase deficiency, Portagen was deemed unnecessary and was withheld.

Conclusion: Unawareness of asymptomatic condition of pseudo-hypertriglyceridaemia in individuals with glycerol kinase deficiency could lead to ineffective management of hypolipidaemic agents.

PO 38
Adrenal anomalies in individuals with a variation in the SF-1/*NR5A1* gene: oligogenic inheritance?

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Background: Loss of function variants in Steroidogenic factor 1 (SF-1/*NR5A1*) are common in differences of sex development (DSD) and manifest with a broad spectrum of phenotypes. Beyond the DSD phenotype, up to 27% of individuals with a SF-1/*NR5A1* variant have anomalies in other organs, predominantly the spleen, seldom the adrenals. Oligogenic inheritance may contribute to the variable phenotype observed in these individuals. This study aimed at investigating individuals with SF-1/*NR5A1* variants presenting with DSD and associated adrenal anomalies to identify additional genetic variants that may explain the adrenal phenotype.

Methods: Within the framework of the SF1next study, we had four patients with a DSD phenotype and adrenal anomalies. These individuals were screened via whole exome sequencing (WES) and analysed with an in-house specific data-filtering algorithm. We used several in silico tools to predict the effect of gene variants on protein function and searched for reported disease-causing variants in literature and the HGMD and ClinVar databases. Variants were classified according to the ACMG guidelines for pathogenicity assessment.

Results: The phenotype of the patients (three 46,XY, and one 46,XX) ranged from opposite sex and severe DSD to typical male external genitalia in 46,XY and typical female external genitalia in 46,XX individual. Among the 46,XY DSD patients, two had adrenal insufficiency and one had partial adrenal insufficiency and polysplenia. The 46,XX DSD female was referred with adrenal hypoplasia and asplenia. SF-1/*NR5A1* variants were identified in homozygosis in one and in combined heterozygosis in three patients. In two patients, we found one (likely) causative variant in an additional gene known to be involved in adrenal pathology (e.g. *NNT*, *CDKN1C*). In the other two patients, our algorithm revealed one potentially deleterious variant in *ADCY1* and *ABLIM3,* respectively that might have modified the observed phenotype.

Conclusion: Our study shows that most individuals with DSD and adrenal anomalies carrying SF1/*NR5A1* variants harbour other deleterious gene variants that may explain the adrenal phenotype. This finding indicates that the SF-1/*NR5A1* gene may not contribute alone to the specific adrenal phenotype of these individuals. Thus, only WES or WGS (whole genome sequencing) may reveal the genetic network involved in complex phenotypes.

PO 39

Prevalence of differences of sex development in Switzerland from 2000-2019

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Background: Reliable data on prevalence of rare differences of sex development (DSD) are lacking. We aimed to estimate prevalence of DSD in Switzerland in a retrospective population-based study including individuals with DSD according to Chicago Consensus, born in Switzerland from 2000-2019.

Methods: Endocrine care centers in all ten Swiss Children's Hospitals and eight private endocrine practices collected DSD data through the I-DSD registry or case report forms. We calculated prevalence for DSD diagnostic groups and analysed time trends in prevalence.

Results: Over the 20-year study period, we identified 561 individuals with DSD. Almost half (n=266, 47%) had sex chromosome DSD, 177 (32%) had 46,XY DSD and 118 (21%) had 46, XX DSD. Causes for 46,XY DSD were disturbed androgen synthesis or action (37/177, 21%), atypical gonadal development (28/177, 16%), or other causes (112/177, 63%). Causes for 46,XX DSD were androgen excess (99/118, 84%), atypical gonadal development (8/118, 7%), or other causes (11/118, 9%). On average, 28 new cases were born with DSD annually. Prevalence was 17 for sex chromosome DSD, 12 for 46,XY DSD and 8 for 46,XX DSD per 100'000 live births and year. One per 7,500 newborn girls had 46,XX congenital adrenal hypoplasia (CAH).

Conclusion: Prevalence of sex chromosome DSD was lower than expected because of underreporting due to late diagnosis. Prevalence of 46,XX CAH is similar to newborn screening data, suggesting good completeness of cases. For complex DSD cases, we expect complete coverage. This study provides a valuable resource for policymaking and (inter)national research on DSD.

PO 40

The Future of VSD Diagnosis: Exploring the Potential of AI in Uncovering New Genes and Improving Patient Outcomes

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Background: Despite numerous documented genetic causes of VSD, the molecular aetiology remains unknown for over half of individuals with variants of sex development. NGS has improved clinical diagnosis, but challenges persist in interpreting results, particularly when mutations are absent in known VSD genes or variants of unknown significance are present. Identifying novel genes solely based on WES is also difficult. Recent advancements in single-cell RNA sequencing provide detailed gene expression profiles of developing human gonads, allowing for the training of deep learning algorithms to uncover previously unknown molecular mechanisms and pathways of sex development. Our approach utilizes a trained neural network to predict potential candidate genes among the remaining SNPs of undiagnosed VSD patients, leading to a deeper understanding of sex development and more accurate diagnoses.

Methods: We analyzed three XX and three XY patients presenting sex reversal using our machine learning approach. Our method prioritized genes exhibiting similar expression patterns to known VSD genes while filtering out genes with ubiquitous expression or expression patterns inconsistent with known VSD genes in developing gonads. Through this approach, we were able to narrow down the list of potential genes from approximately 1000 to just 5 promising novel candidates, whose role in sex development warrants further investigation.

Results: Our analysis revealed promising results in prioritizing candidate genes for further study. By employing machine learning techniques, we identified genes with expression patterns consistent with known VSD genes, offering insights into potential molecular mechanisms underlying sex development. This innovative approach significantly accelerates the selection process for novel genes for in vitro or in vivo studies and holds promise for improving patient outcomes in the future.

Conclusion: Our study demonstrates the effectiveness of a machine learning approach in prioritizing candidate genes for further investigation in individuals with VSD. By leveraging deep learning algorithms trained on single-cell RNA sequencing data, we successfully identified a small set of promising novel candidates with potential roles in sex development. This methodology opens new avenues for research and offers a more efficient means of selecting genes for future studies, ultimately contributing to a better understanding of VSD and improved patient care.

PO 41

Stigma in Differences of Sex Development: A Scoping Review

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Background/Aims: Differences of sex development (DSD) are a heterogeneous group of conditions that affect sex determination and differentiation and are associated with a range of psychosocial impacts including risks for stigmatization. This scoping review evaluated DSD-related stigma experiences as reported by individuals with DSD, caregivers of individuals with DSD, and non-affected individuals (e.g., healthcare providers, siblings, and laypeople).

Methods: In line with frameworks by Arksey and O'Malley (2005) and Levac et al (2010), a multi-step, iterative process was used for the search strategy. Databases utilized included Cochrane Library, PubMed, Ovid MEDLINE (Ovid MEDLINE(R) and Epub Ahead of Print, In-process & Other Non-Indexed Citations, Daily and Versions(R)), (ELSEVIER) Embase, (EBSCO) CINAHL Complete, (EBSCO) Psych Info, (EBSCO) LGBT Life, and (ELSEVIER) Scopus. Peer-reviewed, English language, quantitative or qualitative studies that evaluated stigma or stigma-related attitudes towards individuals with DSD published after 1955 were included.

Results: Searches yielded 5566 articles after eliminating duplicates. Following title/abstract and then full-text screening, 143 full-text articles were included in the review. Results indicated that evaluating stigma was a specific study aim in a minority of publications (18.2%), with evidence for felt (112 articles), enacted (83 articles), and systemic stigma (42 articles) reported across informants and DSD conditions. Few studies utilized validated DSD-specific stigma measures. Although not mutually exclusive, 79 articles assessed stigma via interview (predominantly open-ended questions) while 68 utilized a questionnaire.

Conclusions: Findings indicate that stigma experiences are commonly reported in the literature across the spectrum of DSD conditions, predominantly using open-ended questions, with limited use of validated measures. Felt, enacted, and other types of stigma were observed across DSD populations, even though measuring stigma was rarely a study aim. Scoping review results have implications for clinical care including stigma-related screening and intervention and the need for future research using standardized assessments.

PO 42

ESPE collaborative research project: Gonadotropin Therapy to Restore Mini-puberty for Male Infants with Congenital Hypogonadotropic Hypogonadism (CHH) – A Multicenter International Endeavour to Optimize Reproductive Outcomes

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Background: Males with CHH are born with severe deficiency of gonadotropin releasing hormone (GnRH) and/or gonadotropins. Missing the first wave of hormonal activity of the HPG axis during fetal life may lead to undescended testes and micropenis at birth. In addition, absence of the second wave during "mini-puberty" will leave the number of testicular Sertoli cells insufficiently stimulated for future quantitatively normal sperm production. Sertoli cells of the testes are needed to support the meiotic divisions of spermatogonia that occur from puberty onwards under the stimulation of gonadotropin, leading to the production of elongated spermatides and enable future fertility. In the absence of mini-puberty, responses to central hormone replacement therapy during adolescence or adulthood - to induce testicular maturation and promote sperm production - are severely impaired. Factors besides deficient Sertoli cell expansion that contribute to decreased fertility in males with CHH include cryptorchidism (present in 50%) and testicular trauma caused by surgical interventions to normalize the position of maldescended testes. Currently, some clinicians treat male infants with a small penile size with a 2-4 month course of intramuscular testosterone or dihydrotestosterone (DHT) gel. Cryptorchidism is treated by orchidopexy with or without pre-treatment with nasal GnRH or with injections of human chronic gonadotropin. Whilst these therapeutic approaches may be successful in increasing penile size and further development of the scrotum, they cannot facilitate expansion and development of Sertoli cells. So far, only case reports and small descriptive patient series have been published on hormonal replacement of minipuberty in infants with CHH. These data confirm that treatment with gonadotropins or GnRH is safe, well tolerated and effective.

Aims of the project : 1.To define protocols for *best practice for therapeutic management* during mini-puberty of male infants with CHH, including *systematic review of current literature*.
2.To develop the *infrastructure to allow research into whether central hormone replacement results in improved short and long-term outcomes* regarding

- testes and penile growth
- testes descent
- normalization of Sertoli cell biomarkers
- future spermatogenesis and/or fertility following pubertal induction by central HPG-axis hormone replacement during adolescence or adulthood.

PO 43

Fifteen years of exome sequencing involving >800 cases of DSD. What have we learned?

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Background: Defining the genetic aetiology of DSD is essential not only for genetic counselling, but also to organize both knowledge-based care (medical, surgical, psychological care and fertility preservation), and individually tailored management. The widespread availability of relatively cheap and rapid genetic screening by whole exome sequencing (WES) during the last decade has revolutionized genetic testing with WES often the first line of investigation. Here, we summarise our experience of 15 years of exome sequencing on >800 cases of DSD.

Methods: WES was performed on DNA from individuals presenting with 46,XY DSD (n=592; complete or partial gonadal dysgenesis, testicular regression sequence (TRS), anorchia, rare syndromic forms or unexplained undervirilized male) or 46,XX DSD (n=235; ovarian dysgenesis, MURCS, cloacal extrophy, vaginal atresia, ovotesticular DSD and testicular DSD).

Results: WES established a genetic etiology in 52% of the 46,XY cohort (41.5 % of non-syndromic cases and 56% of syndromic cases). This included pathogenic variants in the genes *NR5A1, AR, ARX, GATA4, ZFPM2, SRD5A2, SOX9, DHX37, DMRT1, MAP3K1, DHH, HHAT, ZNRF3, WT1, LHCGR, CYP19A1, SART3 or MYRF* associated with syndromic or non-syndromic forms of 46,XY DSD. Pathogenic variants in *DHX37, SOX9* and *SEMA3E* were observed in association with anorchia and/or TRS. Likely Pathogenic or Pathogenic variants and variants of unknown significance (VUS) in genes associated with hypogonadotropic hypogonadism were relatively common in the entire 46,XY cohort. 8.6% of the total 46,XY cohort showed evidence for digenic/oligogenic causes. In the 46,XX DSD cohort the genetic diagnostic yield was only 26%. Pathogenic variants were identified in sex-determining genes (e.g. *SRY, NR2F2, WT1, RSPO1, WNT4*) or genes required for ovarian maintenance (e.g. *NOBOX, MCM8, FILGA, TP63*). A low level of Y chromosome mosaicism that was not detected by other approaches was observed in 4% of the 46,XX cohort. In the entire DSD cohort, a high percentage of pathogenic variants (approx. 70%) were novel (not been reported in the literature and are absent from public databases).

Conclusions: Over the past 15 years WES has identified many new genetic causes of DSD (e.g *ZFPM2, ZNRF3 etc*) several of which would not have been identified through the analysis of model organisms (e.g. *DHX37* or *SART3*). However, despite these advances, pathogenic variants in each gene affect only a relatively small number of individuals (e.g. *DMRT1, GATA4, ZNRF3*). Consequently, the number of genes causing DSD continue to increase without a proportionate augmentation of the overall diagnostic yield. Approximately, 50 % of all children with DSD still do not have a genetic diagnosis. Our data indicate that a significant proportion of these unexplained cases are likely due to variants, including discrete single-base pair substitutions, in regulatory elements of genes required for gonad formation.

PO 44

Long-term follow-up of self-reported life experiences in patients with CAH. Focus on psychosocial aspects, difficulties and needs during different periods in life

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Introduction: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is caused by variants in the *CYP21A2* gene and is characterized by impaired cortisol synthesis and overproduction of androgens causing prenatal virilisation of external genitalia in girls. Previous studies have shown that prenatal androgen exposure affects toy-play, interests and many aspects of life including Quality of Life (QoL). However, the consequences and psychosocial aspects for

patients with CAH may differ during different periods in life. We wanted to identify possible vulnerable time periods during childhood, adolescence and in young adults with CAH, and if there were differences related to disease severity in order to offer the best possible care and improve QoL.

Methods: 75 patients (50 women, 25 men, 23-59 y) were included. The participants were asked to retrospectively evaluate their life situation along a "life-line" from childhood onwards using a numeric rating scale (0-10). In addition, a semi-structured interview guide was used with open ended questions asking about disease burden, information, support and suggestions for improvement.

Results: The life-line scores decreased during childhood and adolescence with lowest scores in patients with SW CAH (null and I2splice). Individuals with SV CAH (I172N) and NCAH (non-classic) scored higher but with a similar pattern over time. The decline started earlier in SW CAH compared to SV CAH and NCAH. In early adulthood the life-line scores increased in all except in the null genotype group. Men had higher scores.
A majority of the participants requested more support and information during childhood due to a feeling of exclusion.

Conclusion: Patients reported decreasing life-line scores during childhood and adolescence. SW CAH had lower scores declining earlier, and less improvement as young adults compared to SV and NCAH.
Our results identify a need for improvement of care for patients with CAH when it comes to information, education about their disease and active participation in decision making when preparing young patients for their future life.
More studies are needed to clarify the psychosocial aspects, with a focus on difficulties and needs during different developmental phases and periods in life, in patients with CAH.

PO 45

Clinical profile of children with Disorders of Sex Development who desired for gender transition: a Retrospective chart study

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Background: Gender dysphoria and transition of gender are more prevalent in patients with Disorders of sex Development (DSD).

Methods: A retrospective chart review of the children and adolescents, attending the Multidisciplinary DSD (MD-DSD) clinic in a tertiary care centre in North India from January 2022 to January 2024 was done. Consent and assent were taken from the parents and the individuals to use their clinical and investigational data without revealing their identity.

Results: Of the 76 patients visiting the MD-DSD Clinic, four individuals had gender dysphoria and underwent gender transition socially. Gender dysphoria was evaluated by a psychiatrist and

informed decisions were undertaken by the multidisciplinary DSD board (comprising Paediatric Endocrinologist, Paediatric Surgeon and Psychiatrist) and the individuals and their families. Aspects considered for gender reassignment incorporated the child's and families' wishes, diagnosis, appearance of genitalia, fertility potential, options for medical and surgical intervention. Out the four, all but one expressed the desire to switch to their genotype congruent gender during puberty. These included 46XY DSD with biochemically and genetically proven 17,20 lyase deficiency, 46XY DSD reared as a girl with Partial androgen insensitivity syndrome (PAIS), who wished to transition as a male during puberty, and 46XX DSD reared as male with feminization during puberty with non-yielding laboratory and genetic investigations, who after detailed evaluation had antenatal intake of some androgenic drug. The fourth individual, being reared as female, was a case of salt wasting congenital adrenal hyperplasia (CAH) due to 21 hydroxylase deficiency, who identified and conformed to the male gender since early childhood. All the children and adolescents shall undergo sex affirmation surgery after their legal age of consent.

Conclusions: The most difficult part of management of a DSD patient is gender assignment. Those with gender dysphoria need a multidisciplinary team to help in transition of gender which should involve the individual and their families.

PO 46

Abnormal cosyntropin stimulation test results in term infants without underlying congenital adrenal hyperplasia

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Background: Current newborn screening (NBS) for 21-hydroxylase deficiency is generally accepted to have a low positive predictive value. Patients in whom confirmatory serum 17-hydroxyprogesterone (17-OHP) levels are mildly elevated often proceed to cosyntropin stimulation test (CST) per current recommendations. In our practice, we have identified patients whose CST had abnormalities in adrenal metabolites but were ultimately determined not the have congenital adrenal hyperplasia (CAH). The aim of this pilot study is to describe the cosyntropin stimulation test results in this cohort of patients.

Methods: We conducted a retrospective chart review examining 53 infants (Male: 31; Hispanic: 33) with positive NBS for CAH and elevated unstimulated 17-OHP levels who underwent cosyntropin stimulation testing during the study period of January 2018 to December 2023. We evaluated the initial 17-OHP levels, cosyntropin stimulation testing results, gestational age, and final diagnosis. A Mann-Whitney U test examined group differences in stimulated 17-hydroxypregnenolone and dehydroepiandrosterone (DHEA).

Results: Results of the CST indicated 1 infant (1.9%) had classical salt-wasting CAH, 3 infants (5.7%) had simple virilizing CAH, 16 infants (30.2%) had non-classical CAH, and 33 infants (62.3%) were determined not to have CAH. Of the 33 infants without CAH, 9 (27.2%) were term infants with abnormal CST who subsequently had a normal CAH 6 profile panel.

Of the infants without CAH, the group with abnormal CST results had a higher stimulated 17-hydroxypregnenolone (**Abnormal CST**: *n* = 9, *M* = 4743.67, median: 4398.00, range: 2668-8327; **Normal CST**: *n* = 17, *M* = 3036.82, median: 2499.00, range: 405-9360, U = 34.0, *p* = .021) and higher stimulated DHEA (**Abnormal CST**: *n* = 9, *M* = 2586.67, median: 2340.00, range: 1010-4210; **Normal CST**: *n* = 18, *M* = 1434.06, median: 1240.00, range: 149-4850, U = 33.0, *p* = .012).

Conclusions: Our pilot study describes a cohort of term infants with a transient mild abnormality of adrenal function. Based on the results presented in this study, we propose these patients may have immature 3β hydroxysteroid dehydrogenase enzyme activity. Further investigation is warranted to better delineate this patient cohort and the underlying mechanism for these findings.

PO 47

Diagnosis and management of children with Differences of sex development: trends spanning three decades

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Introduction: Differences in sex development (DSD) encompass various congenital conditions that impact sex determination and differentiation. This study describes the evolution of clinical diagnoses of DSD in children attending a tertiary pediatric center.

Methods: This retrospective cross-sectional study distinguished among children treated for DSD pre-and post-2006 DSD guidelines over three decades.

Results: The cohort included patients diagnosed with 46, XY DSD (n=87, 78.5%), 46, XX DSD (n=15, 13.5%), and chromosomal DSD (n=9, 8%) during 1990-2019. Those with 46, XY DSD presented at a younger age compared to those with 46, XX DSD (0.5±2.5 vs. 6.8±8.1 years, respectively, *P*=0.007), with a higher proportion by age 1 year (94% vs. 60%, *P*=0.001). Forty-four children were diagnosed during 1990-2006 and 67 during 2007-2019. Prenatal diagnosis increased significantly from 4.5% to 25.4%, *P*=0.004). Gonadectomy rates were 22.9% for 46, XY; 6.6% for 46, XX; and 67% for chromosomal DSD. Fewer children underwent gonadectomy during 2007-2019 vs. 1990-2006 (19.4% vs. 36.3%, *P*<0.05) and sex reassignment (1.5% vs. 13.6%, *P*<0.02).

Conclusions: There was an increase in the rate of prenatal diagnosis and a decline in the rates of gonadectomy and sex reassignment over time, reflecting a shift towards earlier, individualized multidisciplinary care facilitated by advanced diagnostics.

PO 48
From patient's urine progenitor cells to Sertoli-like cells

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Background/Introduction: Sexual development in humans relies heavily on the differentiation of gonadal cells, with Sertoli and granulosa cells playing key roles in males and females, respectively. Variations in sex development (VSD) often stem from alterations in these cell types. Understanding the underlying mechanisms of these conditions is essential for effective clinical management, especially considering that the molecular aetiology remains unknown in over 50% of VSD cases. Obtaining primary cells for study is invasive and challenging for patients, and maintaining their unique characteristics in vitro is problematic due to their short lifespan. Moreover, current cell models fail to replicate patient-specific disease mechanisms. Patient-derived cells offer an attractive alternative, allowing for personalized elucidation of disease pathophysiology. Analysing cells from multiple patients can uncover common pathways and provide insights into the origins of these disorders.

Methods: This study focuses on generating and characterizing urinary progenitor cells (UPCs), induced pluripotent stem cells (iPSCs), and Sertoli cells. UPCs were reprogrammed into iPSCs using nucleofection, a viral vector-free method. Sertoli cell differentiation was induced using a combination of signalling molecules. Qualitative characterization involved antibody staining, while quantitative analysis utilized qPCR. Markers such as CD73, CD44, CD146, OCT4, NANOG, SSEA-1, SOX2, TRA 1-81, SOX9, and Claudin 11 were selected for analysis. Sertoli cell functionality was assessed by measuring AMH expression using a bioassay developed in our laboratory.

Results: UPCs expressed CD44, CD73, CD146, OCT4, and NANOG, but not SOX2 and TRA-1-81. iPSCs expressed all stem cell markers examined. Sertoli-like cells expressed SOX9 as well as Claudin 11.

Conclusion: UPC-derived iPSCs present a promising alternative source for generating human cell models directly from patients, potentially advancing basic research in sexual development and reproductive medicine.

PO 49
An unusual case of ovotesticular DSD

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Background: The child was born with a planned caesarean section at gestational week 38. BW 3.14 kg. Perineal hypospadias, with penile length 3 cm, and bilaterally undescended testes was noted. Karyotyping showed that he had a 46,XX/47,XY + 14 (83/17% in blood), chimerism, with different levels in different tissues.

At 3 weeks of age, he had an acute left inguinal hernia repair. At the same time, a left orchidopexy was done and a biopsy of the gonad showed testicular tissue. At one year of age, he had a one stage hypospadias repair, according to Duckett. No utriculus was found at cystoscopy. He developed a mega urethra and a re-do of the hypospadias repair was done at two years of age.

Laparoscopy at 5 years of age revealed no female internal genitalia except an ovotestis on the right side, which was verified with biopsies. Right gonadectomy was done a year later.
The boy was followed through puberty and clinical examination at 15 years of age showed bilateral gynecomastia. He had normal penile growth and the left testis, palpable in a scrotal position, measured 15-20 ml. Since it had an uneven structure, an ultrasound was scheduled to exclude a tumour.

Ultrasound showed no signs of malignancy, but possible blood in the left cranial part of the scrotum. MRI was performed twice, due to movement artefacts initially, with one week interval. The first MRI showed suspected multiple cystic formations in the cranial part of the testes not seen on the second MRI that showed a scrotal hematoma.
This implicates ovulation in an ovotestis.

Conclusion: This is a boy, with ovotesticular DSD, based on chromosomal mosaicism, with a previously reported unusual karyotype and chimerism. The case illustrates that a biopsy taken at a young age showing testicular tissue, does not exclude later functional ovarian tissue in the same gonad.

PO 50
DSD team in Stockholm, 20 years of experience

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Background: The multidisciplinary DSD team at the Karolinska University hospital was formed more than 20 years ago. The core team consisting of specialists in pediatric endocrinology, pediatric urology, psychology, and nursing, aims to meet the new newborn patients and families within the first 48 hours, older patients within 2 weeks. Geneticist and pathologist are included in the diagnostic process, and the extended team includes gynecologists and andrologist.
The core team sees the patients every other year until puberty, including psychological assessment. During puberty the follow up schedule is more flexible depending on diagnosis, pubertal development and need. Upon reaching adult age, the patients are transferred to the care of the adult DSD team.

Method: An overview of patient groups, diagnostics, over the past 20 years is presented. Clinical data, karyotyping and molecular genetic diagnoses are described. Genetic investigations are performed using DSD panels.

Results: A total of 219 pediatric patients with a DSD are followed in the clinic in addition to 83 patients with CAH, girls with Turner syndrome and boys with Klinefelter syndrome.
Sex chromosomal DSD was seen in 16 %.
A total of 143 (65%**)** individuals had 46,XY karyotype. A pathogenic variant was identified in 41%, including for example SF-1, PAIS, CAIS, 5-alfareductase deficiency, 17betaHSD, FRAS1, CGD, PMDS, LHRH receptor and syndromic DSDs. Severe hypospadias with no molecular diagnosis represents 34% in this group.
Among the 219 patients a genetic diagnosis could be confirmed in 45%.

Conclusion: The multidisciplinary disciplinary team follows 219 pediatric patients with a DSD diagnosis, not including CAH or Turner syndrome with no Y chromosome.
We could confirm a genetic diagnosis in about 45% of the cases. Severe hypospadias with 46,XY and no molecular diagnosis represents 34% despite using extensive genetic investigation including DSD panels.

PO 51
How can psychological effects of changes in surgical praxis be evaluated?

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Background: Early genital surgery has been questioned and less surgery is now performed in girls with CAH in many centers . The psychological outcome of this has not been extensively studied and it is therefore important to evaluate the effect of this change in clinical practice. How are patients and families affected psychologically? How do girls with CAH perceive growing up with an enlarged clitoris? How is body image and self-esteem affected?

Method: In a national collaboration we take advantage of the variations in surgical practice between different teams in Sweden. We compare girls who underwent early surgery and girls with the same degree of prenatal virilization and CYP21A2 genotype but who did not undergo surgery. Boys with the same CYP21A2 genotypes are included to study the effect of CAH per se.

Parents are asked about their own situation: semi structured interview, worries for their child and the child's future. Depression, Anxiety, & Stress Scale, Parenting Stress Index, Short Form, Parent Protection Scale Perceived Child Vulnerability, Support and Resources interview, Stigma Scale, Decisional Regret Scale,
Questionnaires to the parents regarding the children: Adjustment Child Behaviour Checklist, Gendered activities Preschool Activities Inventory,

Questionnaires to the children: Children's Depression Inventory, Self-esteem, Harter Pictorial Scale, Body image Scale, Draw a person Self-perception identity.
Questionnaires to the adolescents and young adults: semi-structured interview, Depression, Anxiety & Stress Scale, HADS inventory, Body image Scale, Self-esteem, Short Form, Stigma Scale, semi-structured interview, worries for the future.

The assessment of genital virilization is based on Prader score at birth and how visible the clitoris is when the child is standing up and graded as clearly visible; partly visible; or not at all. Parents and child report perception of the visibility of the child's clitoris (clearly visible; partly visible; or not at all)
A study team from the Karolinska university hospital assesses all patients and families together with the local pediatric endocrinologist to ensure consistency in data collection.
Data collection is ongoing.

Conclusion: We urge other centers to perform similar studies to bring clarity and answers to these important questions, in the near future.

PO 52

Development of an educational and counselling concept as a guideline for psychosocial support of persons with Difference of Sex Development (DSD)

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Introduction: The German guideline on variants of sex development (DSD) recommends interdisciplinary care in a centre that addresses both medical and psychosocial aspects of the respective diagnosis and phase of life. In particular, the need for psychosocial support is emphasised. However, the specific topics and content of adequate medical and psychosocial support have not yet been formulated. The structured education and counselling concept presented here, which was developed by a working group of the BMG-funded project "DSDCare" (2020-2023), closes this gap.

Methodology: An interdisciplinary working group consisting of seven German clinical centers and two self-help organizations was formed to develop recommendations for psychosocial support. The relevant psychosocial aspects for each diagnosis in the respective developmental phase were compiled, discursively validated and agreed upon, taking into account the specialist literature and in exchange with other self-help experts and specialists from the centers' interdisciplinary teams.

Results: The DSD diagnoses were grouped according to common psychosocial aspects.
The result is a comprehensive concept for educating and advising people with DSD and their families. This includes an introduction to the topic of attitudes, a presentation of the medical background, information on informed consent and the relevant psychosocial aspects for each phase of life, divided into a) general DSD-independent, b) general DSD-specific and c) diagnosis-specific topics. The structure provides a quick overview of general information and presents DSD and diagnosis-specific topics at different ages throughout the life course.

Conclusions: Supporting people with DSD is a complex challenge for psychosocial and medical professionals. The education and counselling concept serves to familiarize and deepen existing knowledge about DSD and as a roadmap for patient-centered counselling and empowerment. The compendium will be used, evaluated and adapted over time to reflect experiences as well as ongoing social and medical changes.

PO 53

Rare Cause of Unilateral Inguinal Hernia in Neonate- Transverse Testicular Ectopia with Persistent Müllerian Duct Syndrome

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Background: Assessing newborn with disorders of sexual development (DSD) promptly is crucial for ensuring proper medical intervention and psychological support. Transverse testicular ectopia (TTE) with persistent Müllerian duct syndromes (PMDS) is a rare congenital anomaly that can present as inguinal hernia in neonatal period that requires a multidisciplinary approach for optimal patient care. We present a case of neonate with TTE and PMDS presenting as unilateral inguinal hernia.

Case Report: Term baby born at 39+2 GA was noted to have atypical genitalia at birth, right palpable testis in inguinal region and left was impalpable (EMS was 10). The rest of genital appearance was normal male. A three-month surgical review was planned. However, the child presented to emergency department with scrotal swelling and change in colour. The left scrotum was empty, the right testicle was found in the groin, and a right inguinal hernia was noted. Emergency open right herniotomy was performed. The right testis was noted to be attached to the Müllerian remnant via the vas vessels and left testis was in vessels also identified in the right hernia. All structures returned to abdomen and prompt referral to DSD team was made. Investigation undertaking by DSD team including , FISH (46 XY signal pattern with the presence of the SRY gene on chromosome Y) , anti Müllerian hormone AMH was level low (less than 0.2 pmol/L, normal reference range 140-1130.9 pmol/L) and genetic testing (DSD gene panel, R146) showed 2 pathogenic variant in AMH c208 dup *p*.(Leu70 Profs Ter11); c343_344del *p*. (Leu115Thrfs Ter58) consistent with genetic diagnosis of persistent mullerian duct syndrome and necessary surgical intervention was planned.

Conclusions: TTE with PMDS is a rare condition, which has to be suspected in children, especially neonates, who present with inguinal hernia on one side and cryptorchidism on the other

side. Timely identification and a comprehensive, multidisciplinary approach are imperative for effective management of this condition, promoting favourable outcomes and holistic support for patients and their families.

PO 54
Myelin regulatory factor: an underreported gene associated with syndromic DSD

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Background: The myelin regulatory factor (*MYRF*) gene encodes a transcription factor that plays an important role in CNS, cardiac, pulmonary, urogenital, and diaphragm development. Pathogenic variants have been reported in association with malformations in these systems, often classified as MYRF-related cardiac urogenital syndrome (MYRF-CUGS). The association of *MYRF* mutations with DSD was first described in 2019 (1). Since then, there is growing literature reporting this association, with a broad spectrum of GU abnormalities (1-5). Short stature, thyroid fibrosis, and intestinal malformations have also been reported.

Methods: This is a case report. A literature and chart review were performed.

Results: We describe a 15-year-old 46 XY individual who was adopted from China at age two years. At the time of adoption, the patient was noted to have a phallic stretched length of 2 cm with a 0.75 cm diameter, a urethra and vaginal opening, non-fused labioscrotal folds, and non-palpable gonads. An exploratory laparoscopy revealed a dysgenetic right testis with an ipsilateral vas deferens, a streak gonad on the left, and a double vagina. The child was later diagnosed with short stature, intestinal malrotation, Meckel's diverticulum, and hyperopia. There have been no cardiac, pulmonary, or CNS anomalies identified to date. A DSD gene panel (GeneDx, 2019) including 19 genes was negative. Given the presence of hyperopia, intestinal malrotation, Meckel's diverticulum, and short stature, in association with GU anomalies, a syndromic aetiology was suspected. Whole Exome Sequencing (WES) revealed a heterozygous pathogenic non-sense variant in *MYRF* (p.Arg981Ter).

Conclusion: Pathogenic variants in *MYRF* should be considered in the differential diagnosis for individuals with a DSD. Many commercially available DSD panels do not include *MYRF*, therefore recognizing comorbidities should prompt targeted gene testing or genome sequencing. Additionally, to our knowledge, this is the second report of vaginal duplication in a patient with a *MYRF* mutation (5), thus, this anatomical finding should be recognized as one of the possible GU abnormalities in patients with MYRF-CUGS.

PO 55
Gonadal function and outcome in 46, XX testicular/ovotesticular DSD – preliminary data from the I-DSD Registry study

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Background: Testicular and ovo-testicular 46,XX-DSD are very rare conditions that have a variable presentation and often pose challenging questions regarding long-term outcome of gonadal function.

Methods: Eligible cases were identified in the I-DSD Registry and centres were asked to update the clinical dataset to their last available assessment. The cases were categorised by assigned sex and age categories. Elevated and depressed hormonal levels were defined as those above the 97.5th centile and below the 2.5th centile, respectively, for reference range.

Results: In total, 97 cases were identified from 21 centres. Of these, 19 centres with 57 cases (25 T-DSD, 32 OT-DSD) were willing to participate. The median (range) age at diagnosis (n,18) was 5 months (birth,35y). At birth, 38 cases were assigned males, 17 females and 2 were not assigned. In the first two years of life, 3 out of 7 male cases had an elevated FSH while in adolescence 2 out of 3 were elevated. For female cases, elevated FSH values were observed in the first two years of life in 2 out of 4 cases. In the first two years of life 3 out of 7 male cases had an elevated LH while in adolescence 2 out of 3 patients had elevated levels. AMH in all male cases up to 11 years (n,11) was below the 50th centile for males and in 7 (64%) of these was below the 2.5th centile. In 2 female cases (n,4), AMH was above the female reference range before 1 year of life. In those over 14 year-old where information was available, spontaneous puberty was observed in 3 out of 10 male cases and in 1 out of 2 females. In male cases, the stretched penile length (SPL) was <2.5th centile in 8 out of 9 infants (88%) and in 6 out of 9 adolescents (67%), respectively. In the post-pubertal period, 6 out of 12 (50%) had a SPL <50th centile.

Conclusions: In 46,XX testicular and ovo-testicular DSD, biochemical and physical signs of gonadal insufficiency are frequently present in early infancy and late adolescence irrespective of assigned sex.

PO 56
Development of quality indicators for health care in Differences of Sex Development (DSD)

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Introduction: DSD is an umbrella term for a large number of rare conditions that affect sex development and require lifelong holistic health care - preferably in specialised centres. Limited data are available on the quality of care for individuals with DSD. We describe the development of quality indicators (QI) to assess healthcare quality in this field.

Methods: Ten clinical DSD centres and two self-advocacy groups in Germany participating in the DSD Care project were involved in the development of the QI and a benchmarking system. Following Donabedian's model, the aim was to develop QI to assess the most relevant aspects of structure, process, and outcome quality. Therefore, we analysed guidelines and recommendations, carried out a literature review, and conducted qualitative interviews with key stakeholders in the field of DSD and patients or their carers. QI were discussed in a multi-stage systematic consensus process and assessed in terms of their relevance, feasibility, and practicability.

Results: Starting with 86 preliminary QI based on guideline statements, literature review, and qualitative interviews the process resulted in a set of 38 QI (23 structure, seven process, and eight outcome quality). These QI were found to be relevant, feasible and practical and are considered suitable for the evaluation of quality of healthcare in DSD.

Conclusions: We have developed and adopted a set of 38 QI that consider a wide range of perspectives on the quality of care for people with DSD and their families. They are now used for annual quality benchmarking in the participating specialised centres in Germany.

PO 57

Learning from the past to build the future: Evolution of the Differences of Sex Development-Translational Research Network (DSD-TRN)

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Background/Aims: The Differences of Sex Development-Translational Research Network (DSD-TRN) comprises a 13-year consortium of 17 academic and medical centers and patient advocacy representation across the United States that seeks to deliver evidence to optimize and standardize health care and outcomes for individuals with DSD. This project aimed to evaluate the network's strengths, barriers to overcome, and inform strategies, essential for guiding its future.

Methods: All DSD-TRN members (n=162) were invited to complete an online survey, following a two-day in-person planning workshop of representatives from each participating site and external advisors. Respondents were asked what was working well and what they would like changed in the existing DSD-TRN: 1) clinical registry and 2) organizational structure. Responses to open-ended questions were qualitatively coded into themes.

Results: 105 (65%) DSD-TRN members from 17 centers began the survey and 72 completed it (overall response rate: 44%). Regarding the DSD-TRN registry, respondents commended the quantity of data in the registry, improving standardization of care, collaborative relationships formed, and valuable educational activities. However, they criticized the burden of (extensive) data collection, entry and accessibility, and related lack of support and funding, with questionable direct benefit to patients. Proposed strategies involved streamlining and simplifying registry data, while increasing the quality of data in areas like gonadal pathology. Regarding organizational structure, respondents commended the leadership (expertise and engagement), multidisciplinary teamwork (with regular communication and collaboration), and a mutual commitment around an important cause. Conversely, some criticized aspects of leadership and hierarchical governance, and dysfunction and disengagement amongst some team members. Proposed strategies involved

the need for leadership to understand and address the issues raised, and structural reorganization to enhance leadership and engagement opportunities around clear shared goals and commitments. Respondents favoured matrix governance (authority and responsibility distributed across multiple dimensions), followed by a hierarchical organizational structure, over alternative governance models.

Conclusion: DSD-TRN stakeholders identified strengths, weaknesses, and potential strategies in striking the balance between a healthy and unhealthy learning and research collaborative, essential for guiding next steps to optimize and advance standard of care, research, education and advocacy in DSD.

PO 58

Needs and research priorities: Perspectives of the Differences of Sex Development-Translational Research Network (DSD-TRN)

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Background/Aims: The Differences of Sex Development-Translational Research Network (DSD-TRN) comprises a 13-year consortium of 17 academic and medical centers and patient advocacy representation across the United States that seeks to deliver evidence to optimize and standardize health care and outcomes for individuals with DSD. This project aimed to evaluate DSD-TRN members' perspectives regarding areas of need, to inform and prioritize areas for research, essential for guiding the network's future.

Methods: Representatives from each participating DSD-TRN site and external advisors attended a two-day in-person workshop, focusing on the network's future. Following this workshop, all DSD-TRN members (n=162) were invited to complete an online survey seeking their perspectives on 1) overarching vision and broad objectives, 2) needs and gaps, and 3) priority research areas. Responses to open-ended questions were qualitatively coded into themes and priorities identified at the workshop were quantitatively ranked.

Results: 105 (65%) DSD-TRN members from 17 centers began the survey and 72 completed it (overall response rate: 44%). Most endorsed an overarching vision around improving lives - or

thriving - of individuals with DSD. There was consensus in naming three broad objectives: standardizing and optimizing clinical care, research, and education and training.

Respondents identified wide-ranging areas of need and gaps in care, including long-term outcomes (physical, psychosocial, sexual health, gender, etc.) for different conditions and resulting from different management decisions; support for decision-making; dearth of adult providers; and a call for education at multiple levels. Respondents ranked adult care, education of families and providers, and improving and standardizing gonadal pathology evaluation as the greatest areas of need.

Priorities for the research collaborative network and clinical registry included longitudinal natural history and cohort studies incorporating standardized data collection, a pathology core, genetic biobanking, and emphasizing patient-reported and center outcomes. Other ideas included dissemination and implementation of shared decision-making, and clinical trials. Research around patient decision aids, long-term surgery outcomes, and gonadal cancer risk ranked highest.

Conclusion: The DSD-TRN provides a platform to address unmet needs and improve clinical care through research, education, and advocacy, for those living with DSD.

PO 59

Functional validation of a novel *PBX1* missense variant in a girl with XY sex reversal

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Background: The pre-B cell leukaemia transcription factor encoded by *PBX1* is expressed throughout human embryonic stages. Accumulating cases with differences of sex development (DSDs) have been reported harbouring *PBX1* variants, suggesting a yet elusive role of PBX1 in the gonadal differentiation and sexual development processes.

Methods: We present a syndromic case of 46,XY DSD with sex reversal and gonadal dysgenesis, where whole-exome sequencing analysis found a novel missense variant, c.710G>C (p.R237T), in the highly conserved TALE domain of *PBX1*. We generated stable, inducible Flp-In T-REx™ HEK293 cell lines transfected with plasmids carrying either wild-type (WT) or mutant *PBX1*.

Results: Functional analysis showed that this variant residing within the nuclear localization sequence reduced protein stability and hampered nuclear translocation. The proliferation suppression through the induced expression of Flp-In *PBX1* p.R237T was less prominent than that of Flp-In *PBX1* WT, while the cell adhesion was not different. RNA sequencing analysis found several differentially expressed genes (DEGs) between Flp-In HEK293 *PBX1* WT and p.R237T cells,

with three DSD-related genes upregulated (*MAP3K4* and *EMX2*) and two genes downregulated (*KISS1R* and *HOXA13*).

Conclusions: Our results demonstrated the deleterious functional consequences of this genetic variant. Further research is needed to dwell into the mechanism of *PBX1* in sex determination and development.

PO 60
Histopathological findings of gonads in subjects with differences of sex development

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Background: Multidisciplinary treatment of Differences of Sex Development (DSD) poses significant challenges, including determining raising gender, adapting external genitalia to the assigned or reassigned sex, preserving gonadal function, and mitigating the risk of malignancy. This study aims to identify key histopathological findings in gonads subjected to biopsy or resection at the Pediatric Urology Sector of the Pediatric Surgery Discipline, Escola Paulista de Medicina/Federal University of São Paulo (UNIFESP)/Brazil.

Methods: A retrospective assessment of medical records was performed for patients with DSD who underwent gonadal biopsy or gonadectomy between 1991 and 2023.

Results: Sixty-three patients were assessed, including 11 cases of complete androgen insensitivity (CAIS), 7 patients with partial androgen insensitivity (PAIS), 11 patients with gonadal dysgenesis (GD), 6 patients with ovotesticular DSD (OT-DSD), 18 cases of 46 XY DSD without a definitive diagnosis, and 10 patients with other DSD. Fifteen gonads were biopsied (mean age 5.80 years), and 93 were resected (mean age 6.83 years). All CAIS and PAIS cases were raised as female and presented prepubertal testes, except for one CAIS patient who developed a gonadoblastoma discovered during gonadectomy at age 17. Among GD cases (5 raised as female and 5 as male), 10 cases underwent gonadectomy, and one patient underwent unilateral biopsy, revealing 9 prepubertal testes, 5 streak gonads, and 1 gonadoblastoma in dysgerminomatous progression. In OT-DSD cases (4 raised as male and 2 as female), 3 gonads were biopsied and 10 were resected, showing 1 prepubertal testis, 4 ovotestes, 2 ovaries, and 1 testis with peritubular atrophy and fibrosis associated with Leydig cell hyperplasia. The majority of gonads biopsied in patients with 46XY DSD and other DSD exhibited prepubertal testes.

Conclusions: The decision to preserve or extirpate gonads in DSD has changed in the last 5 years but remains a subject of debate. Molecular studies are currently unable to define malignancy risks in these gonads reliably. Therefore, surgical decisions should involve multidisciplinary discussions with caregivers and patients, considering histopathological findings, tumour risk, raising gender, gonadal location, and fertility.

PO 61

Clinical and surgical challenges in ovotesticular differences of sex development 46,XX: management strategies and considerations

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Background: Ovotesticular differences of sex development (OT-DSD) is a rare condition characterized by histologic demonstration of ovarian and testicular tissue in the same individuals with incidence reports varying from 1:100.000.000 - 1:100.000 live births or in 2-10% of all DSD. This study aims to present two clinical cases with a late diagnosis and discuss the challenges in the clinical-surgical management of OT-DSD.

Methods: Two clinical cases with a late diagnosis of OT-DSD were presented.

Results: Two patients, raised as males, were diagnosed late with OT-DSD and presented with karyotype 46,XX, atypical genitalia, and gynecomastia. The patients underwent different gonadal surgical clinical management. Notably, the resolution of gynecomastia occurred in both the patient who underwent gonadectomy and the one who underwent hormonal blockade for gonadal preservation. There is a lack of long-term outcome data to guide clinical practice for OT-DSD. Decisions regarding the clinical and surgical management of the gonads in patients with OT-DSD pose significant challenges. Endocrine function is variable and may be normal or altered due to gonadal failure. Studies indicate that unless bilateral gonadectomy is performed in childhood, the onset of puberty may be typical. The risk for gonadal tumours in OT-DSD is considered low (2.5-4%) compared to other DSD. Gonadectomy, due to tumour risk, deviations of Mullerian structures, and decreased sexual activity arising from dissatisfaction with appearance or genital function, are the primary risk factors for infertility in these cases. New assisted technologies however, may offer alternative options for fertility in these individuals, including unconventional possibilities for gonadal preservation. Therefore, delaying any definitive procedure until these individuals can actively participate in the decision-making process regarding the clinical and surgical management of their gonads is desirable and should be considered.

Conclusions: OT-DDS is a clinical condition with significant phenotypic variability, posing challenges in decisions related to gender assignment and advice regarding genital and gonadal surgery. The concept of watchful waiting, allowing the affected individuals to participate in decision-making, has been extensively discussed in reference centers.

PO62

Mayer-Rokitansky-Kuster-Hauser syndrome: experience from a gynecological outpatient clinic at a university in Brazil

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Background: Mayer-Rokitansky-Kuster-Hauser Syndrome (MRKH) is characterized as a difference in sex development that affects the formation of the Mullerian ducts, corresponding to 90% of cases of vaginal agenesis. This condition occurs in about 1 in every 4 to 5 thousand live births and is the second most common cause of primary amenorrhea. The aim of this study was to describe epidemiological characteristics of patients with MRKH treated at Genital Malformations Sector at EPM-UNIFESP and compare surgical and non-surgical treatment.

Methods: A retrospective assessment of medical records was performed for patients with MRKH treated at Genital Malformations Sector at EPM-UNIFESP from January 2010 to February 2020.

Results: Of the 169 patients studied, 83 were diagnosed with MRKH. Age at first care ranged from 15 to 33 years old (highest prevalence at 17 years old). The majority of patients were referred from other sectors of the same institution and 19.28% obtained information about the outpatient clinic through social networks. Complaints at the first consultation were a previous diagnosis of congenital malformation, followed by amenorrhea, short or closed vagina and dyspareunia. 58% of patients underwent vaginal dilation and 22% underwent surgical treatment. The surgery provides an immediate increase in vaginal length, followed by a slight reduction after 6 months. The average final vaginal length of patients undergoing surgical treatment and vaginal dilation were 7.07 and 6.34 cm, respectively. The average time to initiate sexual activity was shorter among patients who underwent dilation. Among patients who had not had sexual intercourse prior to treatment, 78% of those who underwent surgery and 63% of those who underwent dilation reported starting their sexual life.

Conclusions: The study demonstrates the preference for dilation treatment in a tertiary university service, as well as similar results compared to surgery. Adequate training and qualification of professionals to care for MRKH can allow patients to receive adequate treatment, avoiding costs and complication rates related to surgery.

PO 63

Surgical and hormonal interventions: The question of children's capacity to consent - Two case reports

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Background: Since 2021, the German "Law for the Protection of Children with Variations of sex development" has been in force. Accordingly, parents do not have the right to consent to treatment that aims to adapt the child's physical appearance to that of a male or female. The aim is to make decisions based on the best interests of the child and, if possible, to wait until the child is capable of giving consent.

Methods: Presented are the course and treatment of two cases with special attention to the child's ability to give consent.
Results: A 13-year-old adolescent who presented to us with a surgical request for penoscrotal hypospadias after four previous operations elsewhere had resulted in fistula formation. Catching up missing diagnostics revealed a 46.XX DSD with residual mullerian ducts. Despite repeated discussions about the diagnosis and reasons for postponing the operation, there seems to be little understanding among parents and child. Peer counselling was suggested but not conducted. To date, it cannot be assumed that the adolescent is in a position to give informed consent.

An 11-year-old child with 46.XX CAH and prenatal virilisation (PraderV), growing up as a boy. The family attended a training program on CAH, learned about the diagnosis, inner genitalia at 46.XX, fertility aspects and physiological changes during puberty. So far, the child has shown no recognisable interest in questions of body development and gender identity, so there has been no opportunity to find out his wishes. Now the first signs of breast development are appearing. The administration of GnRH analogues is considered to suppress further female pubertal development and allow time to discuss and evaluate options.

Conclusions: Assessing the capacity of the child with DSD to give consent is essential for medical interventions (hormonal, surgical) and is a particular challenge during the course of treatment. If the capacity to consent is uncertain, it is difficult to facilitate pubertal development at the physiological age of puberty. Taking time to get to know the child and their family culture, repeated age-appropriate medical information, peer support, psychosocial care, and sensitive encouragement for discussion and reflection appear to be essential.

PO 64

Spatially resolved, whole transcriptome analysis of a pubertal CAIS gonadal tissue

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Background: Androgens play an important role in gonadal development in mammals. Congenitally defective androgen signalling in gonads of adolescents and young adults with CAIS and *CYP17A1* deficiency is associated with exclusive expression of HSD17B3 in Sertoli cells and not in Leydig cells, an expression pattern that is similar to foetal mouse testis, suggesting that the differentiation of both Leydig and Sertoli cells might be affected due to defective androgen signalling in both conditions. In this pilot study, we further characterize Leydig and Sertoli cell differentiation in gonads from adolescents and young adults with CAIS.

Methods: To further assess Leydig and Sertoli cell differentiation in CAIS, one gonad from an adolescent with CAIS (13.7 years old) was profiled with GeoMx digital spatial profiler to characterize 20 regions comprising either Leydig or Sertoli cells. The expression profiles were validated by immunohistochemistry, immunofluorescence and multiplex fluorescent *in situ* hybridization assays in a small cohort of gonads from young adults with CAIS (13.7-19.6 years old) compared to a testis from an adult control (28 years old).

Results: Compared to the control testis, *HSD17B3* mRNA was exclusively detected in Sertoli cells and not in Leydig cells in pubertal and young adult CAIS gonads, which matches the protein expression we reported previously. *GJA1* coding for one of the proteins of the blood-testis barrier in the human testis was expressed in Sertoli cells lower than in Leydig cells as mRNA and was not expressed as protein in Sertoli cells in CAIS gonads.

Conclusions: The expression pattern of *HSD17B3* mRNA in CAIS gonads is identical to the protein expression previously reported in these patients and supports the association of defective androgen signalling with the differentiation of Leydig cells in these patients. Loss of *GJA1* expression is also in line with a previous immunohistochemical assay and suggests defective androgen signalling in these patients might be implicated indirectly in Sertoli cell maturation and blood-testis barrier formation, possibly contributing to germ cell loss in CAIS. Taken together, the results emphasise that androgen signalling might be essential for Leydig and Sertoli cell differentiation for proper steroidogenesis and spermatogenesis in human testis.

PO 65
Spectrum of DSD managed by a newly-established multidisciplinary team in Hong Kong

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Background: Children with differences of sex development (DSD) represent a complex population with wide range of psychosocial and medical needs. Management by a multi-disciplinary team (MDT) is thus essential to coordinate services and optimize care. The Hong Kong Children's

Hospital has established a MDT for DSD since 2020, giving patients simultaneous access to care from various professionals. Herein, we report the spectrum of patients managed by this MDT and evaluated the yield of molecular genetic test. Among patients with 46XY DSD, we hypothesized that the external masculinization score (EMS) is inversely associated with likelihood of identifying a pathogenic genetic variant.

Methods: Patients with DSD followed up in our joint clinic between December 2020 to February 2024 were evaluated in terms of their demographics and genetic diagnosis. EMS scores (0-12) were assigned to all patients with 46XY DSD according to findings from initial physical examination.

Results: Forty-five patients (mean age: 5.6 years, 80% Chinese) were identified, out of which 40 (88.9%) were classified as 46XY DSD, 2 (4.4%) as 46XX DSD and 3 (6.7%) as sex chromosome DSD. Forty-one patients (91.1%) underwent genetic testing either with whole exome sequencing or next generation sequencing with targeted DSD panel. Among patients with 46XY DSD, pathogenic variants were identified in 9 (22.5%). The EMS of this group of patients (median 3, IQR 4) was significantly lower than those who did not have a genetic cause found (median 8.75, IQR 3) ($p < 0.005$). Of these, 3 patients were reared as female, including one with androgen insensitivity syndrome (EMS 0), one with pathogenic variant in *NR5A1* gene (EMS 1) and one with 17b-hydroxysteriod dehydrogenase deficiency (EMS 2). Patients were seen by specialists from various disciplines in their first attendance, with subsequent follow-up arranged according to individual needs.

Conclusion: 46XY DSD constituted the majority of cases in our cohort of children with DSD. Low EMS score may indicate higher likelihood of identifying a genetic diagnosis, although definitive diagnosis remains elusive in over 70% of our patients.

PO 66

Development of the I-HH registry to develop best practice management for hypogonadotropic hypogonadism

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Background: For rare diseases such as hypogonadotropic hypogonadism, a key step in improving understanding is collection of geographically widespread data. Standardised and accessible international data collection can facilitate development of best practice, with implementation and monitoring of outcomes. Clinical priorities for patients and carers include improving accuracy of childhood diagnosis, tailored hormonal therapies at infancy and puberty and optimising future fertility. Our group has led establishment of the first UK protocol for gonadotropin replacement of puberty in males with hypogonadotropic hypogonadism. Following this, we are developing a new electronic registry of hypogonadotropic hypogonadism (I-HH registry, 4th module in the SDM registries series), due to go-live in 2024.

Methods and Anticipated Outputs: The new I-HH module has been developed with input from international stakeholders and clinical experts, to be incorporated within the existing SDM registries. Iterative testing of the developing module is ongoing and will be piloted before going live. Prior to active collection of data within I-HH, a project to review data from patients registered with hypogonadotropic hypogonadism within the existing I-DSD Registries (n=32, 29/32 male, 13/32 anosmic) has been approved. This will serve as a pilot study, to assess current global practice (14 centres, 9 countries) in management of this condition, optimise I-HH and facilitate widespread implementation. Future analyses within I-HH will describe variation in the practice of pubertal induction internationally, including therapeutic regimen, age of pubertal initiation, monitoring practices and response to therapy. Peak height velocity will be used as a surrogate marker of puberty, utilising Superimposition by Translation and Rotation (SITAR) growth curve analysis, to facilitate collection of retrospective data. This database is key also to recording long-term outcomes for young patients, particularly pertaining to fertility in response to therapeutic interventions in childhood.

Summary: I-HH will be able to connect centres worldwide to assess clinical management and health status of patients with this condition, facilitating prospective longitudinal data collection. The analysis of these initial pilot data held in I-DSD will allow benchmarking of current practice, define the impact of differing management protocols, and identify specific unmet needs to support future research, including that using the I-HH registry.

PO 67
Beyond Binary: An interesting case of Differences in sex development (DSD)

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Background: Differences in sex development (DSD) are congenital conditions with atypical development of chromosomal, gonadal, or anatomical sex. Mixed gonadal dysgenesis (MGD) is a rare disorder of sexual differentiation resulting from asymmetrical gonadal development. These individuals may appear phenotypically males or females. The usual cytogenetic finding is a mosaicism of XO/XY. Here, we present a compelling case of MGD who presented in newborn period with atypical genitalia and nonpalpable gonads, possessing a rare karyotype of 47,XYY.

Case report: A 4-year-old child, raised as a girl, presented to us with atypical genitalia since birth. There was no history of failure to thrive or salt-losing crisis. On examination, anthropometric parameters were appropriate for age and vitals were normal. Head to toe examination revealed no dysmorphism or hyperpigmentation. External genitalia score was 4 with a Prader score of 2. Pelvic ultrasound revealed an infantile uterus with no visualized gonads. Synacthen stimulation test was normal. Karyotype analysed in 20 cells revealed 47,XYY and presence of two Y chromosomes was further confirmed by FISH. Investigations revealed FSH and LH of 2.98 mIU/ml and 0.02 mIU/ml, respectively with total testosterone of 6.3 ng/dl and estradiol of 22.4pg/ml. Laparoscopic examination showed bilateral intra-abdominal gonads with left being streaky and hypoplastic uterus. Genitoscopy showed a normal vagina and cervix, while cystoscopy revealed normal urethra and urinary bladder. Gonadal biopsy showed immature testicular tissue with intratubular calcification and features of gonadoblastoma on the right with ovarian stroma alone on the left. Multidisciplinary counselling was provided, and parents decided to rear the child as a female. Hence, bilateral gonadectomy and clitoroplasty was performed at 6 years of age. Hormone replacement and puberty initiation was started at 12 years of age following which she attained menarche after two years. Currently she is 17 years old and is on regular follow up.

Conclusions: Ongoing care for the child with mixed gonadal dysgenesis includes regular monitoring every 6 months for growth, puberty, and health, along with hormone replacement therapy. Psychological support, educational assistance and fertility preservation should be considered.

PO 68

Evidence for *NR2F2*/COUP-TFII involvement in human testis development and 46,XY DSD

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Background: *NR2F2* encodes COUP-TFII, an orphan nuclear receptor that is involved in many essential processes such as angiogenesis, organogenesis, and cell fate determination and

differentiation during embryonic development. It is also required for the development of steroidogenic lineages of the murine fetal testes and ovaries. Pathogenic variants in human *NR2F2* are associated with testis formation in 46,XX individuals, however, the function of NR2F2 in the human testis is unknown.

Methods: Whole exome sequencing was performed on DNA from a 46,XY under-masculinized boy with primary hypogonadism. *In silico* analysis, protein stability, subcellular localization and physical interaction of wild-type and mutant NR2F2 protein with NR5A1 was performed. The effects of mutant NR2F2 on the transactivation of NR5A1 on target promoters was defined.

Results: A *de novo* heterozygous, p.Arg246His variant in *NR2F2* was identified in a 46,XY under-masculinized boy with primary hypogonadism. The variant, located within the ligand-binding domain, is predicted to be highly damaging. Functional studies indicated that the mutation does not impact the protein stability nor the protein subcellular localization. NR5A1, a related nuclear receptor that is a key factor in gonad formation and function, is known to physically interact with COUP-TFII to regulate gene expression. The mutant protein did not affect the physical interaction with NR5A1. However, *in-vitro* assays demonstrated that the mutant protein significantly loses the inhibitory effect on NR5A1-mediated activation of both the *LHB* and *INSL3* promoters.

Conclusions: The data support a role for *NR2F2* in human testis formation and genomic variants involving NR2F2 as a rare cause of 46,XY DSD. This expands the number of genes that function in both male and female sex development, which was originally thought to be regulated by two entirely different gene regulatory networks.

PO 69
Gender Diversity in Intersex and People with Variations in Sex Characteristics

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Historical underrepresentation of LGBTQIA+ individuals in medical research has led to critical knowledge gaps regarding health disparities. To address this, data collection practices are expanding to capture of sex, gender identity, and sexual orientation information (SOGI), particularly in Electronic Medical Records and Laboratory Information Systems. Nonetheless, these efforts often miss intersex individuals and those with variations in sex characteristics (VSCI). The lack of comprehensive VSCI data hinders our ability to improve healthcare for these underserved and underrepresented communities.

The objective of this study was to investigate available data pertaining to gender identity within specific VSCI types. We searched databases like PubMed and Google Scholar using keywords like "gender identity" and specific VSCI terms. Additionally, we analysed data from the 2022 LGBTQ Pennsylvania Health Needs Assessment Survey ("PA survey").

Our findings revealed that a significant portion (up to 20%) of individuals with Müllerian agenesis, Mayer-Rokitansky-Küster-Hauser syndrome, Turner syndrome, and Klinefelter syndrome identify outside the gender binary. Furthermore, the PA survey identified 3% of respondents as intersex, with a notable portion (30%) identifying with non-binary genders. Strikingly, 96% of respondents within the VSCI population in the PA survey identified with non-straight sexual orientations.

This study underscores the growing recognition of gender diversity within the VSCI community. It emphasizes the importance of incorporating SOGI data collection in healthcare settings for VSCI individuals. Furthermore, our findings also reveal significant gaps in current data collection practices, particularly regarding SOGI information for specific VSCI types. Developing targeted and inclusive data collection tools is crucial to ensure comprehensive representation of the VSCI population. This will ultimately allow us to better understand the unique health needs of individuals across the VSCI spectrum and improve healthcare outcomes for these specific communities.

PO 70

Molecular profiling of 46, XY Disorders of Sex Development by Next Generation Sequencing in an Indian cohort

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Background: XY differences in sex development (DSD) are a highly heterogeneous group of conditions, where the molecular aetiology remains unknown in a large number of patients after application of massive parallel sequencing techniques. The yield of genetic testing is variable, ranging from 13% in the clinical setting to 50% in the research setting. Genotypic data are necessary to devise staged and cost-effective strategies for recommendations regarding appropriate genetic testing. Only few South East Asian studies have described the molecular profile of patients with XY DSD, posing the need to urgently genotype these less well-studied cohorts.

Methods: 150 patients with XY DSD were subject to a stepwise approach wherein those with clinical suspicion of 5 alpha reductase deficiency or partial androgen insensitivity syndrome (PAIS) underwent sequential testing for variants in *SRD5A2* and *AR* genes (published data). Patients with no variants identified in the aforementioned genes, and those with other suspected aetiologies were subjected to next generation sequencing (NGS) using a targeted panel of 155 genes.

Results: Of 150 patients enrolled in the study, 75 had a clinical diagnosis of 5 alpha reductase deficiency or PAIS. When testing for variants in *SRD5A2* and *AR* was done sequentially, 25 patients harboured disease causing variants in the *SRD5A2* gene, and 19 patients harboured disease causing variants in the *AR* gene. Of the remaining 106 patients who were subjected to NGS, 46 patients harboured a total of 52 variants (12 pathogenic, 12 likely pathogenic, and 28 variants of uncertain significance) in 28 genes. The most common provisional diagnosis was partial gonadal

dysgenesis (PGD) (n=19, 41.3%), and the most commonly affected gene was *NR5A1* (n=7, 13.5%). The overall yield of genetic testing in our study was 44% (n=66). After exclusion of 5 alpha reductase deficiency and PAIS, the yield dropped to 20.7% (n=22) in the cohort chiefly comprising patients with suspected PGD.

Conclusions: NGS is paramount in arriving at a precise molecular aetiology in patients with XY DSD. However, its utility diminishes in patients with PGD, where copy number variants (CNVs) and variants in non-coding regulatory regions have been assuming progressively greater importance.

PO 71

Profile of patients with Congenital Adrenal Hyperplasia and XX karyotype raised as boys

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Background: The consensus on the management of intersex disorders (2006) recommends that children with Congenital Adrenal Hyperplasia (CAH) and XX karyotype should be raised as girls. In countries with absent universal newborn screening or with gender gaps and male dominated societies, such children are often raised as males. We present a series of 7 boys with XX karyotype and CAH.

Methods: Data were collected on children with CAH and XX karyotype who were raised as boys and had visited the Pediatric Endocrinology services of a tertiary care hospital in India between February 2023 and February 2024.

Results: The median (range) age at initial diagnosis was 0.2 (0.1 – 22.4) years. The initial presentation was ambiguous genitalia and salt wasting in 4 patients, ambiguous genitalia in 2 patients, and isolated salt wasting crisis in 1 patient. The initial Prader stage was 3 in 3 patients, 4 in 3 patients, and 5 in 1 patient. At a median (range) age at last follow up of 9.3 (5.8 – 22.5) years, 4 patients had developed facial hair, 6 patients had developed hoarseness of voice, 2 patients had developed gynaecomastia and cyclical haematuria, and nearly all patients had significantly advanced skeletal age. The median (interquartile range) predicted adult height/adult height was 145.3 (140.4, 146.8) cm. The overall follow up and adherence to treatment was poor in all patients who had been diagnosed in infancy. In those with closure of the growth plates, the dose of steroids was reduced to a median (interquartile range) of 7.5 (5.5, 11.0) mg/m^2/day hydrocortisone equivalents to sustain virilization and prevent feminization from setting in. Two patients required administration of progesterone for cyclical haematuria, and 1 patient who was initially raised as a girl required pubertal suppression with a gonadotrophin releasing hormone (GnRH) analogue in view of gender dysphoria.

Conclusions: Children with XX CAH raised as boys face multiple issues including peripheral precocious puberty, pubertal feminization, short stature, and a range of psychiatric problems. Optimization of medical treatment is challenging in the face of increasing medicolegal

ramifications of early gender affirming surgeries, and necessitates the development of guidelines for appropriate management.

PO 72

Initial results from a 12-week, phase 2, open-label, sequential dose cohort study to evaluate the safety, efficacy, and pharmacokinetics of CRN04894 treatment in participants with classic congenital adrenal hyperplasia (TouCAHn)

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Background: CRN04894 is a potent, orally bioavailable, nonpeptide, first-in-class melanocortin type 2 receptor (MC2R, ACTH receptor) competitive antagonist that is being developed for the treatment of classic congenital adrenal hyperplasia (CAH; 21-hydroxylase [CYP21A2] deficiency) and ACTH-dependent Cushing's syndrome. CRN04894 blocks G-protein activation and subsequent signalling through the MC2R, with an equilibrium binding constant (K_B) of 0.34 nM, and more than 2,900-fold selectivity for the MC2R over other melanocortin receptor subtypes.

A randomized, double-blinded, placebo-controlled, multiple ascending dose (40 to 80 mg/day) study of CRN04894 for 10 days in 49 healthy volunteers demonstrated oral bioavailability, rapid absorption (Tmax of 0.8–1.7 h) and a half-life (23–32 h) and pharmacokinetic profile that allows for once-daily dosing. Once-daily dosing with CRN04894 80 mg at 22:00 hours for 10 days resulted in an average of 75% decrease in 24-hour urinary-free cortisol. The reduction in cortisol-mediated feedback on the hypothalamic-pituitary-adrenal axis resulted in a 5-fold increase in mean plasma ACTH. The most common adverse event was glucocorticoid deficiency (pre-defined as an 08:00 serum cortisol level of <5 µg/dL), reported in 12 participants (11 on CRN04894 and 1 on placebo); all cases were asymptomatic and resolved without treatment.

Methods: TouCAHn (NCT05907291) is an ongoing first-in-disease, open-label, phase 2 study of CRN04894 in participants (≥16 to 75 years of age) with classic CAH. This study is a sequential-dose cohort study designed to evaluate the safety, pharmacokinetics, and adrenal biomarker responses to 12 weeks of daily dosing with CRN04894 in participants with biochemically uncontrolled CAH (baseline A4 ≥ 1.5xULN) who remain on stable doses of replacement glucocorticoid. The principal efficacy endpoints under evaluation include morning androstenedione and 17-hydroxyprogesterone (17-OHP). Results from the first cohort of participants receiving 80 mg once per day (at 22:00) are under analysis.

Results and Conclusions: Initial results from the first cohort of participants evaluated in the TouCAHn study will be presented.

PO 73

Characteristics of Bone Turnover Markers in Children with Turner Syndrome and the Impact of Growth Hormone Treatment

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Background: There is no reported of bone turnover markers (BTMs) related Turner Syndrome (TS) between centres. The study aimed to assess BTMs in prepubertal children with TS and the impact of growth hormone (GH) treatment.

Methods: A prospective, non-randomized controlled study that included 28 prepubertal girls with TS, groups based on age: Group A (ages 3-5), Group B (ages 6-8), and Group C (ages 9-12). Of these, 18 were treated with GH. A control group consisted of 9 healthy prepubertal girls aged 9-12 with matched body mass index (BMI). measured changes in BTMs at baseline, and after 1 and 12 months of GH treatment, comparing between ages.

Results: Group C displayed significantly reduced levels of bone-specific alkaline phosphatase (BAP), Fibroblast Growth Factor 23 (FGF23), and C-terminal telopeptide (CTX) compared to the control group. No differences in collagen type 1 C-terminal propeptide (CICP), alkaline phosphatase (ALP), calcium (Ca), and phosphorus (P) were found between the groups. Within the TS groups, Group C had lower levels of BAP, ALP, and CICP than Groups A and B, while CTX was significantly elevated in comparison to Group A. GH treatment led to a marked increase in ALP, BAP, and CICP within a month, levels of which remained high thereafter, whereas CTX levels did not exhibit a significant change. Post-treatment, P and the Ca-P product significantly rose, but no significant changes were observed in Ca and FGF23. Insulin-like growth factor-1 standard deviation score (IGF1SDS) surged after a month of GH treatment and continued to be significantly higher after a year. Height SDS (HtSDS) and growth velocity (GV) negatively correlated with CTX both at baseline and after a month of treatment, but positively correlated with P at 12 months.

Conclusions: Children with TS experience a persistently lower bone turnover, especially in older prepubescent groups, suggesting a GH/IGF1 axis suppression possibly due to estrogen deficiency. GH treatment seems to temporarily increase BTMs, mainly the bone formation markers. with higher P and lower CTX associated with improved growth following GH therapy.

PO 74

Twin brothers with simple virilizing CAH missed from the newborn screening

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Background: Congenital adrenal hyperplasia (CAH) is included in the neonatal screening (NS) programme in many countries by testing 17-hydroxyprogesterone (17-OHP). However, this method can miss cases. We present two brothers with CAH who were missed from the NS.

Case report: Two twin brothers presented for the first time at 5 years of age because of pubic hair noticed a few months ago. They were born at 37 g.w. with BW 2480 g and 2650 g, respectively. On NS one of the boys (patient 1) had slightly elevated 17-OHP - ***23.88*** ng/ml (ref. <20 ng/ml) which was tested again at 28 days and was normal (9.89 ng/ml). The other boy (patient 2) had normal 17-OHP, and no follow-up was recommended The anthropometric measurements and lab results at presentation are shown on table 1.

Parameter	Patient 1	Patient 2	Ref. range
Height SDS (CDC chart)	**+2.61**	**+2.13**	±2
Bone age SDS (BoneXpert)	**+5.8**	**+5.13**	±2
Testicular volume (ml)	**3-4**	**4-5**	≤3
Pubarche (Tanner stage)	**2-3**	**2**	1
LH (mIU/ml)	<0.1	<0.1	<0.1
FSH (mIU/ml)	**0.63**	**0.652**	<0.1
DHEA-S (umol/l)	4.56	3.72	2.17-15.2
Androstenedione (nmol/l)	**14.3**	**11**	2.1-10.8
Serum cortisol (nmol/l)	347.91	352.82	118.6-618
Testosterone (nmol/l)	**2.54**	**1.93**	0-1.04

Central precocious puberty was considered initially. Brain MRI showed no significant pathology and LHRH agonist was considered. At admission 17-OHP was ordered but received 2 weeks later. The level of 17-OHP was ***80.2*** ng/ml (ref. 0.26-1.48) in patient 1 and ***66.36*** ng/ml in patient 2. Control 17-OHP was ***174.0*** ng/ml and ***193.0*** ng/ml, respectively. Genetic test followed which found the same homozygous ***CYP21A2 (c.92C>T (p.Pro31Leu)*** mutation in both patients associated with classic CAH. The boys were diagnosed with simple virilizing CAH causing peripheral precocious puberty. Treatment was started with hydrocortisone and cyproterone acetate.

Conclusion: The widely implemented 17-OHP test from dry blood spot as NS for CAH has some drawbacks and some patients with simple virilizing CAH can be missed. Thus serious late complications cannot be avoided. Further insight into the inclusion of genetic work-up as part of the initial assessment of patients with borderline 17-OHP NS results is necessary.

PO 75

Genome-wide methylation analysis in patients with proximal hypospadias – a pilot study and review of the literature

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Background: In the majority of individuals with proximal hypospadias no genetic cause is identified even after extensive genetic testing. We hypothesized there might be recurrent differences in DNA methylation in children with proximal hypospadias compared to controls, and possibly also differences between children with hypospadias born small versus appropriate for gestational age, as hypospadias occurs more frequently in the first group.

Methods: 16 Children with proximal hypospadias and XY profile on SNP array and one individual with proximal hypospadias and unexplained XX testicular DSD, all without genetic abnormalities in a DSD gene panel, were included. Six healthy age-matched boys and six age-matched girls undergoing minor surgical procedures served as controls for the XY patients and the XX testicular DSD patient. Genome-wide Methylated DNA sequencing (MeD-seq) was performed on 30bp DNA fragments after digestion using the DNA-methylation dependent restriction enzyme LpnPI. An individual with *H19* hypomethylation served as a positive control.

Results: 1. No recognizable epigenetic signature for proximal hypospadias was identified by hierarchical clustering using DMRs with a fold change ≥2. 2. No difference in methylation pattern between children born small or appropriate for gestational age was observed. 3. At an individual level, hypermethylation of *MAP3K1* was found in three boys with hypospadias. 4. In the XX individual no DMRs in genes associated with XX testicular DSD were identified.

Conclusions: Although no specific DNA methylation pattern was observed in boys with hypospadias, three individuals showed hypermethyation of *MAP3K1* which may play a role in the aetiology of proximal hypospadias, but this needs further study. Comparison to previous methylation studies in individuals with hypospadias proved difficult due to the use of different inclusion criteria, tissues and methods.

PO 76
Gender identity in 46XY differences of sex development (DSD)

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Background: In some patients with DSD, the degree of virilization varies within the same condition. This can lead to confusion and distress with the gender assignment process, especially in the immediate postnatal period. The aims of this study are to describe the common genital appearance and describe the incidence of gender dysphoria in patients with 46XY DSD.

Methods: This is a retrospective cohort study of patients presenting for care from 2007-2021 with a diagnosis of 45X/46XY or 46XX/46XY mixed gonadal dysgenesis (MGD) or 46XY complete gonadal dysgenesis (CGD).

Results: Sixty-two patients were included in the study, including 42 patients with MGD, 20 CGD. Of the patients with MGD, 48% were assigned male at birth and 52% female. No patients reported a gender identity incongruent with sex assigned at birth at the time of most recent clinic visit. The average age at most recent visit was 13 years (range 0-32 years). Of the male-assigned patients, 80% underwent hypospadias repair, the remainder had typical male external genitalia. The majority (16/22) of female-assigned patients had typical female external genitalia, 4 underwent feminizing genitoplasty, and 2 had clitoromegaly with no planned surgery. All surgeries were performed at age ≤5 years, except for one feminizing vaginoplasty performed at 11 years. The two patients with clitoromegaly were age 1 and 12 years at the time of the last visit.

Among patients with CGD, 15% were assigned male at birth and 85% female. No patients reported gender dysphoria. The average age at most recent visit was 15.7 years (range 0-30 years). Of the male patients, 2/3 underwent hypospadias repair and 1/3 had micropenis. Seventy-six percent of female patients had typical female external genitalia, 2 underwent feminizing genitoplasty, and 2 had clitoromegaly with no planned surgery. Surgeries were performed at ≤2. The two patients with clitoromegaly were age 2 and 30 years at time of last visit.

Conclusion: Gender identity of all patients remained congruent throughout this study and appeared congruent with assigned gender and degree of virilization. With careful and thoughtful decision making in the newborn period, the potential for inappropriate sex assignment is low in children with MGD and CGD.

PO 77
What's in a name: imaging nomenclature in differences of sex development

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Background: There is a lack of data regarding accuracy of imaging reports with regards to nomenclature and other descriptive language, especially in reference to gonadal tissue in patients with differences of sex development (DSD). The neutral term "gonad" is preferable (instead of "ovaries" or "testes") to avoid confusion for patients. The aims of this study are to describe the incidence of incongruent nomenclature in imaging reports and identify psychosocial impacts of confusing nomenclature.

Methods: This is a retrospective cohort study of patients presenting for care from 2007-2021 with a diagnosis of complete androgen insensitivity syndrome (CAIS), 45X/46XY or 46XX/46XY mixed gonadal dysgenesis (MGD), and 46XY complete gonadal dysgenesis (CGD), identified by ICD-9 and ICD-10 codes. These are the most common DSD conditions with a mismatch between gonadal tissue and assigned sex at birth. Data were collected on demographics, imaging, diagnosis, and clinical presentation. This study was IRB approved.

Results: 74 patients met inclusion criteria, including 12 with CAIS, 42 with MGD, 20 with CGD. 69 imaging reports were analysed, including 18 pelvic ultrasounds or magnetic resonance imaging (MRI) studies from patients with CAIS, 27 from patients with MGD, and 16 from patients with CGD. In cases of CAIS, no imaging reports referred to "gonads." In cases of MGD, one ultrasound and one MRI noted "gonads." In cases of CGD, one ultrasound and 3 MRI mentioned "gonads." In 32 cases (46%), the DSD diagnosis was known prior to imaging and listed as a reason for obtaining the imaging. Only 4/32 (12%) imaging reports used "gonads" instead of "ovaries" and/or "testes."

Conclusion: Of 69 imaging studies obtained in this study, only 9% used the neutral term "gonads" in lieu of "ovaries" or "testes." Patients are often able to read results prior to discussion with their physician which can cause distress if the reports contain confusing nomenclature. Providers should be cognizant of potential harm with language used in reports.

PO 78
Variations in risk of germ cell tumors in differences of sex development

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Background: Some patients with differences of sex development (DSD) are at elevated risk of germ cell tumors (GCT), usually due to the presence of dysgenetic gonads or intra-abdominal testes. The aim of this study is to better characterize the risk of malignancy for specific DSD diagnoses.

Methods: This is a retrospective cohort study of patients from 2007-2021 with a diagnosis of 45X/46XY or 46XX/46XY mixed gonadal dysgenesis (MGD), 46XY complete gonadal dysgenesis (CGD), and ovotesticular DSD, identified by ICD-10 codes. Data were collected on demographics, imaging studies, diagnosis, pathology reports, and clinical presentation. This study was IRB approved.

Results: 70 patients were included in the study, including 41 patients with MGD, 21 CGD, and 4 ovotesticular DSD. Of the patients with MGD, 16 underwent bilateral gonadectomy and 9 unilateral gonadectomy. Bilateral gonadectomy occurred at average age 4.8 years (range 0-17 years). 8% of patients were found to have gonadoblastoma or dysgerminoma at the time of surgery. The patient with dysgerminoma had solid and cystic regions on pelvic ultrasound; the patient with gonadoblastoma had no concerning findings on PUS. These patients were diagnosed at ages 16 and 12 years, respectively.
Of patients with CGD, 16 underwent bilateral gonadectomy. Surgery occurred at average age 8.1 years (range 0-18 years). More than one-third (37%) of patients were diagnosed with gonadoblastoma and/or dysgerminoma at the time of surgery. Patients with gonadoblastoma were diagnosed at ages 14-15 years and dysgerminoma at ages 10-18 years. One patient with bilateral gonadoblastoma and unilateral dysgerminoma had bilateral echogenic foci in the gonads on ultrasound and no abnormal findings on magnetic resonance imaging (MRI). All other cases had no abnormalities on ultrasound or MRI.
Three patients with ovotesticular DSD underwent unilateral gonadectomy and one patient underwent gonadal biopsy. No cases of GCT were identified.

Conclusion: The risk of GCT varies widely based on the DSD diagnosis. Patients with CGD are at very high risk of developing neoplasms and should undergo prophylactic gonadectomy, either at time of diagnosis or in early childhood. Patients with MGD are also at an increased risk, but likely much lower than those with CGD.

PO 79

Face processing patterns in individuals with gender incongruence or differences of sex development: an eye-tracking study

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Background: Face processing is considered the most highly developed visual perception ability, with research indicating differences between genders. Gender incongruence (GI) refers to person's experience of an incompatibility between gender identity and birth-assigned sex. Differences of sex development (DSD) encompass rare congenital conditions, in which chromosomal, gonadal or phenotypic development is atypical. The study aimed to investigate face processing patterns in individuals with GI or DSD using eye-tracking technology.

Methods: We conducted an eye-tracking study using iMotions software, involving 15 individuals with GI (transgender men) and 20 individuals with DSD conditions (14 with classic congenital adrenal hyperplasia (CAH) and 6 with complete androgen insensitivity syndrome (CAIS), all assigned female at birth). Participants were presented a series of 10 face stimuli (5 females and 5 males), and areas of interest (AOIs) were defined for internal (iAOI) and external (eAOI) facial features. Standard visual scanning parameters were assessed. One-way analysis of variance (ANOVA) was performed for each study group compered to control groups (39 females, 27 males) using IBM SPSS software.

Results: Significant differences were observed between groups, particularly in scanning iAOIs. Individuals with GI exhibited distinct facial processing patterns compared to the female control group, characterized by a longer time to first fixation (TTFF), shorter gaze duration, shorter fixation durations, and a smaller number of fixations ($p < 0.05$). These differences were consistent across both female and male face stimuli. Those with CAH also displayed differing facial processing patterns compared to the female control group, with shorter gaze duration and fixation durations, and a reduced number of fixations ($p < 0.001$), regardless of the stimuli's sex. Individuals with CAH differed also from the male control group in gaze time and fixation duration when processing female faces ($p < 0.05$).

Conclusions: This eye-tracking study enabled to identify differences in face processing among individuals with GI or DSD. The face processing pattern observed in transgender men resembled that of male control group. Individuals with CAH, while differing from the female control group, exhibited differences from both control groups, indicating a unique pattern. Further research involving larger cohorts is necessary to delve deeper into these.

PO 80

The impact of the genetic mutation type in the *CYP21A2* gene on the clinical and laboratory presentation – 2 female newborns case reports

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Introduction: Clinical severity of congenital adrenal hyperplasia (CAH) is correlated with the type of mutation in the *CYP21A2* gene. Most patients with CAH are compound heterozygotes carrying two different disease-causing mutations. The phenotype is defined by the mutation retaining the most enzyme activity.

Case reports: We present two female newborns with similar clinical presentations after the delivery but with extremely different laboratory presentations in the newborn screening results. 1st newborn was born at 37 weeks of gestation with a birth weight of 2720g and birth length of 48cm and received 10 points on the Apgar scale. External genitals were described as Prader IV stage with genital tubercle length 15mm, width 10mm, labioscrotal fusion with the end of urogenital sinus at the base of genital tubercle, AGDu 40mm, AGDl 10mm, and hyperpigmentation was observed. In the screening filter papers, 17-OHP (FIA) was 381,2nmol/l, in blood steroid profiles (LC/MS/MS), the concentration of 17-OHP was 118 mmol/l, 21-deoxycortisol 94,9 nmol/l, and androstenedione 36,9 nmol/l. On the 3rd day of live 17-OHP in serum was 41,02 ng/ml, testosterone >52 nmol/l, androstenedione >10 ng/ml, ACTH 597 pg/ml. Genetic analysis revealed a heterozygotic In2G variant/exons 1-7 deletion.
2nd newborn was born at 40 weeks of gestation with a birth weight of 3580g and birth length of 55cm and received 10 points on the Apgar scale. External genitals were described as Prader IV stage with genital tubercle length 15mm, width 11mm, labioscrotal fusion with the end of urogenital sinus at the base of genital tubercle, AGDu 47mm, AGDl 15mm, and discreet hyperpigmentation was observed. In the screening filter papers 17-OHP (FIA) was 64,75 nmol/l, in blood steroid profiles (LC/MS/MS), the concentration of 17-OHP was 94,8 mmol/l, 21-deoxycortisol 47,7 nmol/l, and androstenedione 14,8 nmol/l. On the 4th day of live 17-OHP in serum was 30,8 ng/ml, testosterone 17,3 nmol/l, androstenedione 4,56 ng/ml, ACTH 262 pg/ml. Genetic analysis revealed a heterozygotic p.Gly111ValfsTer21/ p.Leu309Phe; p.Gln319Ter; c.*12C>T; exons 1-7 duplication.

Conclusion: The mitigating effect of exons 1-7 duplication on the p.Gln319Ter variant was described in the literature in co-occurrence on the same chromosome cases. Despite the co-occurrence in the 2nd patient, we observed significant differences in the laboratory results but not in the clinical presentation, especially in the stage of external genital virilization in presented cases.

PO 81

Genotype-phenotype correlation in classic 21-hydroxylase deficiency congenital adrenal hyperplasia: A single tertiary center experience

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) has a wide range of clinical presentations owing to different underlying pathogenic variants. In our study, we aim to identify some of the most frequent CYP21A2 pathogenic variants and to establish a genotype–phenotype correlation in Egyptian children affected with 21-OHD CAH.

Methods: A cross-sectional observational study included 37 CAH cases representing 29 families with at least one member affected. The studied subjects underwent CYP21A2 gene mutation analysis to determine the presence of large deletion and conversion mutations using single strand conformational polymorphism (SSCP), along with two other point mutations (PMs); Q318X using PstI restriction enzyme and Ala16Thr using amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) techniques. Parents and other family members were tested to confirm homozygosity/compound heterozygosity of affected individuals, delineate the way of transmission if a child had more than two mutations and screen for carrier status in clinically unaffected relatives.

Results: The most frequent mutation detected in 21-OHD CAH cases was Q318X mutation (43%) and it was more prevalent in the SW phenotype. Deletion/Conversion mutations were found in a prevalence close to the worldwide prevalence (27%). Ala16Thr mutation doesn't seem to increase the risk for having CAH. The genotype–phenotype correlation in our patients with the classic form was similar to the worldwide correlation estimated.

Conclusions: Our global genotype–phenotype correlation in patients with the classic form 21-OHD CAH was nearly (87.5%) and this copes with the average worldwide genotype–phenotype correlation estimated.

PO 82

Establishing a regional best practice DSD service in a tertiary paediatric children's hospital

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Background: The Australian Human Rights Commission (AHRC) outlines recommendations for protecting and promoting the rights of those born with variations of sex differentiation (DSD) (Australian Human Rights Commission, 2021). The importance of this has also been recognised on a national and international level (Australia And New Zealand Society For Paediatric Endocrinology and Diabetes , 2022).

Aims: Establish a service delivering on the AHRC report which meets the evolving legal and ethical understanding of managing individuals with DSD (Australian Human Rights Commission, 2021).

Methods: In order to deliver best practice, accountable, and ethical care to children with DSD and their families that aligns with these recommendations an expanded DSD clinical model was required. A briefing note and business case was developed to outline the staffing requirements. A review of the regional case load was undertaken, alongside projected numbers and an evaluation of the required skill set, and standards needed.

Results: A multidisciplinary (MDT) service has been approved from August 2024, consisting of a clinical co-ordinator, endocrinology consultant and trainee, specialist nurse, project officer, clinical psychologist, psychiatrist, social worker, clinical ethicist, genetic counsellor, gynaecologist, general surgeon, and data officer. Initial funding (up to $940,000) has been granted, with a 2-year review period.
A regional database will be developed which links in with national and international counterparts, ANZPED and iDSD.
The core team will be on-call to assess new presentations, implementing best practice. Subspecialty clinics and MDTs will continue with a view to robust minute keeping, data collection, consenting and storage. Archives will enable future review of the decision-making pathway.

Conclusion: Regional service development acknowledges the need to promptly adjust a clinical model to meet the evolving legal and ethical understanding of managing individuals with DSD. Funding has been granted to expand a DSD service that can provide best practice, accountable and ethical care for the children affected in Western Australia.

References: Australia And New Zealand Society For Paediatric Endocrinology and Diabetes . (2022). *Position statement of ANZPED on the clinical care of children with DSD.* Bonnells Bay: Aus. Australian Human Rights Commission. (2021). *Protecting the human rights of people born with variations in sex characteristics in the context of medical interventions.* Sydney: Australian Human Rights Commission.

PO 83

Molecular Cytogenetic Analysis of patients with Disorders of Sex Development associated with Congenital Anomalies: A single Centre Egyptian experience

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Background/Aims: Disorders of sex development (DSD) represent a diverse group of clinical conditions, which have a very wide phenotypic spectrum associated with a complicated molecular background. They are frequently associated with congenital abnormalities, which may occur due to overt chromosomal abnormalities, sub-microscopic copy number variation (CNVs) or as an identifiable syndrome due to a single gene defect. The study aimed at detection of prevalence and cytogenetic profile of DSD associated with congenital anomalies.

Methods: 85 patients of DSD associated with other phenotypic abnormalities were identified among a large cohort of Egyptian DSD patients presented to the clinical genetics department, National Research Centre, Egypt, over a period of 10 years. The patients underwent detailed clinical and genital assessment, They were all subjected to conventional chromosomal analysis of the peripheral blood lymphocytes and FISH analysis when indicated. MLPA and chromosomal microarray (CMA) were performed for selected patients.

Results: The patients represented 11% of all DSD patients and exhibited various clinical abnormalities including dysmorphic features, intellectual disability, skeletal anomalies, autistic features in addition to a range of DSD features including micropenis, undescended testis, ambiguous genitalia and gonadal dysgenesis. 12 patients (14%) had numerical sex chromosomal abnormalities of them 3 had a translocation of a sex chromosome to an autosome; 15 patients (18%) had autosomal abnormalities; 34 patients (40%) had 46,XY karyotype, 18 (21%) patients had 46,XX karyotype. MLPA diagnosed patients with SOX9 gene and DMRT genes deletions. CMA detected variable clinically significant copy number abnormalities in 8 patients, which were correlated with the phenotype.

Conclusion: The study emphasizes the crucial need to improve the clinical utility of genetic analysis in patients with DSD. CMA is recommended to be carried out for all patients with DSD associated with MCA to detect subtle CNV.

PO 84

Outcomes in men with PAIS worldwide: Lessons from an I-DSD Registry platform cohort

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Background/Aims: The androgen receptor (AR) sensitivity is an important determinant of male phenotype expression in XY individuals during fetal life and from the onset of puberty. Partial Androgen Insensitivity Syndrome (PAIS) is a spectrum of various genital phenotypes and gonadal impairments affecting approximately 1 birth in 130,000 individuals. However, there is still very little information on fertility in men with PAIS in the medical literature.

Methods: Fertil'PAIS is an international, retrospective, multi-center, observational study still in progress, evaluating fertility in PAIS men over sixteen years from the I-DSD Registry platform, as well as their genital phenotype at birth, psychological well-being, gender identity, hormonal replacement treatment, and puberty.

Results: Currently, 68 patients with PAIS from 11 different countries have been included, with a median age of 20.2 (16,3-69) years.
97% were identified as male gender, and among the 2 patients who were identified as female at birth, 1 underwent gender transition to male at 16, and 1 had a legal sex change facilitated by parents. Median External Masculinization and Genitalia scores (EMS/EGS) at birth were respectively 6 and 8.5: 79% had a genital tubercle beneath 30 mm, including 50% between 10 and 20 mm; 20% had no labioscrotal fusion; 55% had a scrotal meatus, and only 30% had inguinal or impalpable gonads. Most patients had not undergone gonadectomy or gonadal biopsy and had testes identified by ultrasound.
Additionally, 90% of those for whom information was available had gynecomastia, with a median age of onset at 13.4 years old, and all of them, except one, experienced spontaneous puberty at a median age of 12.7 years old. Some patients desired fertility, but only a few had sperm count, other sperm assessments, or tissue storage, and only one patient sought assisted conception.
Finally, regarding diagnosis, 91% underwent biochemical testing, including 80% for whom this test confirmed the diagnosis, whereas only 30% underwent genetic testing, all confirming the diagnosis.

Conclusion: In conclusion, the phenotype of PAIS men at birth varies greatly, but they mostly exhibit severe variations in genital development and gynecomastia. While most undergo spontaneous puberty, some require hormonal medications, and fertility remains poorly monitored.

PO 85

The segregation of a novel NR5A1 variant in a Brazilian family leads to phenotypes of Primary Ovarian Insufficiency and 46,XY DSD

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Background: Variants in *NR5A1*/SF-1 are associated with a wide variety of conditions, ranging from primary ovarian insufficiency (POI) to 46,XY Gonadal Dysgenesis. This study aimed to determine the inheritance pattern and the pathogenicity of the heterozygous missense variant c.938G>A, p.(R313H) identified in a one-year-old patient with 46,XY partial gonadal dysgenesis (PGD), his cousin, also diagnosed with 46,XY PGD, and his maternal grandmother, with POI.

Methods: Sanger sequencing was performed in exon 5 of *NR5A1* of the proband's mother, brother, maternal uncle, first-degree maternal cousin, and maternal grandmother. In silico prediction tools, such CADD, SIFT Protein, Fathmm, Poly-Phen-2 and Mutation Taster, were utilized to determine the variant's pathogenicity.

Results:
The variant c.938G>A was identified in five members of a Brazilian family, including the proband, his grandmother, his mother, maternal uncle, and first-degree maternal cousin. Among them, the mother and the maternal uncle did not preset any clinical features of DSD. The variant does not have a minor allele frequency registered in gnomAD database, and according to four out of five in silico tools the variant is predicted to be likely pathogenic.

Conclusions:
Evaluating the segregation of the variant c.938G>A within the family under study, different DSD phenotypes were observed. The absence of clinical features in the maternal uncle, who also carry the variant, also catch our attention. Previous publications have suggested a digenic/oligogenic inheritance for some cases of DSD. Functional studies must also be performed to clarify the impact at the variant on protein function. Nevertheless, another substitution in the same amino acid, the p.R313C, has already been described in the literature, wherein the authors demonstrated, through in vitro analysis, a drastically reduction of NR5A1 protein function. This is a novel case that highlights the diversity that an *NR5A1* variant can cause within a family. We aim to gain a better understanding of the genetic background of these individuals and unravel the possibility of a synergistic effect between variants of different genes associated with sex and gonadal development.

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Exploring the underlying gene expression in DSD phenotypes through transcriptome analysis

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Background: Advances in Next Generation Sequencing techniques have enabled the identification of novel variants/genes acting in sex development pathways, several correlated to different Disorders of Sex Development (DSD) phenotypes. However, more than 50% of all the DSD cases remain without a genetic diagnosis, according to most of the research centers. For this reason, we investigated beyond the genetic variants for possible causes of these conditions, to explore the normal and imbalanced gene expression and their role in DSD.

Methods: RNA-seq was performed from paraffin-embedded gonadal material of 12 DSD patients with different phenotypes (Partial Gonadal Dysgenesis, Complete Androgen Insensitivity, and 46,XX Ovotesticular-DSD). Bioinformatic tools, such as dimensionality reduction analysis (t-SNE), differential expression analysis (DE), and gene set variation analysis (GSVA), were employed to explore the data.

Results: We compared the transcriptomes of gonads from our patients with those of individuals of different ages, obtained from public databases (GTEx, ArrayExress). Evaluation of overall transcriptome similarities using a t-SNE plot revealed that all patient samples clustered close to each other and near to adult testis samples, even those with a 46,XX karyotype. Expression levels of sex-determining genes, such as *FOXL2*, *RSPO1, DMRT1* and *NR0B1* (female and male development gene markers), were not within the normal range for each patient's age. DE analysis for different phenotypic groups revealed genes significantly up- and downregulated, drawing our attention to a few involved in hormonal regulation, which were upregulated in most of the groups. Using GSVA for different groups, we observe that patient samples were distributed among the control samples without a distinct pattern, likely due to the gonads acquiring expression programs typical for both ovary and testis simultaneously.

Conclusion: We believe that transcriptome analysis is an important approach for better understanding the causes underlying the different phenotypes observe in DSD. Further investigation in this field can improve our knowledge of gene expression and sex development pathways that lead to DSD.

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Utilising a Differences of Sex Development Multidisciplinary Team checklist to streamline investigations and management for patients with complex hypospadias

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Background/Aims: Patients with complex hypospadias (CH), defined as peno-scrotal hypospadias or any hypospadias with undescended testis, microphallus or bifid scrotum, may have an underlying endocrine or genetic difference of sex development (DSD). Multiple surgical interventions may be required and could result in later dissatisfaction. A checklist-based pathway for CH review was introduced at our hospitals in 2021 to streamline multidisciplinary team (MDT) reviews, resulting in full discussion only for those with significant co-morbidities or known DSD. This study aimed to explore the role of checklist review of CH and associations between clinical phenotype, endocrine and genetic variations and short-term surgical outcomes.

Methods: Data were collected from referrals to our DSD MDT and/or checklist review panel between 2016 to 2024. The incidence of genetic and endocrine abnormalities was correlated with clinical findings including severity of hypospadias by glans, meatus, shaft (GMS) score, chordee, bifid scrotum and descent of testis.

Results: 51 patients were referred with CH. Since the introduction of the checklist 28/35 referrals (80%) did not require full MDT discussion. The median GMS score of the cohort was 11 (IQR 9-11.25). Two of 47 (4%) patients with available endocrine results had a suboptimal testosterone response detected on mini-puberty mapping or HCG stimulation test. Nine of 45 (20%) patients with available genetic test results had a sequence or copy number variant which may be associated with CH. One patient had a syndromic genetic condition not associated with CH on whole exome sequencing, which influenced surgical decision making. The GMS score did not appear to predict the likelihood of an abnormal genetic result. The incidence of genetic variants was higher in hypospadias with undescended testis but did not reach statistical significance (44% vs 13%, p=0.09). The presence of bifid scrotum was noted in 16 children (two with genetic abnormalities) and did not predict an underlying genetic diagnosis (22% vs 42%, p=0.94).

Discussion: This study underscores the utility of a targeted checklist in managing CH and highlights the higher yield of genetic investigations compared to endocrine evaluation. These findings have the potential to contribute to improved patient care and better-informed decision-making.

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DNA methylation level at specific CG-sites within *TRAK1* is linked to the neurocognitive profile in Klinefelter syndrome

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Background: Klinefelter syndrome (47,XXY; KS) impacts neurodevelopment, leading to a neurocognitive phenotype where verbal IQ is generally more affected than performance IQ. Furthermore, KS is associated with alterations to the epigenome and transcriptome. Whether these epigenetic and genetic alterations can be linked to the neurocognitive phenotype remains to be elucidated.

Methods: We performed a comprehensive and integrative analysis of the neurocognitive profile and the methylome in blood from males with KS (n=63) and control males (n=63 (Cohort 1). The results were validated in a second cohort of males with KS (n=22) and control males (n=16) in which transcriptome data were also available (Cohort 2). The findings were further evaluated in neural precursor cells derived from human induced pluripotent stem cells from 47,XXY and 46,XY amniotic cells.

Results: We identified five CG-sites within *TRAK1* where the methylation level correlated to several neurocognitive variables among males with KS, including verbal IQ and performance IQ. The five CG-sites within *TRAK1* were hypomethylated in KS compared to control males (cohort 1). In cohort 2 we identified a similar methylation pattern and demonstrated that the methylation level at these five CG-sites correlated with the RNA expression level of a specific *TRAK1* transcript (ENST00000341421.7). The 47,XXY neural precursor cells also exhibited hypomethylation at the five CG-sites and upregulation of ENST00000341421.7 compared to 46,XY cells. Based on the methylation level of the five CG-sites we were able to develop a model that predicted full-scale IQ among men with KS.

Conclusion: We here demonstrate that the methylation level at specific CG-sites within *TRAK1* in men with KS is linked to the neurocognitive phenotype, indicating a genetic underpinning for the observed neurocognitive challenges in KS.

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A novel mutation in the *CYP11B1* gene causes late-onset congenital adrenal hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) due to 11β-hydroxylase deficiency (11BOHD) is a rare autosomal recessive disorder and the second most common form of CAH. Nonclassical forms of the disease are even more rarely seen.

Case: A 14.5-year-old girl presented with hirsutism and menstrual irregularity. Medical history revealed that she was born to consanguineous parents and had had an orthopaedic operation for a congenital foot anomaly. She walked at 2.5 years of age and had a diagnosis of nonprogressive myopathy based on a muscle biopsy. She had pubarche at the age of 10 years, thelarche at the age of 11 years, and menarche at the age of 13.5 years. She complained of progressively increased body hair starting around 13 years of age. She had noticed a slight enlargement of the clitoris in the last six months. On physical examination, her height was 148.5 cm (-2,3 SD), her weight was 38 kg (-3,3 SD), and her blood pressure was normal. Her pubertal status was Tanner stage 5; she had both vaginal and urethral orifices with a 2 cm clitoromegaly. Ferriman-Galwey's score was 21. On laboratory investigations, 17-OH P was 2.5 ng/ml (0.2-2.65), DHEA-S: 757 ug/dl (44-240), Androstenedione: 10 ng/ml (0.8-2.4), Total testosterone: 188 ng/dl (0.2-38), and ACTH: 180 pg/ml. The peak cortisol level at a standard ACTH test was 16 ug/dl. The molecular genetic analysis revealed a homozygous missense mutation (p.Ala297Val) in the *CYP11B1* gene, which is a likely pathogenic variant according to ACMG.

Conclusion: This case contributes to the literature by adding a new missense mutation in the CYP11B1 gene, leading to a late onset 11BOHD that has not been described before.

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Unraveling the transcriptome of undifferentiated gonadal tissue: insights into cellular composition and developmental arrest

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Background/Aims: Undifferentiated gonadal tissue (UGT) has so far only been identified in individuals with gonadal dysgenesis (GD) and (part of) a Y chromosome, i.e. 46,XY-GD or 45,X/46,XY-GD. Morphologically, UGT consists of gonadal stromal cells with or without primitive sex cord-like structures. It represents a common endpoint in many individuals with 46,XY-GD or 45,X/46,XY-GD, irrespective of the underlying aetiology, and has been hypothesized to represent a developmentally arrested gonad. Here, we aimed to provide insight into the cell types present in UGT and understand its developmental origin by correlating its morphology with its transcriptome.

Methods: Regions of interest were isolated from formalin-fixed paraffin-embedded samples through laser capture microdissection and processed using the Smart-seq3xpress protocol. Bulk RNA-sequencing of UGT from three patients with 46,XY-GD was performed using the Element AVITI™ sequencer. Pre- and postnatal ovaries and testes served as controls, obtained as early as 11 post-conceptional weeks.

Results: We show that the transcriptional landscape of UGT differs significantly from both ovarian and testicular tissues, while concurrently expressing markers that are mutually exclusive in typically developing gonads. The upregulation of markers for early supporting gonadal cells and down regulation of those for Sertoli cells supports a differentiation arrest of the supporting cell lineage. Additionally, there is an overexpression of (pre)granulosa cell markers, such as those of the WNT4/β-catenin signalling pathway. Furthermore, strong expression of interstitial cell lineage markers indicates an overrepresentation of these mesenchymal cells in UGT compared to healthy tissue, possibly due to a lack of supporting cells. This suggests that UGT mainly comprises interstitial tissue. Lastly, differences in transcriptional profiles distinguish UGT with primitive sex cords from UGT without sex cords, in line with the distinct histological features.

Conclusion: UGT has been hypothesized to result from a differentiation arrest of the bipotential gonad. We show that UGT is enriched in interstitial cells, but also comprises early supporting gonadal cells with upregulation of both male and female pathways, thereby strongly supporting the above hypothesis. Transcriptome analysis offers for the first time, insights into the cellular composition of UGT, enhancing our understanding of human gonadal differentiation and how this process is disrupted in DSD.

PO 91
Does Primary Ovarian Failure associate with Monogenic Diabetes Mellitus

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Background: Primary ovarian insufficiency (POI) manifests with delayed puberty, primary amenorrhea, and elevated levels of gonadotropins (LH, FSH). A variability in genetic factors in the origin of POI has been reported so far. Here we are reporting a case of POI with non-immune diabetes mellitus and mild intellectual disability suspected to have TRMT10A syndrome.

Case presentation: A 14 year and 4 months old adolescent female following in pediatric endocrinology clinic for delayed puberty. She is known to have mild intellectual disability with

bad school performance and primary nocturnal enuresis. Parents are consanguineous (first cousin). By examination: she has subtle dysmorphic features, short for age (height: 142cm (-3.1 SD) with BMI:26 (+1.2SD). She has no previous history of hypoglycaemia. At the age of 15yr5mon she developed diabetes mellitus without DKA with absence of acanthosis nigricans.
Investigations: karyotype XX, thyroid function test consist with autoimmune hypothyroidism, HbA1C:8%, anti-GAD: negative, basal LH: 3.6U/L, FSH :23U/L. Pelvic US: uterine & ovaries could not visualised. Pelvic MRI: uterus is rudimentary, no ovaries seen. Bone age close to 14years. LHRH stimulation test showed LH level at 0, 20, 40, and 60 min:3.6, 13.6, 21.9, 24, and FSH: 33, 40,50, 58 respectively.

Discussion: Our patient diagnosed with primary ovarian failure based on the exaggerated response of LH and FSH to LHRH stimulation with the presence of delayed puberty. A recent diagnosis of non-immune diabetes mellitus with background of intellectual disability, raised possibility of monogenic causes of DM. Genetic testing is still pending. She was started on oestrogen replacement therapy, along with metformin, then insulin therapy was added due to poor glucose control.

Conclusion: *TRMT10A* syndrome, a novel syndrome has been recently reported, which is characterized by abnormal glucose homeostasis or non-autoimmune diabetes associated with microcephaly, epilepsy, intellectual disability, failure to thrive and delayed puberty. Primary ovarian failure with DM in a high family consanguinity, raised the possibility of AR genetic causes.

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