CGS CLINICAL GENETICS SOCIETY

VKGN VERENIGING KLINISCHE GENETICA NEDERLAND

UK CANCER GENETICS GROUP

JOINT MEETING

UK / Dutch Clinical Genetics Societies & Cancer Genetics Groups

2nd & 3rd March 2026

Maastricht, the Netherlands

"Shaping the Future of Genetic Medicine"

Introduction and Welcome

Dr. Petra Zwijnenburg
President
Dutch Clinical Genetics Society

Dr. Mohnish Suri
President
UK Clinical Genetics Society

We are delighted to welcome you to the Joint UK–Dutch Meeting of our Clinical Genetics Societies and Cancer Genetics Groups. The theme of this year's meeting, **'Shaping the Future of Genetic Medicine'**, reflects the remarkable pace at which our field continues to evolve. Advances in genomic technologies, data integration, and targeted therapies are transforming the way we diagnose, counsel and care for patients. This meeting brings together colleagues from the UK and the Netherlands to share knowledge, foster collaboration, and shape this future together.

We would like to warmly thank the conference organizers and their teams for assembling an inspiring and diverse scientific programme. The meeting brings together experts, trainees and multidisciplinary partners, highlighting both cutting-edge research and the practical challenges of implementing genomic medicine in everyday clinical care.

As always, the programme spans the breadth of clinical genetics and cancer genetics, with sessions covering new diagnostic strategies, data interpretation, ethical and societal challenges, and the rapidly expanding landscape of gene- and variant-specific therapies. We are honoured to welcome our invited speakers and lecturers, and we thank all session chairs and abstract presenters for their valuable contributions. In particular, we look forward to presentations from geneticists in training, whose work continues to demonstrate the strength and vitality of the next generation of our field.

Perhaps more than ever, this meeting highlights the importance of international collaboration. Many of the challenges we face — from data sharing and variant interpretation to equitable access to genomic testing and therapies — extend beyond national borders. By learning from each other's experiences and working together, we can accelerate progress and improve care for individuals and families affected by genetic conditions. We are delighted to welcome you to this meeting and hope you will find the programme stimulating, collaborative and inspiring.

Joint organising & programme committee

The Netherlands / VKGN

Els Vanhoutte, local host
Mala Misra-Isrie
Bernadette van Nesselrooij *
Edward Leter *, local host
Eva van Walree
Margot van der Mark, conference organiser

UK CGS

Mohnish Suri *
Suresh Somarathi *
Meena Balasubramanian *
Sarah Bowdin
Ian Ellis

UK CGG

Katie Snape *
Cheryl Berlin
Beverley Speight
Terri McVeigh *

* also a member of the abstract reviewing committee

Abstract reviewing committee

Noor Giesbertz
Juliette Schuurmans
Sophie Stroeks
Job Verdonschot
Charlotte Jaggard
Rosalyn Jewell
Olga Tsoulaki

Programme

(Changes reserved)

Day 1: Monday 2 March – Joint programme

Room: Auditorium 2

Time slot		
09:00 - 09:50		Registration
09:50 - 10:00		Opening keynote: **Petra Zwijnenburg**, President of the Dutch Society of Clinical Genetics
10:00 - 11:00		**Session I: Embracing Growing Demand: Perspectives from the Netherlands and the United Kingdom** *Chairs: Els Vanhoutte (NL) & Frances Elmslie (UK)*
10:00 - 10:20		• Undiagnosed Hackathons: Hype or Hope? – **Wendy van Zelst** (NL)
10:20 - 10:40		• Improving the efficiency and clinical utility of genomic testing in the NHS Genomic Medicine Service – **Emma Baple** (UK)
10:40 - 10:50	1	• Expanded carrier screening during pregnancy: reproductive follow-up of 100 consanguineous couples – **Juliette Schuurmans** (NL)
10:50 - 11:00	2	• UK consensus recommendations for constitutional testing for Lynch Syndrome for patients with mismatch repair deficient or microsatellite instability-high non-colorectal/non-endometrial cancers – **Terri McVeigh** (UK)
11:00 - 11:30		***Coffee & tea / Poster viewing***
11:30 - 12:30		**Session II: Mosaicism** *Chairs: Mala Misra-Isrie (NL) & Mohnish Suri (UK)*
11:30 - 11:50		• Vascular Malformations: from Genetic to Precision Therapy – **Laurence Boon** (BE)
11:50 - 12:10		• Prevalence and consequences of *APC* mosaicism in patients with colorectal adenomas – **Diantha Terlouw** (NL)
12:10 - 12:20	3	• Navigating mosaicism in neurofibromatosis type 1: implications for couples considering preimplantation genetic testing – **Vivian Vernimmen** (NL)
12:20 - 12:30	4	• High prevalence of cutaneous postzygotic mosaicism of Patched 1 variants in patients developing multiple basal cell carcinomas – **Ashleigh Jimenez Lemus** (NL)

Programme

12:30 - 14:00		***Lunch / Poster viewing with the presenters (odd numbers)***
12:30 - 12:50		CGS Annual General Meeting - CGS members only Auditorium 2
14:00 - 15:30		**Session III: Re-examination of genomic data and other novel approaches** *Chairs: Saskia van der Crabben (NL) & Diana Baralle (UK)*
14:00 - 14:10	5	• Developing and characterising zebrafish models for Vascular Ehlers-Danlos Syndrome: clarifying VUS through CRISPANT analysis – **Nataliya Pidlisnyuk** (UK)
14:10 - 14:20	6	• Domain-wide mapping of peer-reviewed literature for genetic developmental disorders using machine learning and Gene2Phenotype – **Michael Yates** (UK)
14:20 - 14:30	7	• Counting survivors of 'lethal' skeletal dysplasia; a review of the 100,000 Genomes Project – **Megan Baxter** (UK)
14:30 - 14:40	8	• Exome-wide analysis of rare deleterious variants in 3,569 cases and 21,788 controls reveals no novel sarcoma susceptibility genes – **Alice Garrett** (UK)
14:40 - 14:50	9	• Implementation of the polygenic risk score for breast cancer in clinical practice – **Inge Lakeman** (NL)
14:50 - 15:00	10	• PROTECT-C: Population-based germline testing for early detection and prevention of cancer – **Caitlin Fierheller** (UK)
15:00 - 15:10	11	• CanVar-UK: an international data sharing and interpretation platform for germline variants in inherited cancer susceptibility genes – **Charlie Rowlands** (UK)
15:10 - 15:20	12	• Increasing clinical utility of prenatal exome sequencing: the potential power of Artificial Intelligence phenotype-driven analysis – **Manon Suerink** (NL)
15:20 - 15.30	13	• Integrating enriched case data from national laboratory testing within large-scale case-control analyses (PS4) using a novel statistical likelihood-ratio methodology – **Sophie Allen** (UK)
15:30 - 16:00		***Coffee & tea / Poster viewing***

Programme

16:00 - 17:00		**Session IV: Clinical Genetics Society lecture & President's lecture (VKGN)** *Chairs: Petra Zwijnenburg (NL) & Mohnish Suri (UK)*
16:00 - 16:30		CGS lecture by **Sahar Mansour**: Going with the Flow: 25 Years of Genetic Discoveries in Lymphovascular Disorders and Their Impact on Patients
16:30 - 17:00		President's lecture (VKGN) by **Masoud Zamani Esteki:** From Individual Cells to Secretome of Human Embryos: The Next Era of Preimplantation Genetic Testing
17:00 - 18:30		***Drinks & Bites*** *Brightlands Foyer*
19:00 - 22:00		***Dinner @ SAAM (for registered participants only)***

Programme

Day 2: Tuesday 3 March – Parallel programme

Parallel session Non-Cancer Genetics
Room: Auditorium 2

Time slot		Parallel session (Non-cancer genetics)
09:00 - 09:30		Registration
09:30 - 11:00		**Session Non-Cancer I: Neurodevelopmental and Neurological Disorders** *Chairs: Gijs Santen (NL) & Kate Tatton-Brown (UK)*
09:30 - 09:50		• ReNU syndrome, RNUopathies and the non-coding genome: the Dutch experience – **Stefan Barakat** (NL) -
09:50 - 10:00	14	• Characterization of Rare Genomic Structural Variants Across 2,981 Genomes Reveals Significant Involvements in Recessive Conditions – **Zirui Dong** (HK)
10:00 - 10:10	15	• There is more to NOTCH3 than CADASIL: differential effects on NOTCH3 signaling underlie the diverse phenotypes associated with NOTCH3 frameshift and nonsense variants – **Josephine van Asbeck** (NL)
10:10 - 10:20	16	• Three-dimensional facial gestalt analysis for three neurodevelopmental disorders: Koolen-de Vries, Jansen-de Vries and KBG syndrome – **Jolijn Verseput** (NL)
10:20 - 10:30	17	• DNA methylation profiling in Hao-Fountain syndrome: diagnostic episignatures, nanopore validation, integrative functional analyses and future cellular models – **Liselot van der Laan** (NL)
10:30 - 10:40	18	• Del2Phen: a new clinical tool for providing phenotype information on rare chromosome disorders directly to parents – **Eleana Rraku** (NL)
10:40 - 10:50	19	• A case series to expand the phenotype of PIK3CA germline mutations – **Anne McCabe** (UK)
10:50 - 11:00	20	• Craniofacial effects of vosoritide in treating achondroplasia: results of a worldwide survey and 3D facial imaging – **Agni Hatzakis** (UK)
11:00 - 11:30		***Coffee & tea / Poster viewing***

Programme

11:30 - 12:30		**Session Non-Cancer II: Developing therapies for rare diseases** *Chairs: Anneke Vulto-van Silfhout (NL) & Suresh Somarathi (UK)*
11:30 - 11:50		• Disease mechanisms & intervention strategies for SNAREopathies, disorders caused by mutations in genes that drive the secretion of chemical signals in the brain – **Matthijs Verhage** (NL)
11:50 - 12:10		• Leukodystrophies – it's time for treatment! – **Nicole Wolf** (NL)
12:10 - 12:20	21	• Building the ID-Treatabolome - Toward Personalized Medicine and equitable access to targeted treatments for genetic Intellectual Disabilities – **Eva van Walree (NL)**
12:20 - 12:30	22	• The effects of targeted therapies for achondroplasia go beyond height – **Melita Irving (UK)**
12:30 - 13:30		***Lunch / Poster viewing with the presenters (even numbers)***
13:30 - 14:30		**Session Non-Cancer III: From data to clinical practice: Non-cancer hereditary genetics** *Chairs: Saskia Lesnik Oberstein (NL) & Sarah Bowdin (UK)*
13:30 - 13:40	23	• Over a decade of clinical genomics quality assessments: GenQA's journey in supporting clinical teams – **Melody Tabiner** (UK)
13:40 - 13:50	24	• Sex and Age Specific Genetic Risk of Dilated and Arrhythmogenic Cardiomyopathy: Insights from the SHaRe Registry – **Sophie Stroeks** (NL)
13:50 - 14:00	25	• The hidden burden of genetic testing: evaluating the impact of mainstream testing for monogenic hearing loss in a regional NHS clinical genetics service – **Elizabeth Oakley-Hannibal** (UK)
14:00 - 14:10	26	• Streamlining both the patient experience and genomic testing for Familial Pneumothorax via a UK Rare Disease Collaborative Network (RDCN) – **Robert Legg** (UK)
14:10 - 14:20	27	• Penetrance of cardiomyopathies in families with (likely) pathogenic TTN variants; towards evidence-based recommendations regarding family screening – **Maartje Voors** (NL)
14:20 - 15:00		***Coffee & tea / Poster viewing***

Programme

Parallel session Cancer-Genetics
Room: 2.1 Volga

Time slot		
09:00 - 09:30		Registration
09:30 - 11:00		**Session Cancer I: Changing practice: Gene based to risk based** *Chairs: Marleen Kets (NL) & Katie Snape (UK)*
09:30 - 09:50		• Lifestyle Factors in the Genetic Risk Spectrum for Breast Cancer – **Marjanka Schmidt (NL)**
09:50 - 10:10		• Penetrance and risk of cancer susceptibility genes; observations from population cohorts regarding penetrance – **Leigh Jackson (UK)**
10:10 - 10:20	28	• Implementation of the CanRisk tool for breast cancer families – **Fieke Teertstra** (NL)
10:20 - 10:30	29	• Interpretation of Constitutional Cancer Predisposition in Multiple Primary Tumour Patients from 100,000 Genomes Project – **Diana Prepelita** (UK)
10:30 - 10:40	30	• Personalised risks of second primary cancers after colorectal cancer in Lynch syndrome and the general population: robust population-based estimates from linked national cancer and Lynch syndrome registries, England 1995 to 2022 – **Lucy Loong** (UK)
10:40 - 10:50	31	• Moving towards effective and ethical use of germline data in molecular tumor testing – presenting current challenges and the start of a research project – **Noor Giesbertz** (NL)
10:50 - 11:00	32	• Inherited cancer risks in Multilocus Inherited Neoplasia Alleles Syndrome – **Abbey Cropper** (UK)
11:00 - 11:30		***Coffee & tea / Poster viewing***
11:30 - 12:30		**Session Cancer II: Changing practice: Gene based to risk based** *Chairs: Bernadette van Nesselrooij (NL) & Clare Turnbull (UK)*
11:30 - 11:50		• Prophylactic gastrectomy or endoscopic surveillance in HDGC, time for a paradigm shift? – **Jolanda van Dieren (NL)**
11:50 - 12:10		• Phenotype-first or genotype-first genomic sequencing: implications for counselling carriers of pathogenic RET variants – **Kash Patel (UK)**

Programme

12:10 - 12:20	33	• Maximising opportunities for early cancer detection and prevention through a National Inherited Cancer Predisposition Register (NICPR) – **Helen Hanson** (UK)
12:20 - 12:30	34	• The impact of a mainstream genetic testing pathway and socioeconomic factors on the uptake of germline genetic testing in breast cancer patients: the nationwide GENE-SMART study – **Chiem de Jong** (NL)
12:30 - 13:30		***Lunch / Poster viewing with the presenters (even numbers)***
13:30 - 14:30		**Session Cancer III: Changing practice: variant interpretation and risk management** *Chairs: Encarna Gomez Garcia (NL) & Ros Eeles (UK)*
13:30 - 13:40	35	• Data-informed approach to the interpretation of variants in FH causing hereditary leiomyomatosis and renal cell carcinoma (HLRCC) from Cancer Variant Interpretation Group UK (CanVIG-UK): clinical application under the evolving v4.0 ACMG/AMP framework – **Alice Garret** (UK)
13:40 - 13:50	36	• Impact of surveillance colonoscopy on colorectal cancer incidence and mortality in 4,732 Lynch syndrome patients in English NHS: a national observational cohort study – **Clare Turnbull** (UK)
13:50 - 14:00	37	• Radiological surveillance in BAP1-tumor predisposition syndrome patients using MRI-chest-abdomen – **Coen Bijns** (NL)
14:00 - 14:10	38	• Li-Fraumeni Syndrome in the UK: A national clinical genetics audit of diagnostic trends and cancer surveillance – **Joseph Cristopher** (UK)
14:10 - 14:20	39	• United Against Prostate Cancer (UAPC): Addressing Health inequalities in Prostate Cancer – **María Echevarría Gutiérrez** (UK)
14:20 - 14:30	40	• Assessing the Acceptability of Prophylactic Prostatectomy for People at High Genetic Risk of Developing Prostate Cancer: A Qualitative Study – **Tarryn Shaw** (UK)
14:30 - 15:00		***Coffee & tea / Poster viewing***

Programme

Joint closure
Room: Auditorium 2

Time slot		Plenary session
15:00 - 16:00		**Awards Session** *Chairs: Petra Zwijnenburg (NL) & Mohnish Suri (UK)*
15:00 - 15:20		Ben ter Haar Prize and Lecture
15:20 - 15:45		Awards: • Robin Winter prize • Dutch Science prize • Joint Poster prize • Medical Student essay award
15:45 - 16.00		Closure – Els Vanhoutte

Clinical Genetics Society Medical Student Essay Prize 2025-2026

Medical students in the UK were invited to submit a 2,000 word essay titled 'Newborn genome sequencing: protecting the future or overstepping the present?'.

We are delighted to confirm the winner is:

- **Angelica Nantakan Ubonwan**, a 4th year medical student at the Aston Medical School (link)

Please click on the link to read the essay.

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Practical Information

VENUE
MECC Maastricht
Forum 100
6229 GV Maastricht

WI-FI
Network: MECC free WI-FI (open network)

ROOMS
Auditorium 2: plenary programme and CGS meeting on Monday
parallel programme non-cancer Genetics and awards ceremony on Tuesday
2.1 Volga: parallel programme Cancer Genetics on Tuesday
Brightlands Foyer: coffee, tea, lunches, drinks, posters and exhibition
Trajectum Zuid: conference secretariat
Bar Bistro SAAM: conference dinner (for registered participants only, fully booked)

LUNCH, COFFEE, TEA
All catering will be available in the Brightlands Foyer.
Coffee and tea will be available all day.
All catering is vegetarian.
Other dietary requirements can be requested at the bar.

MOBILE PHONES
Please ensure that Mobile Phones are switched off in the lecture theatre.

SCIENTIFIC PROGRAMME
The Scientific Meetings will take place in Auditorium 2 on Monday and Tuesday, and in Room 2.1 Volga on Tuesday.
Please note that the programme is very full; all sessions will begin promptly. Presenters have been asked to stick strictly to their allocated time. They will be available to answer further questions during the breaks.

POSTERS
There are posters in the Brightlands Foyer. Abstracts in the programme booklet (nrs P1-P30).
Odd numbers will be presented on Monday during lunch.
Even numbers will be presented on Tuesday during lunch.
A poster prize will be awarded to the poster with most votes from the participants. All participants can vote online for their favourite poster (see the QR code on your name badge). The winner will be announced at the awards ceremony on Tuesday afternoon.

Practical Information

EXHIBITION

- **Agilent**
- **GenQA**
- **Twist Bioscience**
- **Centogene**
- **Novogene**
- **Devyser**

ACCREDITATION

The conference is accredited by the Dutch Clinical Genetics Society (VKGN); 10 points in total and has CPD approval; 12 points. The VKGN and the Royal College of Physicians (UK) require participants to sign the attendance register on every day of attendance.
Certificates of attendance will be provided digitally afterwards.

RECEPTION & DINNER

On the evening of Day 1, we will host a reception with drinks and bites for all participants from 17:00 to 18:30.

Dinner will be served at 19:00 at Bar Bistro SAAM. You will find Bar Bistro SAAM in the MECC Maastricht complex.
This includes a walking dinner and three drinks.
The dinner is not vegetarian; participants with dietary requirements can inform the bar staff.

Dinner is *fully booked*. Only those with a coloured dot on their name badge have registered for dinner.

Prof. Dr. Wendy van Zelst-Stams

Head of department
Department of Clinical Genetics
Maastricht UMC+ & Radboudumc

The Netherlands

Undiagnosed Hackathons: Hype or Hope?

The purpose of an Undiagnosed Hackathon (UH) is trying to find new ways and collaborations to solve the undiagnosed diseases, that can't be solved today (approximately 350 million people live with an undiagnosed disease (PLWUD) worldwide). A UH forms the template of creating an interdisciplinary team of individuals (or a 'village') to diagnose more PLWUD, and exchange best practices on how to internationally increase the (genetic) diagnostic knowledge base. The premise of the UH is simple: case studies for a PLWUD that have stumped physicians often as a part of an Undiagnosed Diseases Program will be reviewed. For these PLWUD, new (genetic) data is generated using state-of-the-art technologies for evaluation by a multidisciplinary team, including physicians, diagnosticians, bioinformaticians and translational researchers, with the aim to find the diagnosis. Up to 19 (45 %) of previously unsolved cases of PLWUD in the UH hosted in the Netherlands in 2024 received a diagnosis. Of note, the vast majority of these novel diagnoses were identified from newly generated datasets (opposed to reanalysis of existing data sets), and long-read genomes were most instrumental, validating the importance of complete genomes for clinical variant interpretation. These conclusions were also recently shown at large scale by a Pan-European effort of the Solve-RD project where newly generated long read genomes increased diagnostic yield by > 17 % across multiple rare disease entities. Also here, collaborative efforts bringing together clinical and analytical expertise, referred to as Solvathons, were instrumental for diagnosis.

Prof. Emma Baple

Professor of Genomic Medicine
University of Exeter
Royal Devon University Healthcare
NHS Foundation Trust

United Kingdom

Improving the efficiency and clinical utility of genomic testing in the NHS Genomic Medicine Service

Authors: Emma Baple, Alexandra Pickard, Nirupa Murugaesu, Angela Hamblin, Jane Deller, Maricica Zabrautanu, Polly Tally, Rachael Mein, Zandra Deans, Sue Hill On behalf of NHS England Genomics Unit

Demand for genomic testing has grown since the establishment of the NHS Genomic Medicine Service (NHS GMS), in 2018. This increase in demand is due to the success of adopting and embedding genomics into many clinical pathways and the increase in demand, for example, through the approval of new precision medicines requiring genomic test to confirm eligibility. This increase in demand has in turn driven increased efficiencies in the end-to-end testing pathway, including utilising the most cost-effective technologies and efficient testing, analysis and reporting strategies as well as clinically driven assessment of the utility and benefit a genomic test result may provide. Illustrative examples of how this has been achieved will be provided, including through review of the National Genomic Test Directory (NGTD). NHS England (NHSE) commission the NHS GMS for patients in England. The NGTD outlines the full range of genomic and omic tests that are funded by NHSE, the technological approach for delivery, and test eligibility criteria. The NGTD is updated annually based on stakeholder feedback and updates are linked to NICE Technology Appraisal or approved NHSE National Clinical Policy changes. More than 850,000 tests were delivered in financial year 25/26 through the NHS GMS. Laboratory services are required to submit test volumes, turnaround times and diagnostic outcomes via Patient Level Contract Monitoring Data (PLCM). This data has been used to revise the NGTD. For example, standalone FRAXA testing for intellectual disability (700 tests per month) has been removed due to low diagnostic yield (~0.4%). Patients now receive FRAXA testing as part of genome sequencing for intellectual disability, illustrating the value of ongoing monitoring in informing funding of genomic testing as part of an overarching national testing strategy, which responds to changing technologies and clinical evidence base.

Invited speakers & Lecturers

Prof. Dr. Laurence Boon

Centre for Vascular Anomalies
Cliniques Universitaires Saint-Luc
Brussels

Belgium

Vascular Malformations: from Genetic to Precision Therapy

Vascular anomalies (VAs) encompass a diverse group of vascular lesions categorized into vascular tumors and vascular malformations according to the ISSVA Classification. Vascular malformations are further classified by flow characteristics into slow-flow and fast-flow categories, assisting in accurate diagnosis and treatment planning, which traditionally involves surgery, embolization, or sclerotherapy. Recent advancements in genetic and molecular understanding have led to the development of a molecular classification system based on pathways such as PI3K/AKT/mTOR (PIKopathies) and RAS/RAF/MEK/ERK (RASopathies), enabling targeted therapies.

Diantha Terlouw PhD

Clinical Scientist in Molecular Pathology
Leiden University Medical Center

The Netherlands

Prevalence and consequences of APC mosaicism in patients with colorectal adenomas

A substantial proportion of patients with adenomatous polyposis lack an identifiable germline pathogenic variant in APC. In our study, we aimed to determine the prevalence of APC mosaicism across a broad spectrum of polyposis phenotypes and to suggest recommendations for testing and surveillance. Using targeted next-generation sequencing, we assessed APC mosaicism in a large cohort of 542 patients with unexplained adenomatous polyposis. Overall, APC mosaicism was detected in 9.4% of patients. Among the patients meeting national

hereditary polyposis testing criteria, the detection rate was 14.3%, compared with 2.3% in patients outside these criteria. Detection rates were at least 10% in patients with ≥20 adenomas before age 60 or ≥30 adenomas before age 70. Of the mosaic patients who underwent esophagogastroduodenoscopy, 26% were diagnosed with gastroduodenal polyps. In one of two patients tested, the mosaic variant was detected in semen; however, none of the tested offspring in this cohort inherited the variant. APC mosaicism is a clinically relevant cause of unexplained adenomatous polyposis. We recommend APC mosaicism testing in patients with ≥20 adenomas before age 60 or ≥30 adenomas before age 70. Surveillance should include regular colonoscopy and at least one gastroduodenoscopy, with follow-up guided by findings. Germline testing of offspring should be considered. Moreover, our analyses of the APC gene in this large cohort of adenomas provides evidence suggesting a role of colibactin (a genotoxin produced by pks+ E. coli bacteria) in the development of colorectal adenomas.

Prof. Sahar Mansour
SW Thames Centre for Genomics, St George's, Epsom and St Helier University Hospitals and Health Group London / Cardiovascular and Genomics Research Institute City St George's, University of London London
United Kingdom

CGS Lecture: Going with the Flow: 25 Years of Genetic Discoveries in Lymphovascular Disorders and Their Impact on Patients

In the last 25 years, the world of lymphovascular disorders has seen some exciting changes, thanks to breakthroughs in genetic research. Understanding of the underlying genetic causes has exploded. This has led directly to targeted treatment and better management and surveillance . These advancements have made a real difference in some patients' lives. Studying this group of condition is a paradigm of the development of the diagnostic power of genomics – from linkage to whole genome sequencing.

Invited speakers & Lecturers

Dr. Masoud Zamani Esteki

Head of the Laboratory of Cellular Genomic Medicine
Maastricht UMC+

The Netherlands

President's Lecture: From Individual Cells to Secretome of Human Embryos: The Next Era of Preimplantation Genetic Testing

Preimplantation genetic testing (PGT) has evolved beyond traditional targeted testing to encompass genome-wide analysis through whole-genome sequencing. Haplarithmisis, a conceptual workflow in genetics, enabled simultaneous haplotyping and copy-number profiling from few-cell DNA samples down to single cells, thereby improving diagnostic accuracy and resolution. Haplarithmisis has enabled clinical applications that were previously considered impossible, such as the accurate determination of the origin of aneuploidies to before or after fertilization. Recently, we developed an all-in-one PGT that enables all forms of PGT in a single assay. Specifically, this technology allows detailed assessment of both nuclear DNA and mitochondrial DNA. This all-in-one PGT can determine aneuploidy origin (PGT-AO), which can trace chromosomal aberration to before or after fertilization. Clinical-grade whole-genome sequencing is becoming the backbone of PGT. The future of PGT lies in automation and AI-based, integrative, non-invasive diagnostics. Predictive models powered by multimodal deep learning are emerging to enhance embryo selection by integrating genomic and morphological data. AI-based non-invasive PGT approaches could reduce embryo manipulation and streamline laboratory workflows. Moreover, all-in-one non-invasive prenatal testing (NIPT) approaches have the potential to elevate current NIPT screening programs and reduce the need for invasive follow-up procedures. The convergence of these innovations is set to revolutionize reproductive medicine by improving success rates, reducing unnecessary interventions, guiding timely interventions and enabling responsible, personalized, predictive, and preventive reproductive care.

Invited speakers & Lecturers

Prof. Dr. Ir. Marjanka Schmidt
Senior group Leader, Division of Molecular Pathology and the Division of Psychosocial Research and Epidemiology, NKI-AVL
Professor of genetic epidemiology of (breast) cancer, Department of Clinical Genetics, Leiden University Medical Centre
The Netherlands

Lifestyle Factors in the Genetic Risk Spectrum for Breast Cancer

Genetic predisposition plays a central role in breast cancer risk, yet a significant proportion of breast cancer cases are attributable to modifiable lifestyle factors. Epidemiological data consistently show that factors such as overweight and obesity, especially postmenopausal, physical inactivity, and alcohol consumption elevate breast cancer risk. Conversely, regular physical activity and breastfeeding offer protective effects. Hormonal exposures, such as those associated with oral contraceptive use and hormone replacement therapy, have been linked to a modest increase in breast cancer risk. However, how do these lifestyle factors impact women with an inherited predisposition to breast cancer, such as those with pathogenic variants in BRCA1 or BRCA2, or in moderate-risk genes like CHEK2, or individuals with a high polygenic risk score? Do general public health recommendations apply equally to these high-risk groups? Additionally, does ethnic background play a role in modifying these associations? In this presentation, I will review the current evidence regarding lifestyle factors and breast cancer risk, focusing on their relevance for individuals with genetic predisposition. I will discuss relevant healthcare guidelines and their applicability to high-risk populations. Through case examples drawn from the CanRisk tool, I will demonstrate how lifestyle affects risk within the context of genetic predisposition. For clinicians, integrating lifestyle counseling into routine care, both for the general population and for individuals at high genetic risk, represents a valuable opportunity to reduce breast cancer incidence and improve long-term health outcomes.

Invited speakers & Lecturers

Stefan Barakat, MD PhD

Associate professor, Head of the Non-Coding Genome Research Group
Erasmus MC, Rotterdam

The Netherlands

ReNU syndrome, RNUopathies and the non-coding genome: the Dutch experience

Despite genome sequencing becoming increasingly implemented as first tier genetic test for neurodevelopmental disorders, a diagnostic gap remains leaving at least half of the patients genetically undiagnosed. Most analysis aiming to find disease causing mutations focusses on the protein-coding part of the human genome. The remaining ~98% of non-coding sequencing have long been neglected searching for pathogenic variants, despite harboring important gene regulatory sequences and non-coding genes. Two landmark papers in 2024 described de novo variants that are missed upon exome sequencing in the short nuclear RNA (snRNA) gene RNU4-2 as one of the most frequent causes of syndromic intellectual disability, estimated to explain up to 0.4% of all neurodevelopmental disorders. By now, hundreds of patients have been diagnosed with this new disease entity called ReNU syndrome. More recently, similar dominant disorders caused by variants in the snRNA genes RNU2-2 and RNU5-B1 have been described, with the latest reports even describing recessive conditions for RNU4-2 and RNU2-2; the latter being estimated to have a particularly high carrier frequency. Therefore, together these non-coding RNUopathies, and similar ones yet to be discovered, likely explain more than one percent of all previously undiagnosed neurodevelopmental disorders. To tackle the challenges associated with these novel and unusually frequent conditions, we started a nationwide clinic for ReNU syndrome and related non-coding disease causes at the Erasmus MC in Rotterdam. Within the last year, we have identified and assessed more than 30 patients with these novel conditions at our clinic. Next to functioning as an expert hub for information, family questions and counseling, we initiated a deep-phenotyping and natural history study using the Child Brain Lab at the Sophia Children's hospital and have biobanked a variety of samples for functional studies. These include the generation of patient derived induced pluripotent stem cells allowing modelling of neurodevelopment and drug screens, the identification of disease-associated biomarkers and RNA-based diagnostic approaches. Furthermore, we have generated zebrafish models to gain

understanding of the disease mechanisms and obtain a functional platform to test variants of unknown significance. In my presentation, I will provide an update on the current state of knowledge on ReNU syndrome and other RNUopathies and share our latest insights from these ongoing clinical and fundamental studies.

Dr. Leigh Jackson

Project researcher
University of Exeter

United Kingdom

Penetrance and risk of cancer susceptibility genes; observations from population cohorts regarding penetrance

Introduction The vast majority of penetrance estimates in the literature have come from clinical cohorts and are therefore impacted by ascertainment bias as a result as these groups are enriched for highly penetrant variants. These estimates, while informative for counselling similar families, should be regarded with caution when reporting in a secondary findings or newborn screening (NBS) context in the absence of a phenotype or family history. Population cohorts have different biases such as survivor and healthy volunteer bias but nonetheless present a useful opportunity to assess penetrance of conditions outside of the clinically-ascertained context. Methods We present our findings from numerous gene-condition dyad studies in UK Biobank and All of US, and some important points to consider. Results Penetrance and risk of cancer susceptibility variants in population cohorts are consistently lower than in clinical cohorts. We have shown this for RB1, TSC1 and TSC2 as well as previously for BRCA1, BRCA2, MLH1,MHS2 and MSH6 In Tuberous Sclerosis, we found errors in disease coding meaning our cohort was much smaller than it initially appeared. This is a particular problem for rare disease where coding errors may be more frequent than true cases. Discussion Assessing penetrance in population cohorts is challenging and without careful curation of variants and phenotypes, major errors in risk estimates are possible. Inclusion of benign variants, definition of what constitutes penetrance and errors in datasets will all influence conclusions.

Invited speakers & Lecturers

Prof. Dr. Matthijs Verhage

Head of Functional Genomics, Center for Neurogenomics and Cognitive Research (CNCR), Vrije Universiteit & Amsterdam UMC

The Netherlands

Disease mechanisms & intervention strategies for SNAREopathies, disorders caused by mutations in genes that drive the secretion of chemical signals in the brain.

SNAREopathies are disorders caused by mutations in eight presynaptic genes that together drive synaptic vesicle exocytosis, synaptic transmission and the release of neuropeptides. SNAREopathies are are among the most common monogenic neurodevelopmental disorders and characterized by developmental delay, intellectual disability, and often epilepsy, motor abnormalities and autistic traits. We have studied SNAREopathies, especially caused by mutations in STXBP1/Munc18-1, SYT1, and SNAP25 in patient cohorts, in mouse models and in IPSC-derived patient neurons. Mutations in SYT1 and SNAP25 lead to functional deficits. For SYT1, three classes of functional deficits are emerging. In contrast, all pathogenic STXBP1 mutations cause protein instability, reduced cellular levels, reorganization of the synaptic proteome, changes in neuronal network activity, hyper-excitability, EEG abnormalities and cognitive deficits. We have used the observed cellular and mouse model phenotypes to develop new DNA- and RNA-based intervention strategies. We have used patient neurons, new EEG analyses, and in silico modeling to establish cell-based diagnostics for SNAREopathies and develop personalized treatment decisions based on their emerging predictivity. Finally, we have established ESCO (www.stxbp1eu.org), an EU consortium coordinating a natural history study (NHS) and clinical trials for STXBP1-related disorders. ESCO works together with the European Medicine Agency using in silico trial simulations with real world data from our NHS to design innovative clinical trials that maximize power for limited patient populations. ESCO is nesting different trial modalities in a single NHS serving as a grand historical/concurrent control and providing (Bayesian) priors. In this way, ESCO can evaluate many emerging candidate therapies with a limited patient cohort.

Dr. Jolanda van Dieren

Gastroenterologist
Netherlands Cancer Institute,
Amsterdam

The Netherlands

Prophylactic gastrectomy or endoscopic surveillance in HDGC, time for a paradigm shift?

Hereditary diffuse gastric cancer (HDGC) is a result of pathogenic germline variants in the CDH1 and CTNNA1 genes. Currently, prophylactic total gastrectomy (PTG) is often advised for persons with HDGC, mainly in CDH1 PV. In these PTG specimens, small T1a signet ring cell carcinoma (SRCC) lesions are found in 95% of persons with a CDH1 PV. Conversely, only 10-40% of CDH1 PV develop advanced gastric cancer, suggesting that most lesions behave indolent. CTNNA1 PV are even at lower risk for developing advanced gastric cancer (<10%). Therefore, a current matter of debate is whether advises about PTG could be individualized based on endoscopic surveillance results. Despite improved endoscopic detection rates, the reliability of endoscopic surveillance is still limited and varying among expert centers. To be able to provide a more suitable advice regarding (the timing of) PTG, it is important to first endoscopically identify the SRCC lesions and subsequently distinguish indolent from atypical and possibly more infiltrative lesions in gastroscopy. In a joint Dutch surveillance cohort of over 150 persons with HDGC, we aim to investigate the endoscopic and pathologic distinction between indolent and non-indolent SRCC lesions and to validate this proposed classification system in an international expert consortium.

Invited speakers & Lecturers

Prof. Dr. Nicole Wolf

Child Neurologist
Amsterdam Leukodystrophy Center,
Emma Children's Hospital,
Amsterdam UMC

The Netherlands

Leukodystrophies – it's time for treatment!

Leukodystrophies are defined as genetic disorders primarily affecting brain white matter. All modes of inheritance are possible. Genetic diagnosis is nowadays possible in about 90% of patients. Many diseases are ultrarare, and for a few leukodystrophies, specific variants lead to very specific phenotypes. Therapeutic options are slowly increasing. Ex vivo gene therapy is effective for patients with Metachromatic Leukodystrophy. Allogenic haematopoietic stem cell transplantation is used for several leukodystrophies. Several trials are ongoing, using in vivo gene therapy, antisense oligonucleotides and repurposed drugs.

Dr. Kash Patel

Associate Professor, department of
Clinical and Biomedical Science
University of Exeter Medical School

United Kingdom

Phenotype-first or genotype-first genomic sequencing: implications for counselling carriers of pathogenic RET variants

In this talk, I will present new data on the penetrance of pathogenic RET variants and show how sequencing strategy shapes risk interpretation. Using population-based and clinically ascertained cohorts, we compare phenotype-first and genotype-first approaches and quantify how ascertainment affects estimated disease risk. These differences matter in practice and I will show how this evidence supports more accurate, proportionate counselling

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ORAL PRESENTATIONS

1 – 40

Abstracts

1

Expanded carrier screening during pregnancy: reproductive follow-up of 100 consanguineous couples

Juliette Schuurmans*12, Suming Sun12, Phillis Lakeman3, Vyne van der Schoot4, Christine de Die12, Malou Heijligers12, Vivian Vernimmen12, Arthur van den Wijngaard12, Sander Stegmann12, Aimee Paulussen12*

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3 Department of Clinical Genetics, Amsterdam UMC, Amsterdam, The Netherlands
4 Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands.

Background: Preconception carrier testing (PCT) for autosomal recessive (AR) and/or X-linked conditions can be offered to enhance couples' reproductive decision-making. Consanguineous couples have an increased risk to be a carrier couple for AR conditions. Ideally, testing is performed before conception, but is often requested during pregnancy. The aims for this study were to gain insight into the diagnostic yield and reproductive decision-making of consanguineous couples using PCT during pregnancy.
Subjects and Method: A hundred pregnant consanguineous couples (aged ≥ 18), referred and counselled for PCT by clinical geneticists from all Dutch academic centers were included. Exome-based PCT for AR conditions with a large gene panel (>2000 genes) was performed. Diagnostic yield was defined as the percentage of couples who were identified as carrier couples for a condition they were not yet aware of. Conditions were categorised based on severity. Reproductive decisions were extracted from patients' medical files.
Results: Diagnostic yield was 25% (25/100). AR conditions couples were carriers of were diseases with a range in severity and variable expressivity; examples were Familial Mediterranean Fever and Joubert Syndrome. Pregnant couples made different decisions after test results, including invasive prenatal testing, continuation and termination of affected pregnancies, postnatal genetic testing and decisions regarding peripartum care. In two cases the PCT resulted in explanations for foetal abnormalities that were not explained by prenatal testing.
Conclusion: These results show that expanded carrier testing during pregnancy in consanguineous couples has a high diagnostic yield. Couples use these PCT results to make different reproductive decisions.

2

UK consensus recommendations for constitutional testing for Lynch Syndrome for patients with mismatch repair deficient or microsatellite instability-high non-colorectal/non-endometrial cancers

Terri McVeigh *(1,2), Kevin Monahan (3), Katie Snape (4) on behalf of UK Cancer Genetics Group and National Lynch Syndrome Network*

1. Royal Marsden NHS Foundation Trust
2. Institute of Cancer Research
3. St Mark's Bowel Hospital
4. St George's University Hospital NHS Foundation Trust

Background: Tumour-based testing for microsatellite instability (MSI) and/or mismatch repair (MMR) deficiency (dMMR) to screen for Lynch syndrome (LS) in endometrial, colon and other Lynch Syndrome-associated malignancies. Such features also predict response to checkpoint inhibitors, and as indications for such treatments expand, so too does tumour-agnostic testing for these biomarkers, necessitating development of an aligned tumour-agnostic framework to identify and triage patients requiring testing for Lynch Syndrome or onward investigation.
Methods: We conducted a targeted literature review to determine the proportion of MSI/MLH1 deficiency attributable to MLH1 promoter hypermethylation, Lynch syndrome, and biallelic somatic events impacting relevant MMR genes across different cancer types. These data informed indications for MLH1 promoter methylation triage, germline genetic testing for Lynch Syndrome, and somatic MMR gene testing.
Results: We propose unified indications for MLH1 promoter methylation, germline and somatic MMR gene testing following detection of MSI or dMMR across tumour types. Patients with high-yield tumours (urinary tract, small bowel, pancreatic, adrenocortical, sebaceous carcinoma) should be offered upfront germline genetic testing. A substantial proportion of MSI-high gastric cancers demonstrate underlying MLH1 promoter hypermethylation, necessitating methylation triage for such cancers, in addition to MSI/MLH1 deficient colorectal and endometrial cancers, before consideration of germline genetic testing. Somatic sequencing should be used selectively to identify double-somatic MMR inactivation where resolving hereditary risk will impact family management.
Conclusion: This consensus provides a clear national framework to guide onward investigation following tumour MSI/MMR results, balancing diagnostic yield, resource impact, and clinical utility.

3

Navigating mosaicism in neurofibromatosis type 1: implications for couples considering preimplantation genetic testing

Vivian Vernimmen *1,2, Martine De Rycke3,4, Céline Moutou5,6, Marinus J Blok1,2, Rick van Minkelen7, Malou Heijligers1,2, Masoud Zamani Esteki1,2,8, Christine EM de Die-Smulders1,2, Aimée DC Paulussen1,2*

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We report the molecular genetic aspects of preimplantation genetic testing (PGT) for neurofibromatosis type 1 (NF1) in three international PGT centers between 2004 and 2022. A PGT assay was developed for 281 couples with 218 different variants in NF1. Mosaicism was present in 8% of the sporadic index cases (n=13/168), of which about half were unknown prior to PGT (n=6/13). Mosaicism was significantly associated with multiple exon deletions and two recurrent SNVs. The more frequent occurrence of mosaicism is known for gross NF1 deletions, but not for intragenic deletions and SNVs. With suspected or confirmed mosaic NF1, the potential lower recurrence risk and more severe expression in offspring if the variant is inherited, should be acknowledged in reproductive counseling. For couples with mosaic NF1 in the affected partner who proceed with PGT, extra caution is necessary during test design, as mosaicism for NF1 in the index parent can result in three alleles being transmitted: non-risk allele and risk allele with and without pathogenic variant. This poses difficulties in defining the risk haplotype, transfer policies and can even result in misdiagnosis. We developed a flowchart outlining challenges in and an approach for reproductive counseling, PGT design

and PGT treatment for NF1. Applying this approach to other PGT indications with a high de novo rate and relatively frequent mosaicism, such as familial adenomatous polyposis, could be considered. Our findings significantly impact reproductive counseling for couples with NF1 and PGT molecular design and treatment for those proceeding with PGT.

4

High prevalence of cutaneous postzygotic mosaicism of Patched 1 variants in patients developing multiple basal cell carcinomas

A.J. Jimenez Lemus *(1), A.A.L. Massella Patsea (1), B.J.A. Verkouteren (1), K. Mosterd (1) and M. van Geel (1,2)*

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Background: Basal cell nevus syndrome (BCNS) is a rare genetic disorder, characterized by multiple basal cell carcinomas (BCCs) and associated syndromic features. BCNS results from heterozygous pathogenic variants in the Patched 1 (PTCH1) tumor suppressor gene. Causal germline PTCH1 variants are well established in BCNS, however the prevalence of postzygotic mosaicism for PTCH1 variants in cutaneous BCC cases remains unclear.
Objective: We aimed to investigate PTCH1 mosaicism prevalence in a cohort of patients with multiple BCCs and other BCNS features, lacking germline PTCH1 mutation in blood.
Methods: Multiple different BCCs from 42 patients suspected having BCNS, lacking a germline causal PTCH1 variant in blood, were genotyped for PTCH1 using targeted next-generation sequencing. This cohort study was complemented by a literature review on PubMed, LOVD and EMBASE, to conceptualize the prevalence of de novo PTCH1 variants in BCNS.
Results: Literature review demonstrated that the prevalence of de novo mutations in BCNS patients account for 35.8%. This suggests that mosaicism may be more prevalent in the general population than earlier acknowledged. Accordingly, in our cohort of patients with suspected BCNS, we found 33% of patients with postzygotic mosaicism in PTCH1, sharing a variant in the patient's BCCs. Remarkably, these patients frequently exhibit only multiple BCCs, with no other manifestations of BCNS.
Conclusion: We demonstrate by using this analytic strategy, that many of the so called high frequency BCC patients are ultimately diagnosed as postzygotic PTCH1 mosaic cases. PTCH1 mosaicism may represent a significant proportion of patients with unexplained occurrence of multiple BCCs.

5

Developing and characterising zebrafish models for Vascular Ehlers-Danlos Syndrome: clarifying VUS through CRISPANT analysis

Nataliya Pidlisnyuk *1, Daniel Baird 1, Zuzanna Matelowska 1, Nurhaziqah Supari 1, Emily Woods 2, Jessica Bowen 2, Glenda Sobey 2, Duncan Baker 2, Meena Balasubramanian 1,2*

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Background: Vascular Ehlers-Danlos Syndrome (vEDS) is a life-threatening connective tissue disorder caused by pathogenic COL3A1 variants, characterised by vascular fragility, arterial dissections, and organ rupture. A major challenge in clinical genetics is the high proportion of variants of uncertain significance (VUS), which limits diagnostic confidence and impacts patient management. Zebrafish offer a genetically tractable in vivo system capable of modelling collagen-related disease and generating functional evidence to support variant interpretation.
Aims and Hypothesis: This project aims to establish and characterise a zebrafish model of vEDS by knocking out col5a1, a functional surrogate for COL3A1. An accompanying F0 CRISPANT approach enables early phenotypic analysis. We hypothesise that targeted col5a1 disruption will recapitulate vEDS-like phenotypes, providing a robust platform for functional assessment of patient-specific COL3A1 variants.
Methods: A stable col5a1 knockout line and F0 CRISPANTs were generated using CRISPR/Cas9. Phenotypic characterisation included brightfield imaging, heart rate analysis, and vascular assessment using transgenic lines. In parallel, COL3A1 VUS from the Sheffield Diagnostic Genetics Service were reviewed to prioritise candidates for future knock-in modelling.
Results and Conclusion: Clinical reanalysis reclassified approximately one-third of COL3A1 VUS, underscoring the ongoing need for functional evidence, and identified two high-priority VUS for future modelling. CRISPR/Cas9 editing successfully produced a stable col5a1 knockout line. F0 CRISPANTs exhibited reduced heart rates, increased cardiac oedema, haemorrhagic susceptibility, and altered vascular morphology, mirroring hallmark vEDS features. These findings validate zebrafish as an effective and clinically relevant model for vEDS and establish a platform for functional validation to support COL3A1 VUS reclassification.

6

Domain-wide mapping of peer-reviewed literature for genetic developmental disorders using machine learning and Gene2Phenotype

T. Michael Yates*1,2, Sarah E. Hunt3, Diana Lemos3, Seeta Ramaraju Pericherla3, Elena Cibrian Uhalte3, Morad Ansari4, Louise Thompson4, Simona E. Doneva5, Caroline F. Wright6, Helen V. Firth7,8 and T. Ian Simpson1,9*

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9. Simons Initiative for the Developing Brain, University of Edinburgh, Edinburgh, United Kingdom

Genetically determined developmental disorders (GDD) are rare, heterogeneous conditions for which clinical diagnosis increasingly depends on genomic variant prioritisation and rapid synthesis of genotype–phenotype evidence scattered across the literature. Manual curation of this evidence is labour-intensive, difficult to scale and to keep up to date. We present a domain-wide, automated pipeline that identifies PubMed abstracts describing human case reports/series and maps them to molecularly defined diseases in the Gene2Phenotype database (G2P). The natural language processing system combines a fine-tuned BERT (Bidirectional Encoder Representations from Transformers) classifier (LitDD BERT) to detect GDD-relevant abstracts, a fine-tuned cross-encoder (LitDD Crossencoder) to propose disease candidates, and a constrained large language model to adjudicate final mappings. Trained on 13,738 annotated title–abstract pairs spanning 231 genes and 354 G2P entries, LitDD BERT achieved a precision of 0.83 and recall of 0.94, i.e. 83% of called papers were correct and 94% of correct papers were identified. F1 score (harmonic mean of precision and recall) was 0.89. The cross-encoder reached 0.99 top-5 recall, and the full ensemble attained precision 0.89, recall 0.82, and F1 0.85 on a held-out test set. Applied to the entirety of PubMed,

the pipeline identified approximately 69,000 manuscripts which could be mapped to G2P diseases. Against independent manually curated sets, it retrieved about 70% of manuscripts at both micro and macro levels, indicating generalization across diverse disease mechanisms, differing curation standards and inheritance patterns. The resulting corpus is accessible through G2P and is being integrated into routine biocuration. This work delivers scalable, updateable literature surveillance for GDD, enabling faster evidence review in a diagnostic setting, supporting bioinformatic pipelines, and laying a foundation for downstream case-level extraction and standardized phenotype integration.

7

Counting survivors of 'lethal' skeletal dysplasia; a review of the 100,000 Genomes Project

Megan F. Baxter *(1,2), Rhoda Akilapa (1), Jenny C. Taylor (2), Melita D. Irving (1)*

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2. Centre for Human Genetics, University of Oxford, Oxford

Introduction:
Identifying the aetiology of a patient's disease is essential for appropriate counselling and access to targeted treatments. Skeletal dysplasia is traditionally cited as having a 20–30% prenatal or perinatal lethality. Increasing however anecdotal reports describe long-term survivors in these classically lethal skeletal dysplasia. This raises the question of whether individuals with variants in classically lethal genes are being identified and, if so, whether specific genotypic factors influence survival. These concepts may extend to other congenital disorders involving essential developmental genes.
Methods:
A targeted literature review generated a curated list of genes associated with lethal skeletal dysplasia, informed by the 2023 Skeletal Nosology. Solved rare-disease cases from the 100 000 Genomes Project (100kGP) were assessed for variants in classically lethal or potentially lethal genes. Variants were evaluated for predicted molecular effects and recurrence in available literature.
Results:
One hundred and ten genes were identified as associated with classically or potentially lethal disease. Multiple individuals within the 100kGP harboured variants in genes canonically linked to lethal skeletal dysplasia yet are surviving beyond the perinatal period. These individuals did not exhibit molecularly "milder" variants, and literature review confirmed that several of these variants had previously been reported in lethal presentations.
Conclusion:
Survival despite canonical lethal genotypes suggests genuine phenotypic heterogeneity rather than uniformly attenuated variants, supporting interpretation of skeletal dysplasia as a phenotypic spectrum. This framework can be applicable to non-skeletal dysplasia conditions involving essential genes, highlighting the value of broader, less stringent variant analysis in rare disease diagnostics re-analysis.

8

Exome-wide analysis of rare deleterious variants in 3,569 cases and 21,788 controls reveals no novel sarcoma susceptibility genes

Garrett, Alice*(1); Kuzbari, Zeid(1); Wade, Isaac(1); Rowlands, Charlie(2); Larkeryd, Adrian(1); Turnbull, Clare(1)*

(1) Division of Genetics and Epidemiology, Institute of Cancer Research

Background: Sarcoma is a rare cancer of the bones and soft tissues representing ~1% of adult and ~15% of childhood cancer diagnoses, with >70 histological subtypes. Although sarcomas are associated with germline pathogenic variants in TP53 and other genetic rare syndromes, unlike breast/colorectal cancer, no established susceptibility genes account for substantial portions of risk. Previous sarcoma susceptibility studies have been of modest size, limited by phenotype rarity and heterogeneity.
Methods: We identified whole exome and/or genome germline sequencing data from sarcoma cases of any age from the 100,000 Genomes Project, The Cancer Genome Atlas, the Genetics of Multiple Cancers Study, the International Sarcoma Kinship Study, the Childhood Cancer Survivor Study and the Children's Oncology Group. We identified four ethnicity-matched control datasets and organised cases and controls into four "analysis pillars". We performed within-pillar equivalency optimisation and implemented gene-level rare variant burden testing with multiple variant prioritisation strategies in each analysis pillar, using the SAIGE-GENE method. We combined individual analysis pillar results through random-effect meta-analysis.
Outputs: In total, data from 3,569 sarcoma cases and 21,788 controls were analysed, by far the largest sarcoma case-control analysis to-date. There was an estimated ~80% power to detect novel sarcoma susceptibility genes at odds ratio of ≥5 and ≥0.17% population frequency. Results suggested that additional sarcoma associations likely exist amongst established cancer susceptibility genes, but that these are likely of small effect size and/or low frequency, and therefore arguably of limited clinical utility.

9

Implementation of the polygenic risk score for breast cancer in clinical practice

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2. Sequencing Analysis Support Core, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands.
3. Department of Human Genetics, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Polygenic Risk Scores (PRS), which combine common genetic variants associated with breast cancer, can help refine breast cancer risk. Currently, the most widely used PRS for breast cancer is PRS313, based on 313 genetic variants. In the Netherlands, the BOADICEA risk prediction model- accessible via the CanRisk webtool - is routinely used in clinical genetics centers and supports the integration of PRS313 into risk assessments. Currently, PRS313 is mostly calculated using SNP-array data, which limits its compatibility with next-generation sequencing (NGS)-based clinical workflows. Therefore, a PRS313 test is not yet available in diagnostic laboratories in the Netherlands.
Since 2023, validation of the PRS313-test is started in the Leiden UMC and Radboud UMC. Key challenges in this process include accurate calling of variants in low-complexity regions, deviations in variant allele frequencies compared with the gnomAD database, and the presence of variants that cannot be detected using NGS-based methods. For validation of the NGS-based PRS313-test, PRS scores generated from array-based variant calls are compared with those obtained through NGS. We aim to begin offering the diagnostic PRS313-test in 2026 to healthy women referred to the clinical genetics centers for presymptomatic testing of a familial variant in a breast cancer gene.
In our presentation, we will provide an overview of the implementation process of the PRS313 in the Netherlands, including current challenges and progress. This will cover solutions for technically challenging variants within the NGS workflow, validation outcomes, and discussion points related to ethnicity and the potential addition of an HBOC panel.

10

PROTECT-C: Population-based germline testing for early detection and prevention of cancer

1. Ranjit Manchanda on behalf of the PROTECT-C study team and collaborators.
2. Grace Norman 3. Rosie Corbie 4. ***Caitlin Fierheller*** *5. Jingsong Zhao*
6. Subhashenee Ganesan 7. Jaqueline Sia 8. Rosa Legood 9. Gareth Evans
10. Adam Brentnall

Aims
The primary objective is to evaluate the impact of population-based genetic-testing on identification of pathogenic/likely-pathogenic variants (PVs) in high and moderate-penetrance cancer susceptibility genes (CSGs): BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2/MLH1/MSH2/MSH6 compared with family-history/criteria-based genetic-testing. Secondary objectives include the impact of testing common variants on identifying women at moderate/high-risk of breast cancer (BC) and ovarian cancer (OC) using personalised risk prediction (using CANRISK) in general population women; along-with the impact on health behaviour, psycho-social health, quality-of-life, patient experience, uptake of screening/prevention and cost-effectiveness.
Methods
PROTECT-C is a fully end-to-end digital, prospective cohort study recruiting 5,000 women >18years irrespective of personal/FH of cancer, through self-referral and NHS Digi-Trials. Participants access a bespoke app (Android/Apple/Web) developed with clinical, research, and patient input and includes nine animation videos in six languages. Recruitment, access to information, consent, return of results, genetic-counselling access, all occurs via the App and includes a dedicated helpline for counselling support. Consenting individuals receive a saliva-kit by post. Individuals with a PV, VUS, or increased personalised breast/ovarian cancer risk (using CANRISK) are referred for NHS risk management pathways, while relatives may access cascade-testing. Separate work-streams evaluate return of VUS-results; qualitative analysis; and health-economic analysis. Follow-up: 8 years.
Expected Results: PROTECT-C will provide data on PV-carriers, VUS, increased risk individuals detected along-with patient experience, satisfaction, helpline usage, App-usability, psychosocial outcomes, quality-of-life, patient experience, uptake of screening/preventive interventions. Qualitative 1:1 sub-study will provide data on patient experiences. Health-economic sub-study will inform cost-effectiveness of population testing vs. FH-based testing approaches (NICE methodology).

11

CanVar-UK: an international data sharing and interpretation platform for germline variants in inherited cancer susceptibility genes

Charlie F. Rowlands*(1), Subin Choi(1), Sophie Allen(1), Alice Garrett(1), CanVIG-UK Steering and Advisory Group (CStAG); CanVIG-UK (Cancer Variant Interpretation group UK); Clare Turnbull(1,2)*

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(2) The Royal Marsden NHS Foundation Trust, London, UK

Identification of pathogenic germline variants in cancer susceptibility genes (CSGs) allows access to vital surveillance, management, treatment and counselling options for patients and their families. Guidance for interpretation of variants in specific CSGs by Variant Curation Expert Panels recommends the use of diverse in silico predictive tools, functional studies and population datasets. Critical to the interpretation of germline CSG variants is the collation of detailed clinical data, sharing of which is often crucial to reach an assignment of pathogenicity/benignity. The CanVar-UK website was created as a platform for the centralisation of key data sources for CSG variant interpretation and to provide a direct means of clinical data sharing. For all possible single nucleotide coding variants in a curated set of 116 CSGs, CanVar-UK displays corresponding scores from 11 in silico tools, 25 functional studies and four genetic epidemiology datasets, alongside population allele counts from gnomAD v4.1 and UK Biobank. Also displayed for variants in key genes of clinical interest are proband testing counts from the NHS National Disease Registration Service to allow quantification of case-control signal. A discussion forum functionality allows users to email the CanVar-UK user base to request additional data to assist in variant classification, or issue reclassification alerts. CanVar-UK has been widely adopted by NHS clinical genomics staff working in inherited cancer susceptibility, with over 860 registered NHS users and a rapidly growing non-NHS user base of over 650 individuals from 57 countries. CanVar-UK therefore plays a valuable role in the interpretation of variants in CSGs.

12

Increasing clinical utility of prenatal exome sequencing: the potential power of Artificial Intelligence phenotype-driven analysis.

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7. Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
8. Nostos Genomics GmbH, Berlin, Germany.

Purpose
Analysis strategies of prenatal exome sequencing (pES) range from limited gene panels to exome-wide analyses, with both extremes having advantages and disadvantages. We investigated whether Artificial Intelligence (AI) variant interpretation software might be a viable alternative.
Methods
We included 233 parental-foetal trios. The validity of the AI platform (AION by Nostos Genomics) was evaluated and diagnostic variants, Variants of Uncertain Significance (VUS) possibly linked to the phenotype, and Incidental Findings (IF) identified with AI were compared to the clinical diagnostic work-up and the application of two Genomics England gene panels (Foetal Anomalies and DDG2P).
Results
Diagnostic yield of AI and both gene panels was 14.2% (N = 33 cases). In clinical diagnostic work-up, one additional diagnosis was made that was missed with AI and gene panel analysis. The number of prioritized variants was not significantly correlated with the specificity or number of HPO-terms. Newer releases of the AI software were inversely correlated with less prioritized variants (p-value < 0.001).

The total number of diagnoses, VUS and IF did not significantly differ between the four modalities.

Conclusion

AI could aid the often-laborious interpretation of variants and make curating gene panels redundant. This is crucial in prenatal care, where the increasing number of referrals and time pressure of advancing gestation are challenging.

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Integrating enriched case data from national laboratory testing within large-scale case-control analyses (PS4) using a novel statistical likelihood-ratio methodology

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Background: Prospective and historic (back to 1998) germline testing data have been collated across all English diagnostic testing laboratories by the National Disease Registration Service (NDRS), forming a dataset of over 85,000 HBOC patients tested for BRCA1/BRCA2, offering great potential to inform UK variant classification. We have developed a methodology for leveraging enriched nationally-collected datasets within case-control analysis via adjusted integration with unselected datasets using novel likelihood ratio tools.
Methods: We estimated enrichment of pathogenic variants in clinically-ascertained laboratory data from both NDRS (England) and Ambry (USA) using prevalence of protein truncating variants, and paired this data with equivalent population controls. Using our published PS4-LRCalc tool, which enables application of case-control evidence towards both pathogenicity and benignity, we calculated a combined log likelihood ratio (LLR) across five datasets (three unselected, and two enriched).
Results: Data were combined for 10,819 missense variants from 325,255 female breast cancer patients and 671,350 controls of Western European ancestry for five breast cancer susceptibility genes (BRCA1, BRCA2, PALB2, ATM, CHEK2). A combined LLR was produced for 4,921 missense variants; 861 variants received evidence towards pathogenicity (LLR≥1), and 3,629 received evidence towards benignity (LLR≤1).
Conclusion: This novel variant-level methodology leverages value from nationally collected laboratory variant data and empowers flexible incorporation of case-control data (PS4) into variant classification, ultimately reducing the number of VUS classifications.

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Characterization of Rare Genomic Structural Variants Across 2,981 Genomes Reveals Significant Involvements in Recessive Conditions

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Background: Current methods experience challenges in precisely identifying and determining genomic structural variants (SV) composition. Here, we introduce SCARD (Split-read, Chimeric read-pAirs, and Read-depth Difference), an integrated approach optimized for detection and characterization of rare SVs using genome sequencing data.
Methods: We evaluated the rare SV (with minor allele frequency <1%) detection performance using 16 clinical cases with 18 previously ascertained exonic deletions/duplications. Additionally, we described clinically significant, loss-of-function (LoF) SVs involving genes associated with autosomal recessive (AR) disorders across 2,504 individuals and 477 trios/probands from the 1000 Genomes Project. Finally, we compared our SVs in 15 cases to that of HiFi datasets, and those results from 13 SV detection methods (13callers).
Results: SCARD accurately detected all 18 exonic deletions/duplications, ranging from 490bp to 24.5kb, outperforming other methods that only achieved 15/18 at best. Among 2,504 genomes analyzed, we identified 429,259 rare deletions/duplications and 7,795 structural rearrangements, with 10.7% of deletions/duplications (46,032/429,259) and 40.1% of structural rearrangements (3,126/7,795) being novel to that from 13callers. Notably, 45.2% (1,133/2,504) of the subjects carried LoF SVs involving AR disorders related genes. In 477 trios, the de novo rate for rare SVs was 0.5% (383/77,349). Lastly, among the 15 cases with HiFi datasets, the accuracy by SCARD were 97.9% (2,905/2,967). In comparison, 13callers missed or misinterpreted 325 of 2,905 validated rare SVs (11.2%) reported by SCARD.
Conclusions: Our study demonstrates that SCARD enables comprehensive, genome-wide identification and precise delineation of rare SVs and revealed a high carrier rate of AR disorders contributed by rare SVs.

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There is more to NOTCH3 than CADASIL: differential effects on NOTCH3 signaling underlie the diverse phenotypes associated with NOTCH3 frameshift and nonsense variants

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NOTCH3 is a transmembrane receptor that regulates developmental processes and vascular smooth muscle cell fate. NOTCH3 frameshift and nonsense variants cause two distinct phenotypes: a non-CADASIL small vessel disease (SVD), and the congenital dysmorphic lateral meningocele syndrome (LMS). Here, we analyzed which NOTCH3 variants result in each phenotype and whether these differentially affect NOTCH3 signaling. Individuals with a NOTCH3 frameshift or nonsense variant were ascertained in UK Biobank, 8 hospitals from Europe, Asia, and the United States, and literature. Their clinical records and neuroimaging were analyzed, and nonsense-mediated decay was examined with Sanger sequencing. Subsequently, NOTCH3 variants were cloned and NOTCH3 signaling was assessed using CBF1 reporter assays. Of the 122 UK Biobank cases and 93 clinically ascertained cases, 46 had an SVD phenotype and 17 an LMS phenotype. In cases with an SVD phenotype, degradation of the mutant mRNA was confirmed, while in LMS cases, that clustered in the far C-terminal end of the protein, the mutant mRNA escaped nonsense-mediated decay. These mRNA strands encoded truncated NOTCH3 receptors that lack the C-terminal PEST domain, required for protein degradation. Accordingly, LMS variants showed a strong increase in NOTCH3 signaling, while SVD cases showed reduced signaling. Overall, we conclude that the phenotype of NOTCH3 frameshift and nonsense variants depends on variant location and subsequent effect on NOTCH3 signaling. These findings enable a correct interpretation of NOTCH3 variants in the clinical setting, and illustrate how the diverse roles of NOTCH3 in embryogenesis and vessel homeostasis may lead to two highly dissimilar phenotypes.

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Three-dimensional facial gestalt analysis for three neurodevelopmental disorders: Koolen-de Vries, Jansen-de Vries and KBG syndrome.

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Diagnosing children with developmental disorders is often challenging due to the large number of rare syndromes and their variable clinical presentations. While next-generation sequencing has improved diagnostic yield, results are frequently inconclusive, highlighting the continued importance of detailed phenotypic assessment. Three-dimensional (3D) facial imaging has shown advantages over traditional two-dimensional (2D) photographs in syndrome identification, offering new opportunities for more accurate diagnosis. In this study, we explored the benefits of 3D shape analysis for three syndromes seen at the Radboudumc expertise clinic for neurodevelopmental disorders: Koolen-de Vries syndrome (KdVS), Jansen-de Vries syndrome (JdVS) and KBG syndrome. Each patient's facial shape was aligned with a 3D growth curve derived from healthy controls, which allowed us to objectively evaluate how their features compared to their age- and sex-matched average. This analysis validated previously recognized features for all three syndromes and led to the identification of a novel phenotypical feature for JdVS, namely supraorbital grooves. The consistency of the facial features for each of these three syndromes was then calculated using a cosine distance analysis and compared with that of 19 other dysmorphically well-characterized syndromes, both for the overall face as well as for eight facial segments. In line with current understanding the consistency was highest for KdVS and features of JdVS and KBG syndrome were more diverse in this cohort. These results highlight the potential of 3D imaging for neurodevelopmental disorders, enhance current diagnostic knowledge and provide a foundation for future 3D shape analysis of these three syndromes.

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DNA methylation profiling in Hao-Fountain syndrome: diagnostic episignatures, nanopore validation, integrative functional analyses and future cellular models

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Hao-Fountain syndrome is a rare neurodevelopmental disorder caused by pathogenic variants in USP7. DNA methylation episignatures have emerged as powerful tools for the diagnosis of neurodevelopmental disorders, but their integration with genetic variant detection and functional interpretation remains an important next step. In this study, we applied a multi-layered epigenomic approach to characterize Hao-Fountain syndrome and explore future diagnostic and functional applications.
Genome-wide DNA methylation profiling of whole blood samples from individuals with pathogenic USP7 variants identified a robust and reproducible disease-specific episignature, supporting its clinical diagnostic utility. To evaluate whether genetic and epigenetic information can be combined in a single assay, long-read nanopore sequencing was applied to USP7 cases. Nanopore-based methylation profiles showed strong concordance with array-derived episignatures, while simultaneously enabling detection of sequence variants and copy number variants, highlighting its potential as a unified diagnostic test.
To investigate the functional relevance of the observed methylation changes, integrative expression quantitative trait methylation (eQTM) analyses were performed in both whole blood and patient-derived fibroblasts. These analyses identified significant cis- and trans-acting methylation–expression relationships, implicating genes involved in chromatin regulation, transcriptional control, and neurodevelopmental pathways. Comparison across tissues revealed both shared and tissue-specific regulatory effects, providing insight into how USP7 dysfunction impacts gene regulation in different cellular contexts.
Finally, induced pluripotent stem cell (iPSC) lines were successfully generated from peripheral blood of Hao-Fountain syndrome patients, establishing a platform for future mechanistic and developmental studies.

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Del2Phen: a new clinical tool for providing phenotype information on rare chromosome disorders directly to parents

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Most structural chromosome aberrations are rare and heterogeneous, leaving clinicians and families with limited prognostic information. The Chromosome 6 Project aims to address this gap by making personalized clinical information accessible in real time. To achieve this, we developed Del2Phen, a tool that generates aberration-specific phenotype information for chromosome disorders. Using the project's large cohort, we optimised this tool for chromosome 6 deletions. Based on the coordinates of the chromosome aberration of a new patient, Del2Phen identifies individuals with a similar deletion or duplication. Clinical descriptions are then generated by summarising developmental, medical, and behavioural features within this group of genotypically similar individuals. Genotypic similarity is determined using knowledge on gene haploinsufficiency and established gene-phenotype relationships. Optimal genotypic similarity parameters for chromosome 6 deletions were defined as: (i) concordance in the involvement of genes known to have a highly penetrant phenotypic effect and (ii) the highest possible overlap in haploinsufficiency gene content that yields groups of at least 15-20 genotypically similar individuals. These parameters provided reliable and comprehensive phenotype descriptions for the full range of chromosome 6 deletions. Del2Phen offers a quick and reproducible approach to generating personalized clinical information for rare chromosome disorders. Although currently optimized for chromosome 6 deletions, it is transferable to other chromosomes and is easily adaptable for duplications, given sufficient data is available. Del2Phen will be integrated into an interactive website where families and clinicians can access its output, addressing the currently unmet information needs and improving understanding of these rare disorders.

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A case series to expand the phenotype of PIK3CA germline mutations

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Background & Aim:
PIK3CA mutations typically arise post-zygotically, resulting in the phenotypically broad PIK3CA-related overgrowth spectrum (PROS) Over 1,000 cases have been reported allowing clinical guidelines to be established. In contrast, germline PIK3CA mutations are rare, with only 26 published cases. Their phenotype and management remain poorly defined. We report a new case series to expand the known phenotype.
Methods:
7 individuals with germline PIK3CA variants were identified. Clinical features including growth and neuroimaging data were systematically extracted. Seven additional cases are under recruitment.
Results:
We report seven individuals with confirmed germline PIK3CA mutations. Macrocephaly was universal (mean SD+5.9). 5/7 individuals were overweight or obese. Developmental delay was present in 6/7 and autistic traits were identified in 4/7. MRI imaging was performed in 5 cases and abnormal in 4/5 including polymicrogyria (3/5), thick corpus callosum (3/5) and prominent perivascular spaces (3/5). Vascular birthmarks were frequent (5/7). 3/5 males had hypospadias. The mutational spectrum of our cohort differed from that commonly seen in somatic PROS. The rate of novel variants was high with minimal overlap with previously reported somatic variants.
Conclusion:
Germline PIK3CA mutations produce a recognisable but distinct clinical phenotype from somatic PROS. Similarities can be seen with megalencephaly-capillary malformation-polymicrogyria syndrome (MCAP) with significant macrocephaly, neurodevelopmental and MRI features but without somatic asymmetry or polydactyly. Emerging distinct phenotypic features include hypospadias and obesity. Our findings substantially expand the clinical and molecular spectrum of germline PIK3CA-related disease and highlight the need for tailored management guidelines.

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Craniofacial effects of vosoritide in treating achondroplasia: results of a worldwide survey and 3D facial imaging.

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Achondroplasia is caused by a recurrent, pathogenic variant in the gene encoding the fibroblast factor receptor type 3, FGFR3. Consequently, the FGFR3 signalling pathway is activated, resulting in inhibition of endochondral ossification and disproportionate short stature.
However, achondroplasia is a multisystemic medical condition involving disruption of all skeletal elements, including the craniofacial bones. This leads to severe neurological and respiratory complications conferring a fifty-fold increase in sudden infant death, from stenosis at the foramen magnum and both central and obstructive sleep disordered breathing. Additionally, a high incidence of ENT and dental issues occur, as well as macrocephaly and midface hypoplasia. These impact both health and function on a day-to-day basis.
Vosoritide is a precision medicine developed to counteract FGFR3 over-activation, thereby modifying bone growth. Whilst this manifests in the clinical trial setting as a sustained 1.57cm/year additional growth of the long bones, we sought to determine the effects of treatment on the craniofacial skeleton in the real-world. Here we describe the results of a patient reported outcome survey of the effects of the drug on facial shape and mobility, quality of voice, the ability to eat and swallow, and the ENT and respiratory effects, involving 200 subjects receiving vosoritide worldwide. In addition, we report the effects on facial structure as determined by sequential 3D imaging, used to determine remodelling that can then be correlated with functional changes. These data represent key benefits that are beyond height in managing this complex skeletal dysplasia condition.

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Building the ID-Treatabolome - Toward Personalized Medicine and equitable access to targeted treatments for genetic Intellectual Disabilities

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Background: Intellectual disability (ID) affects 2–3% of the global population. Current genomic technologies achieve diagnostic yields of up to 50%; more than 1,750 genes are implicated. Disorder-specific therapies are emerging for an increasing number of rare genetic disorders. Therapeutic evidence, however, remains dispersed across literature and is difficult to access in clinical practice. Consequently, patients may miss out on available targeted interventions, resulting in avoidable harm. The ID-Treatabolome project aims to establish the first open-access, systematically curated database that links ID-associated genes to targeted interventions.
Methods: Using standardized systematic review methodologies, we identify, appraise, and classify peer-reviewed evidence on disorder-specific therapies for the 1,966 disorders currently designated by SysNDD as definitively associated with ID. This FAIR-compliant (Findable, Accessible, Interoperable, Reusable) dataset is intended to support rapid, genetics-informed treatment decision-making. A pilot review encompassing the alphabetically first 369 genes has been completed, with a full scoping review ongoing.
Results: For these 369 genes, screening 14,532 titles and abstracts yielded 71 publications describing 30 ID-associated disorders (8.1%) with at least one targeted treatment. Pharmacological interventions were most frequently reported (28/71, 39.4%), followed by nutritional therapy (17/71, 23.9%) and vitamin or trace-element supplementation (11/71, 15.5%). Preliminary gene-therapy evidence was identified only for Canavan disease.
Conclusion: This pilot demonstrates that targeted treatments are available for 8.1% of ID-associated disorders. Ongoing advances in e.g. drug repurposing and gene therapy will expand these opportunities. Generating up-to-date, publicly accessible treatment information in the ID-Treatabolome database will support clinicians, patients and families in improving clinical outcomes.

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The effects of targeted therapies for achondroplasia go beyond height

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Several clinical trials have demonstrated that precision medicines targeted to the overactivation of the FGFR3 signalling pathway and developed to treat achondroplasia, the most common type of skeletal dysplasia condition, achieve a sustained increase in longitudinal bone growth. Evidence of the effects that are beyond height have taken longer to demonstrate though. Emerging data are now showing that the associated multisystemic complications are also amenable to medical therapy. These include craniofacial complications, such as severe neurological compromise, and respiratory and ENT effects, lower limb bowing, spinal canal stenosis with risk of paralysis, and generalised, chronic pain. Disproportionate short stature itself confers functional and psychosocial difficulties for affected individuals, also potentially responsive to treatment.
This presentation will describe the different mechanisms developed to counteract the inhibition of endochondral ossification seen in FGFR3-related short stature that also encompasses hypochondroplasia. The multisystemic consequences of these conditions will be further highlighted and the evidence in both the clinical trial and real-world settings of the effect of medical therapies demonstrated. This will include the effect on the lower limb mechanical axis, the foramen magnum dimensions, spinal canal anatomy, craniofacial structure through 3D imaging, and changes in body proportion on health-related quality of life.

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Over a decade of clinical genomics quality assessments: GenQA's journey in supporting clinical teams

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Aims: To describe the development, implementation, and impact of GenQA's unique External Quality Assessments (EQAs) for Clinical Geneticists and Genetic Counsellors, and to evaluate how these case-based assessments support education, benchmarking, professional development, and improved service quality.
Methods: In response to a European Society of Human Genetics initiative to establish clinical quality assessment in 2011, GenQA developed online EQAs that simulate routine clinical practice using real patient scenarios. In 2014, four Clinical Genetics EQAs - Cardiovascular disorders, Dysmorphology, Monogenic disorders, and Oncogenetics - were launched to assess appropriate test selection, genomic result interpretation for final diagnosis, and follow-up advice. A Genetic Counselling EQA introduced in 2021, expanded into two discipline-specific schemes in 2025, further evaluates counselling and communication skills. Anonymised submissions from centres across the world are marked by an international expert panel using professional guidelines and returned with tailored score reports and learning points. Programme design has been refined through participant feedback and an appeals process. The four core EQAs achieved ISO 17043 accreditation in 2025.
Results: EQA Summary reports promote collective learning and support training across clinical genomics services. Clinicians can use these EQAs to review and enhance practice, address errors in test selection and interpretation, and strengthen counselling skills. Benchmarking against global peers enables objective performance evaluation, while targeted support is provided to centres with sub-optimal results.
Conclusion: GenQA's accredited clinical EQAs offer a scalable, standardised educational framework that strengthens professional competency, improves consistency in genomic decision-making, and supports high-quality patient care across the clinical genomics pathway.

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Sex and Age Specific Genetic Risk of Dilated and Arrhythmogenic Cardiomyopathy: Insights from the SHaRe Registry

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Background: Dilated (DCM) and arrhythmogenic cardiomyopathy (ACM) are progressive myocardial disorders with phenotypic and genetic overlap. Although a male predominance is recognized, it is unclear whether this extends to specific

genetic subtypes and whether sex affects age-dependent penetrance in pediatric and adult populations.

Methods: We studied genetically tested adult and pediatric DCM/ACM patients and asymptomatic genotype-positive relatives in the multicenter SHaRe Registry. Sex distribution across DCM/ACM genes was assessed using logistic regression. Age at diagnosis, as a proxy for penetrance, was evaluated by sex and genotype using Kaplan–Meier cumulative incidence estimates.

Results: Among 3,410 adults, a male predominance was present across genotype-positive (57%), genotype-negative (62%), and VUS groups (62%), with notable gene-specific variation. Females were less likely to have TTN truncating variants (OR 0.42, 95% CI 0.33–0.54, $p<0.01$) but more likely to have DSP variants (OR 3.3, 95% CI 2.35–4.78, $p<0.01$) and non-TTN sarcomeric variants (OR 1.68, 95% CI 1.15–2.47, $p<0.001$). Age at diagnosis was generally similar between sexes, except among TTNtv carriers, where males showed earlier onset (median 45 vs. 51 years, $p=0.003$). Pediatric-onset cases (n=174; 60% male) displayed distinct genetic features, with sarcomeric and PKP2 variants enriched compared with adults (OR 5.5, $p<0.01$ and OR 2.8, $p<0.05$, respectively), and demonstrated a bimodal onset in infancy and adolescence.

Conclusion: Sex- and gene-specific differences shape disease prevalence and onset in DCM/ACM. TTNtv affects males more frequently and earlier, whereas DSP and non-TTN sarcomeric variants are more common in females. Pediatric disease is predominantly driven by sarcomeric variants and PKP2. These findings support age- and sex-tailored surveillance strategies.

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The hidden burden of genetic testing: evaluating the impact of mainstream testing for monogenic hearing loss in a regional NHS clinical genetics service

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Introduction: The downstream implications of mainstreamed genetic testing for clinical genetics service delivery in the NHS remain ill-defined. We undertook a retrospective review of electronic patient records of 120 individuals with variants identified by the NHS R67 monogenic hearing loss test between 2021 and 2025 to evaluate this.
Methods: Variants classified using ACMG guidelines were scored for genotype–phenotype correlation (0–2). Clinical workload was quantified per proband and family unit using time-based activity modelling, incorporating clinical appointments, MDT meetings, genetic test orders, onward referrals, and correspondence. Time spent on care coordination, organisation of family testing outside standard service areas, case preparation and background research was also recorded.
Results: 120 patients were reported to have genetic variants (70% AR and 30% AD). 21 (17%) had variants of uncertain significance (VUS) (38% AR and 61% AD). The mean calculated workload for each patient was 225 minutes (range 115 minutes for GJB2 disease and 535 minutes for ultrarare variants). The mean workload for patients with confirmed disease was 217 minutes (180 minutes AR and 240 minutes AD). In contrast, the mean workload for VUS was 320 minutes (303 minutes AR and 308 minutes AD).
Conclusions: The investigation of monogenic hearing loss is therefore associated with diagnostic complexity that generates substantial downstream workloads in relation to variant interpretation and family follow-up. As a model for rare disease this study offers a scalable framework to assess other NGS service demands on clinical genetics services and guide resource optimisation across rare disease services.

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Streamlining both the patient experience and genomic testing for Familial Pneumothorax via a UK Rare Disease Collaborative Network (RDCN)

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Familial spontaneous pneumothorax (FSP) accounts for up to 14% of primary spontaneous pneumothoraces. 26% of probands have a clinical genetic diagnosis of whom approximately 50% have Birt-Hogg-Dubé syndrome (BHD). Mainstream NHS genetic testing for FSP in England is currently undertaken using a gene panel and clinical criteria developed for the 100,000 genomes project. We analysed national and regional data to assess the proportion of genetic diagnoses in cases of familial pneumothorax attained through different testing routes using data from (i) the Rare Disease Collaborative Network (RDCN) for FSP (n=77 patients); (ii) North East and Yorkshire Genomic Laboratory Hub (GLH, n=68 patients); (iii) Cambridge University Hospitals (n=53 patients). The overall diagnostic yield in FSP cases referred for genetic testing was 24%. The diagnostic yield in patients reviewed via the RDCN was 38%. We found that 17% of patients referred to the RDCN had previously had clinical genetics assessments which were not clinically indicated using RDCN referral criteria. 31% of patients reviewed by the RDCN did not require onward referral to Clinical Genetics services. Multidisciplinary review of clinical and radiological data was found to inform genetic testing. 35% (9/35) probands with pulmonary cysts reviewed by the RDCN had a molecular diagnosis of BHDS. Significantly, 20% of these individuals had cysts without a history of pneumothorax. Our data show that a specialist multidisciplinary approach is effective in increasing diagnostic yield and reducing demand on clinic appointments. This serves as a model for effective genetic multidisciplinary care in other rare disease settings.

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Penetrance of cardiomyopathies in families with (likely) pathogenic TTN variants; towards evidence-based recommendations regarding family screening

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Introduction: Truncating variants in TTN (TTNtvs) are associated with (dilated) cardiomyopathy ((D)CM). Due to TTNs complexity, TTNtvs are often classified as 'likely pathogenic' (LP). This results in defensive family screening recommendations. Results of a recent Dutch study reinforce the use of a less defensive genetics-first screening approach in relatives from families with an LP variant in genes associated with DCM in general. To add gene-specific substantiation, our study investigates the penetrance and age at diagnosis of cardiomyopathies in families with an (L)P variant in TTN specifically.
Methods: 131 subjects aged 10-77 years from families with a (L)P TTN variant counselled at the Radboudumc were included. Using a cross-sectional design, data on medical history, genetic test results and clinical outcomes were extracted from electronic patient files and analysed.
Results: Penetrance of cardiomyopathies ≥30 years was 57.5% in LP variant carriers, 50.0% in pathogenic variant carriers, and 6.3% in non-carrying relatives. Penetrance increased mildly with age. Most affected subjects developed DCM. Penetrance was higher in men vs. women (p=0.032), 1st vs. ≥2nd degree relatives (p=0.021), and subjects with vs. without a history of another possible (D)CM aetiology (p=0.031). Age at diagnosis ranged 19-77 years (mean 51.4±14.6), and was not sex dependent. Discussion: We suggest that penetrance of cardiomyopathies in carriers depends on age, sex and degree of kinship. As the few cases of (D)CM diagnoses in non-carrying relatives were probably not related to the familial genetic predisposition, our results support a genetics-first screening approach in families with a LP TTN variant.

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Implementation of the CanRisk tool for breast cancer families

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Problem description: The use of personalized risk estimations in women with an increased risk of breast cancer leads to more effective and targeted screening by providing the right care to the right woman. However, personalized risk estimations are very time-consuming and therefore an optimal screening advice is often not feasible.
Solutions: Previous research has shown that CanRisk is a valid and clinically useful risk prediction tool that can provide personalized risks by combining DNA test results, a polygenic risk score, family history, breast density and personal risk factors. However, support in electronic patient records and pedigree software is needed to enable use of CanRisk in standard care.
Aims: To implement CanRisk at all Clinical Genetic departments in the Netherlands by automating and standardizing its use for personalized risk estimations for breast cancer for at least 80% of the women for whom this is relevant. We focus on counselees without breast cancer, who visit a Clinical Genetic department and undergo a DNA test for the breast cancer genes.
Project plan: Implementation will start with making IT adjustments to enable automated input of variables in CanRisk. Educational sessions will be organized and case scenarios for risk estimation will be circulated and discussed with participating departments to support uniform use. To inform non-clinical genetic healthcare professionals as future users, informative sessions will be organized. Attention will be given to communication and understanding of CanRisk to support long-term acceptance. The implementation of CanRisk will be evaluated with regard to the implementation objective.

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Interpretation of Constitutional Cancer Predisposition in Multiple Primary Tumour Patients from 100,000 Genomes Project

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Background: Multiple primary tumours (MPTs) are frequent in the general population and are a feature of hereditary cancer syndromes. Most studies of MPT are epidemiological in nature but genetic data linked to MPT cohorts ascertained from various sources can assist with determining genetic testing criteria in this context. We used the 100,000 Genomes Project (100KGP) to define the prevalence of pathogenic/likely pathogenic (PLP) variants in cancer predisposition genes among participants with MPTs.
Methods: Participants with MPTs were identified by linking 100KGP to national cancer registry data recoded to ICD O 3.2 and applying ICD O3 MPT rules, supplemented by rare disease recruitment categories “Multiple Primaries” and “Tumour Syndromes”. Germline whole genome seqeuncing was analysed across 140 curated cancer predisposition genes. Rare, high quality variants were filtered using custom annoations, then classified with ACMG/CanVig-UK/ClinGen criteria.
Results: We screened 16,965 individuals in 100KGP and identified 3850 individuals with MPTs. Overall, approximately 10% of MPT patients harboured a PLP variant, rising to approximately 15% in those with more than two cancers under age 50. For each carrier we coded tumours as on target or off target relative to the gene specific spectrum and we also summarised common tumour type combinations.
Conclusions: In this large, national MPT cohort, germline PLP variants are common. Although less frequent than in clinically ascertained cohorts, these findings align with a recent UK Biobank study, indicating that reflex germline testing and refined clinical criteria may be useful.

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Personalised risks of second primary cancers after colorectal cancer in Lynch syndrome and the general population: robust population-based estimates from linked national cancer and Lynch syndrome registries, England 1995 to 2022

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Improving colorectal cancer (CRC) survival and increasing Lynch syndrome testing requires personalised second cancer risk estimates for counselling. Methods: We performed a retrospective cohort study linking three national English datasets of cancer registrations, Lynch syndrome patients and NHS germline mismatch repair tests held in the National Disease Registration Service. Risks and predictors were evaluated using standardised incidence ratios (SIRs), Kaplan–Meier cumulative incidence, and Cox proportional hazards regression. Results: The whole cohort (ALL) comprised 600,635 patients with CRC of whom 2,517 had Lynch Syndrome (LS) (MLH1:951, MSH2:872, MSH6:379, PMS2:315) and 3,369 had negative germline MMR tests (LS-Neg). SIRs for subsequent CRC were ALL:1.07 [95%CI 1.05-1.09], LS:15.2 [13.5-17.1], LS-Neg:5.25 [4.46-6.14]. SIRs for extracolonic subsequent cancers were ALL:1.04 [1.04-1.05], LS:3.35 [3.06-3.65], LS-Neg:1.47 [1.32-1.64]. In LS, site specific SIRs were elevated for canonical LS-associated cancers but also for breast 2.18 [1.63-2.86] and soft tissue cancers 5.26 [1.93-11.5]. Ten-year cumulative risks for CRC were MLH1:9.3%, MSH2:12%, MSH6:6.4%, PMS2:4.3%, and for extracolonic cancers were MLH1:12%, MSH2:19%, MSH6:20%, PMS2:8.2%. In multivariable models, CRC location, stage and age at diagnosis, synchronous CRC, gender, ethnicity, comorbidity, LS status and chemotherapy for the first CRC, were independently associated with the hazard of extracolonic second cancers. Conclusion: We present robust population-based estimates of second primary cancer risks for the growing population of CRC survivors, and evaluate tumour, patient and treatment factors that modify that risk, supporting the shift from gene-based to risk-based practice.

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Moving towards effective and ethical use of germline data in molecular tumor testing – presenting current challenges and the start of a research project

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Molecular tumour diagnostics (MTD) plays a central role in precision oncology. Its role in cancer care has expanded in recent years. With the advent of MTD, there is increasing overlap between oncological care and clinical genetics. Whether, and how likely, it is to uncover a hereditary predisposition in MTD depends on the specific test performed. Dutch guidelines categorise these tests into four groups. Category A tests carry a negligible possibility of identifying a hereditary predisposition, while categories B and C present a moderate likelihood of identifying a possible hereditary predisposition. Follow-up germline genetic testing is necessary to confirm or rule out the genetic predisposition. Category D MTD tests can directly reveal a hereditary predisposition as DNA from normal cells is sequenced separately from tumour DNA. As MTD expands to broader techniques such as whole-genome sequencing, interpretation increasingly requires matched tumour-normal sequencing (category D). Currently, in the Netherlands, germline test results are not routinely reported in MTD, mainly because it is unclear what should or should not be disclosed, and how this should be structured in clinical practice. Approaches could range from very restrictive—excluding direct germline analysis—to full disclosure of all pathogenic germline variants, with many positions in between. In the presentation, I will discuss current challenges in the use of germline data and outline the research plan for a project in which we aim to formulate a policy proposal by combining ethical analysis with empirical research.

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Inherited cancer risks in Multilocus Inherited Neoplasia Alleles Syndrome

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Routine gene panel testing has identified patients with two or more germline pathogenic variants in different cancer susceptibility genes (CSGs), a condition referred to as multilocus inherited neoplasia alleles syndrome (MINAS). Although more data are being collated, some aspects of MINAS remain under-investigated. Details for MINAS cases were extracted from the North East & Yorkshire Genomic Medicine Service laboratory datasets and clinical records. Comparison with a representative set of single CSG patients aimed to address whether MINAS is associated with more severe or distinct clinical manifestations. Individuals with pathogenic or likely pathogenic germline variants in two or more CSGs were included. Age at first cancer diagnosis, number of primary cancers, metastatic spread, and family history, were evaluated between the MINAS and the control cohorts by semi-quantitative analysis. Fourteen MINAS cases were identified and compared to 219 single CSG controls. MINAS showed a tentative association with earlier first cancer diagnosis (41.5 vs 47.0 years), higher metastasis incidence (50.0% vs 21.9%), and stronger family history (100% vs 68.5%), with no obvious increase in multiple primary cancers (7.1% vs 25.1%). Although statistical power was limited by sample size, these findings contribute to existing MINAS compilations; a previously unreported MINAS combination involving NTHL1 (biallelic) and ATM was encountered. These findings support the known trend for a slightly more pronounced cancer predisposition in MINAS. Further research in large cohorts is required to clarify subtler correlations and examine the effects of specific rare gene combinations for personalised clinical management and treatment.

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Maximising opportunities for early cancer detection and prevention through a National Inherited Cancer Predisposition Register (NICPR)

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NICPR, launched on 1st July 2025, is the result of a collaboration between the National Disease Registration Service (NDRS), NHS England programmes (Cancer, Genomics, Screening) and UKCGG with the overarching aim of improving clinical care of individuals with monogenic cancer susceptibility.
NICPR captures real-time data on all individuals with a likely pathogenic/pathogenic variant in a cancer susceptibility gene (CSG) in England via Regional Genetics Services (RGS). NICPR encompasses a dynamic list of ~120 CSGs linked to the National Genomic Test Directory and currently runs in parallel to the National Lynch Register.
As of 01/12/2025, 3192 NICPR real-time submissions have been made, including 59 genes. As expected, the greatest number of submissions are for breast cancer CSG (BRCA1=1056, BRCA2=772, PALB2=253, CHEK2=189, ATM =141).
In addition, 46,125 retrospective submissions have been collated by RGS following comprehensive review and curation of historic clinical and laboratory records.
This world-first national dataset of individuals at increased cancer risk provides significant opportunities for improved clinical care, audit and research. For example, novel and accurate data on incidence, prevalence, demographics and geography of CSG carriers supporting equitable service planning and delivery, potential referral route into national cancer screening and for centralised communications regarding updated clinical management.

Abstracts

NICPR can be linked to other national datasets, such as the cancer registry and Hospital Episode Statistics providing a unique research opportunity to improve knowledge of cancer risks and long-term outcomes.
An up-to-date summary of data submissions and use-cases for NICPR will be presented on behalf of the NICPR Steering Group.

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The impact of a mainstream genetic testing pathway and socioeconomic factors on the uptake of germline genetic testing in breast cancer patients: the nationwide GENE-SMART study

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In patients with breast cancer it is not known on a large scale whether the mainstream genetic testing (MGT) pathway, improves the overall genetic testing uptake and reduces disparities in genetic testing. In this nationwide retrospective cohort study, we examined the impact of MGT on the uptake of germline genetic testing in general and in socioeconomic status (SES) subgroups in particular.
We selected all breast cancer patients, from the Netherlands Cancer Registry diagnosed between Jan 1, 2017, and Dec 31, 2022 who were eligible for genetic testing according to the patient characteristics. The primary outcome was the uptake of genetic testing. The effect of MGT and SES on the uptake in general and for different levels of SES was analyzed by multivariate logistic regression.
A total of 12,190 breast cancer patients were included. Overall genetic testing uptake was 67%; 63% for referral to a genetics department, and 78% for MGT ($p<0.001$). Patients with low SES showed significant lower odds of receiving genetic testing compared to high SES (OR 0.71, 95% CI 0.61-0.83). MGT showed significantly higher odds of receiving genetic testing compared to referral to a genetic HCP in general (OR 2.48, 95% CI 2.14-2.87) and within SES groups.
MGT showed a significant increase in the uptake of genetic testing among all eligible breast cancer patients and for all SES groups, which strongly encourages further implementation of MGT. Educating HCPs on current disparities in genetic testing uptake is essential for further reducing disparities.

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Data-informed approach to the interpretation of variants in FH causing hereditary leiomyomatosis and renal cell carcinoma (HLRCC) from Cancer Variant Interpretation Group UK (CanVIG-UK): clinical application under the evolving v4.0 ACMG/AMP framework

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Background: Gene-specific adaptations of the 2015 ACMG/AMP v3.0 variant interpretation framework, undertaken by international variant curation expert panels (VCEPs), have enabled incorporation of gene-specific parameters to clinical variant classification. However, FH, a cancer susceptibility gene causing hereditary leiomyomatosis and renal cell cancer (HLRCC), is not currently under VCEP review. The Cancer Variant Interpretation Group UK (CanVIG-UK), a national clinical-laboratory network, aimed to develop an approach for quantifying the evidence allocatable for phenotypic specificity for this highly distinctive syndrome (evidence codes PP4 for v3.0, LOC_PHE and CLN_AFF for v4.0).
Methods: We collated FH germline testing data from four diagnostic laboratories for 387 individuals with an HLRCC-phenotype and for 1,780 individuals with unselected renal cancer. Via comparison to ancestry-stratified population data from UK-Biobank/gnomAD v2/1KGP, we calculated likelihood ratios (LRs) quantifying the different likelihoods for observation of a very rare missense variants (VRMVs) between phenotypically ascertained groups and population controls. Scientific literature and expert review informed other gene-specific adaptations for classification of exemplar variants.
Results: The VRMV-LR for the HLRCC-phenotype, excluding recurrent variants, was 57.81 (95% CI 39.79-82.71), equivalent to 5.54 evidence points, justifying +4 under LOC-PHE and +1 per proband under CLIN_AFF (v4.0). The equivalent VRMV-LR for

unselected renal cancer cases was 1.68 (95% CI 0.54-4.61), or 0.71 evidence points (no evidence applicable).
Conclusion: The VRMV-LR provides an objective measure of phenotypic specificity. The ACMG/AMP (draft) v4.0 evidence codes LOC-PHE and CLIN_AFF provided a clearer framework for interpretation and classification of rare missense variants in a gene with a highly specific phenotype.

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Impact of surveillance colonoscopy on colorectal cancer incidence and mortality in 4,732 Lynch syndrome patients in English NHS: a national observational cohort study.

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Evidence for colonoscopic surveillance for colorectal cancer (CRC) in Lynch syndrome (LS) is mixed. We conducted an observational cohort study of 4,732 people with LS using the English National LS Registry linked to national datasets of NHS hospital episodes and registered cancers. The study period was 01-January-2010 to 31-December-2022. We assessed adherence to national surveillance guidelines, analysing the colonoscopy frequency and using logistic regression to determine predictors of adherence. We sought to determine the impact of regular surveillance on CRC incidence, stage and mortality, by comparing age-specific annual incidence rates, cumulative risks, and stage distributions of CRC in patients with regular surveillance versus those without. Finally we used Kaplan-Meier methods and Cox Proportional Hazards regression to investigate the impact of regular surveillance on CRC-specific and all-cause mortality. Surveillance at a mean interval of ≤3 years was associated with lower CRC-specific and all-cause mortality, but without observed change in total CRC incidence, even after adjustment for confounding variables. There was no strong evidence of stage shift. By contrast, surveillance at a mean interval of ≤2 years was associated with higher CRC incidence, particularly for early-stage cancers, with no corresponding fall in late-stage cancers, which may indicate overdiagnosis. In this non-randomised setting, the observed reduction in all-cause mortality amongst regularly-surveilled LS patients, may indicate selection bias alongside a possible influence on CRC-specific mortality. Randomised controlled trials are required to definitively assess effectiveness of colonoscopic surveillance in LS.

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Radiological surveillance in BAP1-tumor predisposition syndrome patients using MRI-chest-abdomen

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Aims: Patients with the BAP1-tumor predisposition syndrome (BAP1-TPDS) have a life-time risk of 85% to develop ≥1 malignancy. Thus, the use of MRI-chest-abdomen (MRI-CA) imaging is recommended for regular cancer screening. However, evidence evaluating the yield is lacking. We aim to assess the clinical utility of MRI-CA in BAP1-TPDS patients at baseline and follow-up.
Methods: We prospectively followed 66 patients with BAP1-TPDS seen at the Leiden University Medical Center from July 2017 till September 2025.
Results: Out of the 66 patients with BAP1-TPDS, 42 were female (63.6%). In total 181 MRI screenings were performed, with a mean of 2.7 ± 1.2 screenings per patient. The median age at baseline was 49 years (range 25-74 years) and 52 years (range 30-74 years) for subsequent screenings. Initial screening led to an imaging or invasive intervention in 15.2% of scans, compared to 5.2% of subsequent screening. 3 (4.5%) cancers were detected at baseline MRI- CA, and 1 (0.9%) at subsequent screening. At baseline the sensitivity and specificity MRI-CA were 60% and 88.5%, respectively, with a positive predictive value (PPV) of 30%, negative predictive value (NPV) of 96.4%, false-positive rate (FPR) of 11.5% and false-negative rate (FNR) of 40%. The subsequent screenings showed a sensitivity of 50%, specificity of 95.8%, PPV of 16.7%, NPV of 99.1%, FPR of 4.4% and a FNR of 50%.
Conclusions: These findings provide important data for counseling BAP1-TPDS patients and show that MRI-CA is an effective screening tool, comparable to MRI screening in other tumor predisposition syndromes.

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Li-Fraumeni Syndrome in the UK: A national clinical genetics audit of diagnostic trends and cancer surveillance

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Background and aims: Li-Fraumeni syndrome (LFS) is increasingly diagnosed through expanded genetic testing. Intensive cancer surveillance is recommended, but outcomes within UK regional genetics services (RGS) have not been systematically evaluated. This national audit aimed to characterise trends in LFS diagnosis and evaluate provision, uptake and outcomes of cancer surveillance, with a focus on whole-body MRI (WB-MRI).
Methods: All 24 RGS were invited to participate in a national audit. Demographic data and diagnosis route were collected. Cancer surveillance and outcomes were captured over a 12-month period (July 2024 to June 2025).
Results: Thirteen RGS have responded to date with a total of 395 individuals with LFS included (mean age 36 years, range 3–89 years). Seven diagnoses were made between 2001 and 2005 compared with 174 diagnoses between 2021 and 2025, demonstrating rapid expansion of the UK LFS population.
Overall, 344 individuals (87%) were offered cancer surveillance. WB-MRI was available to 227 individuals (60%), of whom 164 (69%) underwent scanning during the audit period. Across all surveillance modalities, 69 findings were identified, leading to 82 additional investigations or clinical reviews, 17 invasive procedures, and 5 cancer diagnoses. WB-MRI accounted for 68% of surveillance findings and 80% of cancer diagnoses.
Conclusion: This audit demonstrates rapid expansion of the UK LFS population, and the substantial clinical workload associated with cancer surveillance. WB-MRI generates most surveillance findings and downstream investigations but also detects most surveillance-identified cancers. These findings emphasise the importance of care pathway design and adequate resourcing to manage the downstream consequences of surveillance.

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United Against Prostate Cancer (UAPC): Addressing Health inequalities in Prostate Cancer

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Prostate cancer remains the most common male cancer in the UK. Longstanding health inequalities disproportionately affect African and African-Caribbean men, who have twice the incidence of prostate cancer compared with white men and are more likely to experience aggressive disease. Family history of prostate and breast cancer is also related to a higher risk. Addressing disparities requires targeted awareness, early detection, and equitable access to genetic testing.
United Against Prostate Cancer (UAPC) is a pilot program developed to address these inequalities across the East Genomic Medicine Service Alliance (GMSA) region. Based at University Hospitals of Leicester, the project brings together clinicians, laboratory scientists, researchers, cancer charities, community organisations, and peer patient champions. Central to UAPC is meaningful community engagement: we co-created culturally sensitive outreach events, training materials, and educational resources—including case studies and awareness videos—ensuring information reaches high-risk groups. This collaborative approach aims to break down systemic barriers, improving awareness, trust, and access to early detection services and testing.
Alongside community work, UAPC implemented a new somatic tumour testing pathway for metastatic castrate-resistant prostate cancer. Thirteen patients were recruited from across the region, and two BRCA2 alterations were detected. Subsequent germline testing confirmed one inherited variant, enabling timely genetic counselling and early referral for at-risk relatives.
UAPC highlights how community-led initiatives, combined with greater access to and uptake of genetic testing, can help address prostate cancer inequalities. The model has attracted regional interest and supports wider national efforts to improve awareness, early diagnosis, and outcomes in high-risk communities.

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Assessing the Acceptability of Prophylactic Prostatectomy for People at High Genetic Risk of Developing Prostate Cancer: A Qualitative Study

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Background: Prostate cancer (PrCa) affects 1-in-8 people in the UK with half the cases occurring due to genetic factors. These include rare variants in cancer predisposition genes including BRCA2, and common genetic variants. Prophylactic, or 'risk-reducing' mastectomy and oophorectomy has been shown to prevent mortality and be acceptable for healthy women with known genetic risks. Prophylactic prostatectomy is currently not a standard procedure but could be offered to individuals at increased risk for PrCa as a future preventative healthcare approach. Aim: Prior to developing a feasibility study offering prophylactic prostatectomy to people at high genetic risk, we wanted to better understand patients' perspectives on acceptability and identify the information and support needs of individuals contemplating this procedure. Methods: We conducted semi-structured interviews involving 22 diverse participants at higher genetic risk of PrCa, some of whom had undergone prostatectomy as part of cancer treatment. Interviews were audio-recorded, transcribed and analysed using reflexive thematic analysis. Findings: Preliminary analysis suggests that acceptability towards prophylactic prostatectomy is influenced by factors including experience and trust of existing PrCa screening, intolerance of uncertainty, potential side-effects of surgery, family history, genetic risk status and perception of risk, age/life-phase, partner influence and personality type. Analysis is ongoing and will be presented in full. Conclusion: Our study will provide a wealth of in-depth perspectives on whether prophylactic prostatectomy may be an acceptable future option for some men living at increased risk of PrCa.

POSTER PRESENTATIONS

P1-P30

P1

Beyond Clinical Genetics; clinical coding and healthcare usage of individuals with inherited cancer predisposition in primary care -an exploratory study using UK Biobank

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Background: 5-10% of cancers arise due to cancer susceptibility genes (CSG). Once a CSG diagnosis is made, Clinical Genetics advise on cancer risks, early cancer detection or risk-reducing interventions with advice to see Primary Care (PC) if symptoms develop. Recording of CSG diagnosis and healthcare usage in PC has not been formally studied.
Aims:
Use UK Biobank to
- assess how well CSG diagnosis is captured in PC
- study concordance between CSG carriers identified in PC and UKBB
- evaluate impact of a CSG diagnosis in PC

Methods:
UKBB data was obtained for individuals with linked whole genome sequencing, cancer registry and PC data (N=23,0028). Genetic diagnosis (GDx), was defined as individuals with pathogenic CSG variants. Clinical diagnosis (CDx), was defined from PC data.
Results: Only 35/116 CSGs had a corresponding clinical code in PC data. 193/230,0028 (0.08%) individuals had a CSG-CDx, including 99 with BRCA1 or BRCA2. In comparison, n=1124 had a CSG-GDx. There was only 72/1124 (6.41%) concordance between CSG-CDx and CSG-GDx.
Undiagnosed individuals (GDx but not CDx) had higher usage of PC (RR=1.16, $p<0.001$).
Conclusions: Ability to record CSG diagnosis in PC is limited. Concordance of individuals with CDx and GDx was low, which may be a result of poor coding or because genetic testing has not been undertaken. Improved clinical coding in PC is required.
Study of PC healthcare use provided interesting insights but was limited due to small numbers. Different approaches (e.g. via National Inherited Cancer Predisposition Register) are required to evaluate PC healthcare usage of CSG carriers.

P2

Cognitive and functional impairment and psychiatric morbidity and their correlation to MRI findings in RVCL-S

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Background: Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations (RVCL-S) is an autosomal dominant disorder caused by mutations in TREX1. It neurological phenotype is characterized by focal neurological complaints and vascular dementia. We aimed to investigate the neuropsychological status of presymptomatic and symptomatic patients and whether MRI characteristics (white matter hyperintensities (WMH) and cerebrovascular reactivity (CVR)) were related to cognitive impairment, psychiatric morbidity and functional disability.
Methods: TREX1 mutation carriers (MC) (n=29) and matched healthy controls (n=29) underwent a comprehensive set of neuropsychological tests. Additionally, the relationship between MRI abnormalities and cognitive, psychiatric and functional measures was examined.
Results: Overall, TREX1 MC demonstrated greater cognitive and functional impairment, as well as higher psychiatric morbidity, compared to the control group. MC aged <50 demonstrated no cognitive differences compared to controls, but had more depressive symptoms (p=0.047). In MC over 50 years CVR in both white matter en gray matter correlated with overall cognitive functioning p=0.003 and p=0.008. Decreased CVR in gray matter was associated with impaired memory (p<0.001) and praxis (p=0.046). A higher WMH load was associated with worse executive functioning (p=0.024) in patients older than 50 years. Furthermore, in young MC (aged <50) overall psychiatric morbidity correlated with reduced CVR in gray matter (p=0.030).
Conclusions: RVCL-S patients demonstrate cognitive impairment as well as psychiatric morbidity and functional impairment. Depression occur early in the disease course and might therefore be a useful early marker. Increased WMH volume and decreased cerebrovascular reactivity correlate with cognitive impairment in RVCL-S.

P3

Mosaicism in Tuberous Sclerosis Complex - outcomes of a UK national audit

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Background
Pathogenic or likely pathogenic variants are identified in 85% of patients with a clinical diagnosis of TSC. Of the 15% in whom no variant is identified, many are somatic mosaics for a variant in TSC1 or 2 (Giannikou et al 2019). Deep sequencing has not been widely available in diagnostic laboratories but following an application to the National Genomic Test Director, this has been offered since April 2023 as R228.3. We conducted a national audit to assess the uptake, yield, clinical utility and sample type of the test.
Methods
We contacted the three laboratories that provide this test for details of clinicians that had referred samples for R228.3. Clinicians completed a proforma outlining basic demographics, sample type, clinical presentation and outcome of testing for each sample they had referred.
Results
Between April 2023 and April 2025, 145 DNA samples extracted from blood, skin and saliva were submitted for deep sequencing to the three laboratories. Anonymised clinical information was provided for 58 (40%) referrals. The overall diagnostic yield was 40% but was tissue dependent. Mean allele frequencies varied from 0.8% to 16%. The incidence of intellectual disability and epilepsy was lower than reported in natural history studies in keeping with milder disease (Kingswood et al, 2017).
The identification of variants facilitated prenatal testing for 4 patients and family testing in a further 8 families.
Conclusion
Deep sequencing for TSC1/2 in this UK cohort has confirmed observations from other groups and provided families with options not previously available to them.

P4

Hidden in the introns: WGS reveals LINE-1 Insertion leading to RARS2-deficiency

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Aim: To demonstrate how whole-genome sequencing (WGS) can identify pathogenic variants missed by whole-exome sequencing (WES).
Methods: A dysmature female newborn presented with severe unexplained respiratory failure, central hypotonia, autonomic dysfunction and elevated blood lactate- and FGF21 levels. An underlying mitochondrial disorder was suspected. Extensive genetic testing, including multiple WES-based panels for Mendelian disorders, pulmonary arterial hypertension, cardiomyopathy, interstitial lung disorders and mitochondrial disorders, as well as genome-wide CNV-analysis and mtDNA sequencing, yielded no diagnosis. A Human Phenotype Ontology (HPO)-based WGS analysis, followed by a manual inspection of BAM-files was subsequently performed.
Results: WGS identified a maternally inherited likely pathogenic frameshift variant in RARS2. Recessive RARS2-related mitochondrial disorders are associated with hypotonia, infantile encephalopathy, feeding problems and developmental delay, consistent with the patient's phenotype. A second variant was initially not detected; however, manual review of the BAM files revealed a paternal deep intronic Long Interspersed Nuclear Element-1 (LINE-1) insertion in intron 7 of RARS2, initially classified as a variant of unknown significance. RNA sequencing showed that this insertion causes the inclusion of a pseudo-exon, leading to a premature stop. Preliminary results of Western blotting show a strong decrease in RARS2 protein expression. Based on these functional findings, the diagnosis of RARS2 deficiency was confirmed.
Conclusion: WGS identified RARS2 deficiency as the likely cause of the infant's clinical presentation, whereas extensive WES-based analyses yielded no results. This case highlights the added diagnostic value of WGS over WES, especially for detecting deep intronic variants. However, calling rare intronic variants remains challenging.

P5

Birt-Hogg-Dubé syndrome and Pulmonary Arterial Hypertension: An update on a decade of clinical and genetic observations in the Dutch centres of expertise

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Background:
Birt-Hogg-Dubé syndrome (BHD) is an autosomal dominant condition affecting skin, lungs and kidneys, caused by pathogenic variants in FLCN, detectable in the majority of patients.
Pulmonary Arterial Hypertension (PAH) is a progressive disease caused by increased resistance in the small pulmonary arteries. In approximately 5% of PAH patients a genetic cause is identified. For both conditions, Amsterdam UMC is a center of expertise. Over the years several cohort studies were performed and the genetic cause in multiple gene elusive families was found. Here some key findings from these studies are presented.
Results:
BHD 1. We evaluated renal screening compliance and outcomes in 199 patients. Compliance to recommended renal screening was high. Of patients known to be under surveillance, 83% was screened annually and 94% at least bi-annually. 2. We examined available data on colorectal pathology in BHD patients and their unaffected relatives. No evidence for an increased prevalence of colorectal carcinoma was observed. 3. A family with suspected BHD but without FLCN variant was studied in detail. The proband was initially diagnosed with suspected BHD without FLCN mutation, given the presence of fibrofolliculomas. In addition, multiple large lipoma and renal cancer were present in multiple relatives. A heterozygous missense variant in PRDM10 (p.Cys677Tyr) was identified co-segregating with the phenotype. In vitro analysis showed loss of FLCN mRNA and protein levels due to the PRDM10 variant.
PAH 1. We reported on the outcomes of genetic testing in a cohort of 126 patients. 2. CAPNS1 was identified as a rare recessive cause of PAH. 3. The results of the ClinGen initiative for PAH will be discussed. 4. The importance of re-evaluation over time in gene elusive families are illustrated by the recent detection of the genetic cause in two such families using WGS.

P6

Usher syndrome type 1B with co-occurring neuropsychiatric comorbidities

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Aims: The aim of this study was to characterize the co-occurring neuropsychiatric conditions of a 27-year-old female with known Usher syndrome type 1B with congenital hearing loss and retinitis pigmentosa.
Methods: In-depth neuropsychiatric assessment included review of medical records, medical history taking, medical, psychiatric and neuropsychological evaluations, and EEG.
Ophthalmologic and hearing assessment have been conducted by ophthalmologist and ENT specialist as part of standard follow-up.
Results: History: First child of healthy unrelated parents. Born at GA 42+5. Normal delivery. BW 3750 g. Hearing impairment was first detected at age 6 months. Diagnosed with severe congenital bilateral sensorineural hearing loss at age 1 year. Cochlear implants from 2 years and 7 months. Pre-implantation cerebral and temporal bone CT scans were normal. Normal speech and language development. Genetic testing at age 10 confirmed compound heterozygous mutations in MYO7A indicating Usher syndrome type 1B. Cognitive abilities above the normal range at age 21.
Our assessment showed ADHD, mild autistic traits and severe executive impairment compromising daily functioning. Normal EEG. Evaluation of vision showed visual field defects. Corrected visual acuity: OD 1,0 (-3,25 -1,75 2°) OS 1,0 (-3,75 -2,25 170°). We initiated treatment with stimulant medication methylphenidate for ADHD, psychoeducation and behavioral management.
Conclusion: This case of co-occurring Usher syndrome type 1B and neurodevelopmental conditions highlights the importance of a thorough neuropsychiatric assessment. Emerging gene therapies for MYOA7 related vision loss could further improve the functional outcomes and quality of life of affected individuals.

P7

Genome sequencing reveals high diagnostic yield in children with severe sporadic developmental language disorder and normal intelligence

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A developmental language disorder (DLD) is a neurobiological condition characterized by impaired language development despite adequate linguistic input. The role of monogenic causes in the pathogenesis of DLD is largely unknown and diagnostic genetic testing is rarely offered. This study assessed the diagnostic yield of genome sequencing in severe DLD and investigated the underlying genetic foundations.
We designed a prospective cohort study involving trio-based genome sequencing in 25 individuals (aged 3-25 years) with severe DLD, normal intelligence (non-verbal IQ ≥70), no autism spectrum disorder diagnosis and no first-degree family history of DLD or neurodevelopmental disorders.
(Likely) pathogenic variants were found in nine individuals, reflecting a molecular diagnostic yield of 36%. The genetic findings were diverse, encompassing single nucleotide variants (n=4), copy number variants (n=4), and a sex-chromosome aneuploidy (n=1). In seven individuals, the disease-causing variant occurred de novo. All (likely) pathogenic variants have previously been associated with neurodevelopmental disorders. Importantly, the genetic diagnosis provided actionable insights for clinical management and follow-up for all nine individuals.
This study reveals a high prevalence of rare (mainly de novo) genetic variants in individuals with severe and sporadic DLD, in the context of normal intelligence.

Abstracts

Our findings show extensive overlap between the molecular background of DLD and that of other neurodevelopmental disorders. Collectively, our results strongly advocate for implementing routine (trio-based) genetic testing in individuals with severe and sporadic DLD.

P8

A catalogue of pathogenic variants in familial atrial fibrillation derived from a systematic literature review

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Background: Atrial fibrillation (AF) is a common arrhythmia associated with stroke and heart failure. In a subset of cases, AF manifests at a younger age, without known risk factors, and clusters within families. These familial AF cases are suspected to have a (near-)monogenetic substrate. We aimed to characterize published cases and summarize monogenetic causes. Therefore, we systematically reviewed literature on young familial AF to delineate patterns in genetic results and symptomatology.

Methods: PubMed and Embase were searched for studies describing young familial AF cases using the following inclusion criteria: (1) at least two affected family members, (2) at least one individual diagnosed with AF before age 60, and (3) genetic testing was performed. Data was collected on family history, age of diagnosis, symptoms, ECG/echo parameters, and genetic results.

Results: 128 studies were identified. After variant reclassification, 117 unique pathogenic or likely pathogenic (PLP) variants were identified, mostly in genes associated with cardiomyopathies or ventricular arrhythmias. Most variants were identified in TTN (17.1%) SCN5A (13.7%), and KCNQ1 (8.5%). Reported symptoms and ECG/echo findings did not differ between PLP carriers and non-carriers; however, PLP carriers were significantly younger at AF onset (33.3+/-14.5 years vs 45.6+/-13.2 years, $p<0.05$).

Conclusion: We present a catalogue of 117 reported monogenetic PLP variants associated with young familial AF. Most variants are found in TTN, SCN5A, and KCNQ1, genes also associated with other cardiac conditions, and PLP carriers are significantly younger at disease onset. This emphasizes the importance of genetic testing in individuals with early-onset familial AF.

P9

Cortical Malformation Broadens the Phenotype of PIP5K1C-Related Disorder

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A recently described ultrarare neurodevelopmental syndrome caused by de novo missense variants in PIP5K1C has highlighted the essential role of phosphoinositides (PIs) in human brain development. PIs are found at synapses and regulate diverse processes including autophagy, actin cytoskeleton dynamics and endosomal trafficking. Reported individuals present with intellectual disability, developmental delay, seizures, acquired microcephaly, visual abnormalities and dysmorphisms. We report an additional individual presenting with profound intellectual disability, short stature, infantile epileptic spasms syndrome, joint contractures, dysmorphic features, microcephaly and polymicrogyria. We identified a de novo c.662A>G (p.Tyr221Cys) missense variant in PIP5K1C during reanalysis of exome data. In contrast to previously reported individuals with PIP5K1C-related disorder, who showed either normal or non-specific brain imaging findings, imaging in our individual demonstrated polymicrogyria. The novel finding of a cortical malformation aligns with the known role of PIP5K1C in neuronal migration, through its regulation of actin dynamics. Our findings further support the pathogenicity of de novo variants in PIP5K1C and expand the associated phenotype to include polymicrogyria. It also emphasizes the importance of periodic reanalysis of genomic data, as well as dissemination and sharing of emerging genetic discoveries, which can directly improve outcomes for individuals with rare neurodevelopmental disorders and their families.

P10

Clinical profiling of postzygotic mosaicism in hereditary cancer genes: analysis of 27 individuals in 18 families

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Postzygotic mosaicism (PZM) describes the presence of two or more populations of cells with different genotypes in one individual developed from one fertilized egg. Genotype-phenotype relationships in PZM remain underexplored due to limited case accumulation. To establish diagnostic and management protocols for PZM patients with hereditary cancer syndromes (HCS), this study conducted clinical profiling of PZM cases at our hospital. This study included individuals suspected of having HCS who underwent genetic testing from 1998 to 2024. All initial genetic tests were performed using blood samples. Eighteen individuals were identified as harboring PZM variants in the APC, TP53, MEN1, PMS2, RB1, or STK11 gene by FISH, Sanger sequencing, multi-gene panel testing or combination thereof. The phenotype of the PZM patients ranged from similar to milder than that assumed for the HCS cases without PZM. Among 8 patients with RB1 PZM, 3 developed bilateral retinoblastomas and 4 developed unilateral retinoblastomas, while the remaining patient was diagnosed with leiomyosarcoma. One patient with MEN1 PZM developed pancreatic neuroendocrine tumors without exhibiting other characteristic MEN1 features. Buccal mucosa was collected from 4 individuals for validation analysis, which detected the PZM variants at a similar allele frequency to that of blood. Cascade testing of 9 individuals who were offspring of probands with PZM revealed that none carried the same variant as the proband. The number of patients diagnosed with PZM is expected to increase as mutation detection technologies continue to advance. Accumulating additional evidence regarding PZM is essential for improving risk assessment and management of HCS.

P11

A GWAS meta-analysis to uncover the molecular aetiology of posterior urethral valves.

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Aim: Posterior urethral valves (PUV) are the commonest cause of kidney failure in boys. Although a genetic origin is suspected for PUV, its molecular aetiology remains largely unknown. Hence, we performed a genome-wide association study (GWAS) meta-analysis of three study cohorts to better characterize the role of common variants in PUV.
Methods: Summary statistics from two previously published GWAS (Van der Zanden, 2022; Chan, 2022) were combined with an additional unpublished cohort. In total, 1,037 PUV cases and 17,170 matched controls were included. All cases and controls were male and of European ancestry. Variants were called using DNA microarray genotyping (948 cases, 8,823 controls) or whole-genome sequencing (89 cases, 8,347 controls). Quality control included standard measures. Genome-wide logistic regression analysis was performed with principal components as covariates. 4,694,037 autosomal variants were analyzed using the inverse-variance approach in METAL.
Results: 14 loci showed suggestive association ($P < 10\text{-}5$) with PUV. The variant with the strongest association (OR 0.70, 95% CI 0.61-0.80, $P = 1.81 \times 10\text{-}7$) was located at the Chr1q21.1 region that is associated with known genomic disorders (OMIM

#612474/612475). Large and rare duplications at this locus have been previously implicated in PUV. Further post-GWAS analyses are pending.
Conclusion: In this large-scale European GWAS meta-analysis in PUV, suggestive association was seen at 14 loci. The strongest association was found within a genomic disorder locus for PUV, potentially influencing gene dosage. Additional analyses will be performed and presented.

P12

A diagnosis of Poretti-Boltshauser syndrome due to uniparental disomy

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Poretti-Boltshauser syndrome (PBS) is an autosomal recessive neuro-ophthalmological condition caused by biallelic variants in the LAMA1 gene, located in the short arm of chromosome 18. PBS is characterised by cerebellar changes including dysplasia, cerebellar vermis hypoplasia and cysts. Visual problems such as high myopia, retinal dystrophy, and eye movement abnormalities may be present. Other reported features include hypotonia, motor and speech developmental delay and variable cognitive function.
Here, we describe the case of a child who presented at 3 months old with horizontal nystagmus and was later found to have alternating esotropia and high myopia with macrophthalmia. The patient had significant motor and speech delay with early hypotonia. MRI imaging showed cerebellar dysplasia with small cystic structures in the periphery of the cerebellum and inferior vermian hypoplasia with enlargement of the fourth ventricle and cisterna magna.
Duo whole exome sequencing was performed including the patient and their mother. The patient was found to be homozygous for the pathogenic LAMA1 nonsense variant c.4324del p.(Val1442Ter). The patient's mother was found to be heterozygous for the same variant. Paternal testing was not possible; however, there was evidence of increased homozygosity across chromosome 18 in the patient. Genome-wide single nucleotide polymorphism (SNP) analysis suggested there was mixed maternal isodisomy and heterodisomy, consistent with maternal uniparental disomy of chromosome 18, UPD(18)mat.
To our knowledge, this is the first case of PBS caused by UPD. This case portrays a rare genetic mechanism as the underlying cause of PBS, clarified using multiple genetic technologies.

P13

Three generation family with Chung-Jansen syndrome

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Chung-Jansen syndrome (CJS) [OMIM # 617991] is characterized by obesity, neurodevelopmental delay, visual and behavioral problems. It is caused by heterozygous (likely) pathogenic PHIP variants. Dysmorphic features are fairly distinctive and include prominent eyebrows, anteverted nares, and large earlobes. We here report a three generation-family with CJS. The index, his mother and maternal grandmother have CJS due to a heterozygous pathogenic deletion (c.4125_4137del, p.(Tyr1375*)) in PHIP. They present with developmental delay, obesity, mild visual problems and/or sleeping problems. Nephrocalcinosis was seen in the index case. The heterogeneous phenotype of CJS is well demonstrated in this three generation-family with CJS. As far as we are aware our case 3 is the oldest (62 years) patient with CJS reported in the literature to date, contributes to the knowledge about adult patients and illustrating the variable expressivity and intrafamilial variation of this condition. At present, no clinical guidelines are available for CJS. The developing for such guidelines could in the future provide support for the clinical care of these patients. Since renal anomalies have been previously reported and nephrocalcinosis may represent a new feature of this syndrome, we recommend renal ultrasound of all other CJS cases to further establish this possible association.

P14

Diagnostic yield and clinical impact of Prenatal Exome Sequencing in the Netherlands

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Prenatal exome sequencing (pES) is an important testing modality in pregnancies affected by congenital anomalies, enabling tailored pregnancy management and empowering parents in their decision for termination or continuation of the pregnancy. This study aimed to determine the diagnostic yield and to assess clinical impact on pre- and postnatal management and during follow-up. We performed a multicentre cohort study with prospective data collection, using data from questionnaires, medical files and the Dutch paediatric healthcare system. Data were collected at four timepoints: (I) directly after pES counselling, (II) one to two weeks after receiving the pES result, (III) six to eight weeks after the end of the pregnancy – either full-term pregnancy or TOP – and (IV) six months after live birth. In total, 231 pregnancies were included. Diagnostic yield was 14.7%, incidental findings were reported seven times. When pES detected a genetic diagnosis, parents opted significantly more often for termination ($p < 0.001$). Parents who received a diagnosis indicated significantly more often that they made this decision based on the pES result ($p < 0.001$). There were no significant differences in development of liveborn children at 6 months of age in relation to the pES result. This research shows the substantial diagnostic yield and the significant clinical impact both objectively measured in pregnancy outcomes and subjectively as indicated by parents. These results warrant widespread implementation of pES, but national policies need to be drawn up on when to offer pES and what results to report to parents.

P15

The genetic landscape of CAKUT: preliminary results from a WGS study

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Congenital anomalies of the kidney and urinary tract (CAKUT) are the major cause of chronic kidney disease in children. Historically, the genetic diagnostic yield for CAKUT remains relatively low, reaching at most 20% across study cohorts. The ArtDECO consortium is founded to enhance our understanding of CAKUT etiology and ultimately improve clinical outcomes. Four coordinated work packages examine monogenic and complex genetic factors, gene-environment interactions, and functional models. This study is part of the monogenic work package and reports on a WGS dataset of 318 patient-parent trios. Sequencing was performed by deCODE Genetics, and variant annotation and prioritization are conducted using the Variant Interpretation Pipeline (VIP). At submission, the analysis is ongoing and follows a tiered filtering strategy. We first assess known pathogenic and likely pathogenic variants in CAKUT- and mendeliome-associated genes. Subsequently, we filter de novo and rare coding variants in these genes, as well as de novo and ultra-rare (MAF<0.0001) variants in genes without associated phenotype to identify potential novel candidate genes. Additional filtering steps include non-coding variants that may affect splicing or (candidate) gene regulation. Filtered variants are further evaluated using multiple criteria, including Franklin pathogenicity scores, gnomAD population metrics and a combination of AI-based predictions such as AlphaMissense and SpliceAI. In conclusion, ArtDECO aims to broaden our understanding of the etiology of CAKUT, improve diagnostic yield and provide new insights into the biological pathways involved in kidney development. We will present the most up-to-date results at the time of the meeting.

P16

Cancer Variant Interpretation Group UK (CanVIG-UK) in 2026: updates on an exemplar national subspecialty multidisciplinary network

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Cancer Variant Interpretation Group UK was established in 2017 in response to the publication of the 2015 ACMG/AMPv3.0 guidance for the interpretation of sequence variants. Its initial purpose was to bring the UK clinical-laboratory community together to implement ACMG/AMPv3.0 guidance consistently for cancer susceptibility genes (CSGs). Still convening for monthly national meetings, the remit of CanVIG-UK has encompassed additional activities delivered under the following objectives:

1. Creation of a national multidisciplinary professional network and regular forum.
2. Training and education.
3. Detailed specification for germline cancer genetics of the UK-ACGS Best Practice Guidelines for Variant Interpretation.
4. Ratification of additional guidance in germline cancer genetics relevant to the UK clinical-laboratory community.
5. Development of an online platform to facilitate information sharing and variant interpretation within the UK clinical-laboratory community (CanVar-UK).
6. UK contribution to international variant interpretation endeavours.

We will present a trajectory of CanVIG-UK activities 2017-2026 aiming to support consistency in UK clinical CSG variant interpretation. We will include the results of a survey of CanVIG-UK members conducted in November 2025, with responses from 159 CanVIG-UK members, including 111 clinical scientists (/trainees) and 23 Clinical Genetics consultants. The utility of the CanVIG-UK recommendations for variant interpretation was highly rated, with consultation ≥4 times/month of both the consensus guidance and the gene-specific guidance reported by 74/111(67%) of clinical scientists. 42/111(38%) of clinical scientists reporting using CanVar-UK daily to assist with variant classification, with a further 32/111(29%) reporting using it at least weekly, with high utility rated for all features offered.

P17

Cost Analysis of Cancer Surveillance Versus Cancer Treatment in PTEN Hamartoma Tumor Syndrome: EU PREVENTABLE Project

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PTEN Hamartoma Tumor Syndrome (PHTS), caused by germline pathogenic variants in PTEN, entails a high lifetime risk of breast cancer up to 76%, and up to 22% for endometrial and thyroid cancer. While genetic testing and surveillance are recommended, the cumulative healthcare costs remain unexplored. This study evaluated the clinical outcomes and healthcare costs of prevention versus treatment in European PHTS patients. Within the framework of the Horizon Europe PREVENTABLE project, a matrix of clinical patient trajectories was constructed across six modules: genetic diagnosis, risk-assessment, surveillance, treatment of early- and advanced stage cancer, and follow-up. Costs for each clinical procedure were estimated using diagnosis-related groups and public reimbursement rates. An IT tool was developed for systematic registration of patient data from seven European centers. Among 234 PHTS patients, 152 patients were cancer-free prior to genetic testing and received surveillance. During surveillance, 11 patients were diagnosed with cancer. In this prevention group, the median costs per patient were €10,510 (IQR: €5,420-€20,606). Among 63 patients with cancer prior to genetic testing, 56 patients received surveillance. In this treatment group, the median costs per patient were €56,604 (IQR: €33,773-€97,830). These preliminary results suggest that cancer prevention is cheaper than cancer treatment in PHTS

patients. Gaining data of the costs associated with cancer prevention and treatment of PHTS patients is essential for optimal allocation of healthcare resources and ensuring sustainable care delivery. The results will be finalized in the coming months, and we look forward to sharing those results at the Joint Meeting.

P18

Clinical Recommendations for the management of familial chordoma

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Background:
Chordoma is a rare malignant slow growing bone tumour of the axial skeleton that typically presents in adulthood, but can occur in childhood. The majority of cases are sporadic. Duplications in the TBXT gene are the only currently recognised cause of familial chordoma, reported in a small number of families worldwide. Due to the rarity of the condition, no clinical management guidelines for individuals at increased risk of chordoma have been published to date.
Aims:
Prompted by a family in whom an underlying inherited genetic susceptibility was strongly suspected, but in whom the genetic diagnosis was at first elusive, and the clinical need to appropriately manage at-risk family members, we sought to achieve clinical consensus recommendations.
Methods:
We convened a clinical expert group including Clinical Genetics, Pathology, Radiology and Neurosurgery to reach consensus on management of at-risk family members. The group considered site, modality and frequency of screening for chordoma in individuals at increased lifetime risk, including those with confirmed TBXT duplications or potential at-risk family members where strong clinical suspicion of familial chordoma exists.
Conclusion:
The agreed consensus recommendations included non-contrast MRI head and spine every 2-3 years between ages 5-18 and non-contrast MRI head and spine every 1-2 years from age 18 onwards, ideally to be undertaken in a centre with chordoma expertise. A request for addition of clinical testing of TBXT duplications to the NHS National Genomic Test Directory has been submitted.

P19

A service evaluation of whole genome sequencing in primary brain tumours at a tertiary UK Neuro-oncology centre: closing the gaps

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Aims
Whole Genome Sequencing (WGS) provides comprehensive genomic profiling of brain tumours. This requires multi-speciality working and the support of a dedicated Genomes team, based within Clinical genetics. This project reviews the current WGS pathway infrastructure within a large tertiary UK neuro-oncology unit.
Methods
Patients with primary brain tumours eligible for WGS as per NHS/GLH criteria were identified from theatre lists between January-December 2024. Electronic patient records, histopathological reports and WGS reports were analysed. Rates of adequate sample collection and completed WGS reports were recorded. Uncompleted WGS reports were analysed for root cause.
Results
104 patients were identified as eligible for WGS. Of these, 70 (67.3%) had adequate frozen tissue taken at time of surgery to facilitate WGS. The Genomes team consent patients for WGS and track samples from the point of collection to ensure all samples proceed. From the samples collected, all have progressed to one of three categories: WGS report, low DNA content, clinical reason to abandon testing. The weekly GTAB meeting led by the Genomics Medicine team and clinical scientists works closely with clinicians to interpret results and identify potential therapeutic targets/clinical trials.
Conclusion
BNOS and Darzi reports separately recommend the routine use of WGS for all patients with primary brain tumours. This audit demonstrates the rapid adoption of this tool in clinical practice with a robust multi-disciplinary clinical pathway. The Genomes team facilitate sample processing to a conclusion in all instances and are imperative to WGS interpretation.

P20

Mainstreaming whole genome sequencing in Paediatrics: A service evaluation assessing the impact of mainstreaming WGS and subsequent impact on a Clinical genetics service

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Aims
Mainstreaming genomic testing is a significant part of the NHS 10-year plan. One of biggest referrers to clinical geneticists are paediatricians. We conducted a service evaluation to assess the impact paediatric mainstreaming has had for a clinical genetics service based in Hampshire, UK.
Methods
Paediatrician referrals for WGS via the local genomic practitioner team were reviewed over a 32-month period from paediatricians within a sub-region in Wessex and compared against the geneticist covering that region. Referral numbers were assessed over time and the impact this had on formal referrals to clinical genetics and the subsequent impact on geneticist workload were evaluated. Result types were also review from both clinical genetics and mainstream referrals.
Results
Referrals for WGS from mainstream paediatricians significantly grew while referrals for WGS from a geneticist decreased. WGS diagnostic yields were lower when requested by a mainstream paediatrician. All mainstream patients with positive /VUS findings were subsequently referred to clinical genetics. Approximately a quarter of mainstream patients with a negative result were formally referred to clinical genetics.
Conclusions
Paediatricians referring patients directly for WGS rather than formally referring to clinical genetics significantly reduced the number of appointments, and associated workload, within clinical genetics. Those referred to clinical genetics post-WGS with positive/VUS findings were able to be triaged to see the most appropriate person (consultant vs genetic counsellor). The reason for a lower diagnostic yield from mainstream paediatricians remains unclear and requires further investigation. Genomic mainstreaming requires clinicians to adapt to a constantly evolving landscape.

P21

Influence of non-sex specific risk factors on the development of a dilated cardiomyopathy in men and women with a titin truncating variant

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Background: Truncating variants in TTN (TTNtv) are the most prevalent variant in genetic dilated cardiomyopathy (DCM). Disease expression differs between male and female carriers, potentially due to variation in non-genetic risk factors.
Aim: To evaluate the prevalence and impact of (multiple) non-sex specific risk factor in male and female DCM patients and asymptomatic TTNtv family members.
Methods: TTNtv carriers were included from the mCMP-registry of Maastricht and the HMD-registry of Trieste. Individuals were classified as DCM patients (LVEF<50%) (n=175) or asymptomatic family members (LVEF>50%) (n=87). Risk factors assessed were: obesity, hypertension, hypercholesterolemia, diabetes mellitus type II, chemotherapy, atrioventricular block, bundle branch block, exercise level, smoking, and alcohol consumption. Univariable and multivariable logistic regression analysis were performed to assess risk factors of DCM development.
Results: DCM patients have more risk factors compared to asymptomatic family members ((odds ratio 5.13 [2,49-10.55], p<0.001). In males, obesity (odds ratio (OR) 11.97, 95% confidence interval [1.51-94.86], p=0.019), low exercise (OR 3.89 [1.75-8.65], p=<0.001), smoking (OR 4.64 [1.87-11.50], p<0.001) and daily alcohol consumption (OR 5.64 [1025-25.44], p=0.024) are associated with DCM development. In females, low level of exercise is the only predictor of DCM development (OR 4.85 [1.50-15.73], p= 0.008).
Conclusion: Patients with DCM due to a TTNtv have more additional risk factors compared to their asymptomatic family members who carry a TTNtv. Obesity, daily alcohol consumption, low levels of exercise and smoking are related to DCM development in males, whereas low exercise is the only additional risk factor for DCM in female TTNtv carriers.

P22

Does the Leeds Clinical Genomics Service (LCGS) VHL Clinic meet the UKCGG recommended guidelines for VHL syndrome surveillance? An audit on clinical compliance and service evaluation.

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Aims and Methods
von Hippel–Lindau (VHL) syndrome is a rare, multi-system condition associated with benign and malignant tumours. Early detection through surveillance reduces morbidity and mortality. Following publication of the 2024 UKCGG VHL Surveillance Guidelines, this study evaluated adherence to recommended surveillance by the LCGS VHL service. In this single-centre retrospective review spanning 56 months, surveillance data from 40 patients with confirmed VHL were analysed to assess compliance and identify trends.
Results
Compliance varied considerably between modalities. CNS surveillance had the highest adherence, with over 90% of patients receiving guideline-compliant brain and spine MRI every 3 years. For abdominal MRI/ultrasound, 36.8% met the annual recommendation, rising to 63% when a 14-month interval was applied. Although renal findings were consistently documented, only 44% of scans reliably reported pancreatic findings.
Surveillance typically performed at the annual VHL clinic namely urine catecholamine testing, blood pressure monitoring, and retinal screening, showed low compliance at 12 months (5.6%, 5.9% and 5.3%, respectively). When assessed at a 14-month interval, adherence improved substantially to 50%, 70.6%, and 73.7% of patients respectively. Overall, extending the interval 14 months improved adherence across most modalities.
Conclusions
This evaluation demonstrates variable adherence to VHL surveillance guidelines, with minor delays across several modalities. Improved adherence at 14 months likely reflects scheduling delays related to patient availability and clinic capacity. Strengthening coordination between specialities, enhancing patient education, standardising abdominal imaging reporting, and exploring patient and clinician perspectives may further optimise early detection and improve outcomes for individuals with VHL.

P23

RCEM Episignature: Refining the Phenotype in Three New Cases

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Aims: Despite major advances in diagnostic techniques, finding a genetic diagnosis in a child with congenital abnormalities can still be challenging. Recently a common DNA methylation episignature was identified for patients with “recurrent constellations of embryonic malformations” (RCEM). Because the phenotypic spectrum associated with this signature is not yet fully known the clinical utility of this signature remains to be established.
Methods: In this study, we describe the clinical characteristics of three unrelated patients with congenital anomalies and a positive signature for VACTERL/OAVS RCEM after negative exome analysis.
Results: None of the included patients fulfilled the diagnostic criteria for VACTERL or OAV spectrum. Therefore they would not have been diagnosed based on clinical features alone. Two of three patients had a duodenal atresia. All had normal growth and development.
Conclusion: These cases further delineate the clinical manifestations of patients with this episignature and highlight potential atypical manifestations.

P24

UK National Mosaic Variegated Aneuploidy Audit

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Introduction:
Mosaic Variegated Aneuploidy (MVA) is a rare autosomal recessive disorder marked by chromosomal instability during cell division. It spans both rare disease and cancer genetics, as affected individuals often present with growth failure, dysmorphism, developmental delay and have an increased risk of developing cancer.
Aims:
MVA has less than 100 cases reported in the literature. This UK wide audit aimed to establish the prevalence of the condition, the associated phenotype and review clinical cancer screening recommended for patients.
Methods:
A small working group was formed to conduct the audit. We developed a template to capture both genotype and phenotypic data. All UK Genetics Centres were approached to nominate a representative to assist in identifying patients and performing retrospective phenotyping.
Results:
9 patients were identified with an age range of 4 to 60 years old. Causative genes identified included BUB1B, BUB1 and TRIP13. From a cancer perspective, 3 patients had a cancer diagnosis – embryonal rhabdomyosarcoma, Wilm's tumour and granulosa cell tumour of the ovary. 3 patients had regular clinic follow up and screening; screening choices included Whole Body MRI and abdominal ultrasound scanning.
Growth impairment was a regular finding; of the children included in the cohort all had some degree of growth restriction with microcephaly a prominent feature. Several adults had reported short stature.
Conclusion:
This is the first National Audit of MVA within the UK and to the group's knowledge, worldwide. To progress this further we want to capture more UK cases and consider a European wide audit.

P25

Constructing benign truthsets for validation of MAVEs: current status and a novel systematic approach for empowerment of PS3

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Quantification of applicable strength for MAVE-based evidence requires construction of clinical variant truthsets against which to evaluate per-assay performance. Limited availability of validation variants, and bias and circularity therein, remain substantive obstacles to the quantification of MAVE strength for many genes. We aimed to quantify the extent to which currently available truthsets of missense variants would enable robust clinical validation of forthcoming MAVEs. We further sought to develop new approaches to address the lack of available clinically classified benign missense variants for use in MAVE validation. We present quantitative analyses indicating that scarcity of available high-confidence ClinVar classifications will limit our ability to undertake clinical validation of any new MAVEs for the majority of 116 cancer susceptibility genes. We present an approach for proactive-systematic generation of benign missense variant truthsets for assay validation. We demonstrate that, for eight hereditary breast and ovarian cancer genes, proactive-systematically generated validation variant sets would allow application of equal or greater strength of evidence for pathogenicity (PS3) compared to using existing sets of ClinVar classifications. We demonstrate a substantial unmet need regarding availability of missense variants for MAVE validation. We present a proactive-systematic approach to benign missense truthset generation allowing overall improvement in applicable evidence strength for MAVEs, even in genes with scarce existing classifications. Improving clinical validation truthsets is key to unlocking the value of MAVEs in improving our ability to classify variants as benign or pathogenic (and out of the VUS status assigned to so many rare missense variants).

P27

The 'BRCA-DIRECT' testing pathway: overview of study outcomes from direct-to-patient testing across different contexts (1. hospital-based breast cancer mainstreaming, 2. retrospective cancer patients ascertained via record linkage, and 3. Jewish populati

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The BRCA-DIRECT pathway was designed to reduce demand for clinical time-resource in more 'generic' aspects of the germline genetic testing pathway, enabling targeted use of limited clinical resource and facilitating expanding demand for testing. The pathway involves home-based saliva sampling, standardised provision of written and digital pre-test information about testing, and patient access to a genetic counsellor telephone helpline. We provide a post-test genetic counselling appointment in rapid timeframe if a pathogenic variant or VUS is identified ahead of onward clinical genetics referral.
We first undertook a randomised trial of a digital pathway for mainstream cancer susceptibility testing in people diagnosed with breast cancer (n=1,140), followed by wider roll-out as a transformation mainstreaming programme in 15 breast units across Greater London (n=3,515). Adapting the pathway, we have undertaken a national pilot programme of unaffected, community testing (for people with Jewish ancestry, n>44,000). We are also currently piloting national retrospective testing of individuals identified via integration of multiple national datasets as diagnosed historically (>5 years ago) with high-risk breast or ovarian cancer and no record of NHS BRCA-testing (n=~22,650 over 3 years).
Here we will present a comparative analysis across the different use-cases of the 'BRCA-DIRECT' pathway identifying features that favour successful implementation either universally across contexts or context-specifically. This will involve review of testing uptake and outcomes, genetic counsellor time requirements, utilisation of the genetic telephone helpline, and patient satisfaction, as well as the perspectives and learnings from the team delivering the pathways.

P28

X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia or N-linked glycosylation defect (XMEN) in a female patient

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X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia or N-linked glycosylation defect (XMEN) is caused by hemizygous loss-of-function mutations in the magnesium transporter 1 (MAGT1) gene. This X-linked condition has only been described in male patients, and a phenotype in female relatives has not been reported. Here, we present for the first time a female patient with characteristics fitting with XMEN-syndrome, harboring a heterozygous deletion in MAGT1. She has a IgG1-subclass deficiency, asthma, and recurrent respiratory tract infections. Her son has as IgA, IgG1, 2, and 4 deficiency, asthma, eczema, and recurrent respiratory tract- and skin infections. Her son is currently being tested, if he indeed carries the same deletion and suffers from XMEN-syndrome then she is likely the first reported female patient. Skewed X-chromosome inactivation could be the underlying mechanism.

P29

Does the facial dysmorphism associated with Fetal Valproate Spectrum Disorder vary with dose of exposure, polytherapy, gestational timing or patient age? – A literature review.

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Sodium valproate (VPA) is an established teratogen, with neurodevelopmental and congenital malformation associations well defined. In 2025 NHS England established a northern pilot Fetal Exposures to Medicines MDT service. The service aims to clarify diagnosis and advise on health for 100 patients of any age with pregnancy antiseizure medicine exposure. For those exposed to VPA facial dysmorphism is a key part of the 2019 diagnostic criteria for Fetal Valproate Spectrum Disorder. However, how the facial gestalt varies with dose of exposure, polytherapy, gestational timing or patient age is not defined. We completed a literature review of VPA exposure cases to explore this. 138 case reports from 1970 to 2025 were identified. 37 cases were excluded due to incomplete information. 72 monotherapy cases and 29 polytherapy cases were identified with doses ranging from 300mg -6600mg total daily dose (Median 1200mg, IQR 800-2000). 85% of included cases were below the age of 5yrs, none documented the adult phenotype. 36.7% of cases included a photograph. The pattern of dysmorphic features described was more extensive than those listed in the 2019 guidance. Cases exposed to over 1000mg VPA had a greater number of features listed. However, reporting of specific features was inconsistent and, where a photograph was included, unreported dysmorphic features were frequently observed. Statistical comparison of dysmorphic features across dose categories was therefore precluded. To inform assessment and development of updated diagnostic criteria, systematic recording of dysmorphic features is required in VPA exposed patients with a range of exposure doses and assessment age.

P30

First report of a biallelic POLD1 variant carrier with synchronous colorectal cancer and polyposis

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We present a 32-year-old patient from our outpatient clinic diagnosed with colon cancer in both the sigmoid and rectum. Additionally, he presented with over 30 adenomas, mostly distally located. Germline genetic analysis by whole exome sequencing (WES) identified a homozygous POLD1 variant, c.1379T>G, p.Leu460Arg, situated within the exonuclease domain. This variant has only been described twice in the literature.
IHC of the tumors showed no mismatch repair (MMR) deficiency, while WGS revealed an ultra-high mutation load with POLD1 and MMRd-related mutational signatures. Interestingly, despite the positive IHC MMR, microsatellite instability and MSH2 somatic pathogenic variants were also identified.
The patient comes from a consanguineous family, in which the same POLD1 variant has been detected in a heterozygous form in several relatives affected primarily with polyposis. Previously, two fifth-degree relatives had visited our outpatient clinic for polyposis coli (+/-25 and 11 adenomas, respectively) both at age 27. WES showed they were both heterozygous carriers of the c.1379T>G variant in POLD1. These relatives are the (consanguineous) parents of a healthy eight-year-old daughter who has not yet been tested for the variant. In addition, they had a daughter who died postnatally due to metabolic abnormalities (ADSL deficiency) and multiple miscarriages, with an unknown cause.
This is, as far as we know, the first reported case of a homozygous POLD1 variant associated with early-onset colon and polyposis, suggesting a potential autosomal recessive inheritance pattern in this family.