28th Meeting of the Irish Society of Human Genetics

Friday 12th of September 2025
Maynooth University

PROGRAMME

09:00 Registration, Tea & Coffee, Poster Viewing & Sponsor Visits

09.50 Welcome address: ISHG Chairperson Dr Deirdre Donnelly

10:00 Keynote address I: Gene-environment interactions and Vitamin D, Prof Lina Zgaga, Trinity College Dublin

10:45-11:15 Oral presentations (Basic) Plenary I (each x8mins+2mins Q&A), Chairs: Dr Lorna Lopez & Dr Edmund Gilbert

11:15 Tea & Coffee, Poster viewing & Sponsor visits

11:45 Keynote address II: Reflections on the distinct genetic disease epidemiology of Northern Scottish populations: How should we seek to maximise health? Prof Zosia Miedzybrodzka, Aberdeen University

12:30 Oral presentations (Basic) Plenary II (each x8mins+2mins Q&A), Chairs: Dr Therese Murphy & Dr Bronagh O'Hici

13:00 Lunch, Poster viewing & Sponsor Visits

14:15 AGM

14:30 Keynote address III: Mitochondrial Disease: Principles, Presentations and Prevention, Prof Robert McFarland, Newcastle University

15:15 Oral presentations (Clinical) Plenary III (each x8mins+2mins Q&A), Chairs: Dr Lisa Bradley & Dr Deirdre Donnelly

15:45 Tea & Coffee, Poster viewing & Sponsor visits

16:15 Keynote address IV: Forensic Science in Ireland, Dr Charlotte Murphy, Forensic Science Ireland

17:00 Oral presentations (Clinical) Plenary IV (each x8mins+2mins Q&A), Chairs: Dr Lisa Bradley & Dr Deirdre Donnelly

17:20 Honorary Membership Presentation to Prof Andrew Green. Introduction: Dr Lisa Bradley

17:45 Presentation of Prizes, wine & cake reception

19:00 Meeting closes

Abstracts

Sponsorship: All content was reviewed and approved by the Irish Society of Human Genetics Society Committee, which holds full responsibility for the abstract selections. The society has no disclosures.

Presenting authors are underlined in contributor list

ORAL PRESENTATIONS

OP01 Governing for a Sustainable Genomic Database: The Genome of Ireland Case Study

Dr. Ciara Staunton[1,2], Dr. Laura Whelan[3], Dr. Ifeolutembi Fashina[3], Prof. Aedin Culhane[4], Mr. Jack Glynn[3], Prof. Markus Helfert[5], Dr. Edmund Gilbert[3], Dr. Naveed Khan[5], Dr. Eva Szegezdi[6], Ms. Nuala Ryan[7], Ms. Laura Kavannagh[8], Dr. Russell McLaughlin[9], Prof. Gianpiero Cavalleri[3]

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The Genome of Ireland (GoI) is a national initiative that aims to sequence the genomes of at least 1,200 participants to create a long-term research resource. This cohort aims to include newly sampled individuals as well as participants drawn from existing studies. The resulting dataset is intended to be used indefinitely to support health and genomic research in Ireland and internationally. While the GoI represents an important milestone in Ireland's precision medicine landscape, it is fraught with legal, ethical, and governance challenges. Central among these is how to design and implement a governance framework

that not only supports current research but also enables future access, reuse, and maintains trust over time.

We present the GoI as a case study to examine how to govern a dataset to ensure its sustained use. We outline how the GoI governance framework has sought to incorporate data protection, participant rights, dynamic consent models, and public and patient involvement not only to enable responsible data use, but to support long-term social license and operational continuity.

Drawing on the experience of designing the GoI governance framework, we identify the legal and ethical challenges encountered, such as managing consent for future unspecified research, ensuring data security, addressing access for secondary use, and planning for long-term oversight. In doing so, we offer key recommendations for how databases in Ireland should be governed to ensure their sustained use.

OP02 Genome-wide Association Studies of Social Participation and Occupational Engagement in the UK Biobank

Ms. Evie Doherty[1,2], Dr. Aodán Laighneach[1,2], Ms. Mia Casburn[1,3], Dr. Fergus Quilligan[1,3], Prof. Gary Donohoe[1,4], Prof. Dara M Cannon[1,3], Prof. Derek W Morris[1,2]

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Psychosis is a clinically heterogenous disorder associated with significant difficulties with social and occupational function (psychosocial disability; PD). While environmental and cognitive factors are identified predictors of PD, the genetic contribution remains unclear. Here, we investigated the hypothesis that objective social participation (SP) and occupational engagement are genetically influenced. We performed mixed-linear-model genome-wide association studies of these phenotypes in the UK Biobank (*N*~404,500) and a series of *post-hoc* analyses including Mendelian randomization (MR) to interpret findings. SP was defined as the frequency of social visits and leisure activities based on response to questionnaires. Occupational engagement was represented by two variables; occupational function (OF) and the established Not in Education, Employment, or Training (NEET) measure, both derived from employment status responses. We identified 17 independent loci for SP, with a SNP-based heritability of 4.1%. A list of contributory genes included *CSE1L*, *TNRC6B*, *STAU1, CDH7*, *GBE1*, *ZNF536, DDX27*, and the known schizophrenia risk gene, *TCF4*.

The regulation of synaptic signalling was implicated in the biology of SP by gene-set analyses. SNP-based heritability for OF and NEET were 1.8% and 1.2% respectively and *DRD2* was associated with both phenotypes. Reduced SP and occupational engagement demonstrated genetic correlations with an increased risk for neuropsychiatric disorders, socioeconomic deprivation, lower cognitive ability, loneliness, neuroticism, and chronic pain. MR indicated that attention-deficit hyperactivity disorder and schizophrenia were causal for reduced occupational engagement. Overall, PD has a genetic component with shared genetic links and relationships with neuropsychiatric disorders and health related traits.

OP03 Erythemal UV at place of residence associated with melanoma, squamous cell carcinoma, and basal cell carcinoma skin cancers in a gene-UV interaction study

Dr. Rasha Shraim, Prof. Ross McManus, Prof. Lina Zgaga

Trinity College Dublin, Dublin, Ireland

Background: Sun exposure (UV radiation) is the foremost environmental exposure associated with skin cancer risk. This effect is usually linked to DNA damage or immunosuppression and mediated by the exposure pattern: squamous cell carcinoma (SCC) is often linked to long-term exposure, basal cell carcinoma (BCC) to excessive intermittent exposure and melanoma to recreational exposure and sunburn history. Studies often use proxies of sun exposure like sunburns or nevi.

Methods: We evaluated the risk of skin cancer in the UK Biobank using sun exposure-adjusted models. Based on residential address, we calculated for each participant summer and winter ambient erythemal UV doses using satellite weather data. Genome-wide association tests were carried out within each cancer type for additive and joint effects (i.e. 2 degrees of freedom test). Models were also adjusted for ‘time spent outdoors’ and included 5:1 controls with no history of cancer.

Results: 2,968 melanoma, 3,366 SCC, and 20,475 BCC European-ethnicity incident cases were identified. Both winter and summer erythemal UV doses were significantly associated with the risk of each cancer. The joint test showed evidence of gene-sun exposure interactions in over 35 SNPs within each cancer. Further GxE tests suggested

interactions with summer and winter UV in melanoma, summer time outdoors in SCC, and winter UV in BCC. Downstream pathway annotation supported a key role for immune functions in BCC.

Conclusion: Ambient sun exposure at place of residence and time spent outdoors uncover genetic variants in skin cancer and support the presence of distinct seasonal effects.

OP04 Demography of Bronze and Iron Age Ireland through the lens of Ancient DNA

Ms. Catherine Butt, Dr. Valeria Mattiangeli, Dr. Lara Cassidy

Smurfit Institute of Genetics, Trinity College Dublin, Dublin, Ireland

The European Bronze Age was characterised by the arrival of steppe-based ancestry, leading to the reduction of Early European Farmer (EEF) ancestry, which was dominant throughout the Neolithic, while the European Iron Age is linked with smaller scale movements throughout the continent. However, the goings-on of this period in Ireland have remained elusive, with only three genomes from the Early Bronze Age published thus far. This time is a particularly important time in Irish history as it contains a window for Celtic language entry. Here we present a collection of new Irish genomes from the Bronze and Iron Age. Our findings show that patterns of EEF ancestry in Ireland are distinct to those in Britain. This points to varied migration patterns in Ireland and Britain, possibly pointing to different Celtic language entry points. We use ChromoPainter and Identity-by-Descent (IBD) segments to better define these patterns and find ancestry contributions from Britain, the continent, as well as persistence of Neolithic ancestry well into the Irish Middle Bronze Age. This is in stark contrast to England where we see a near total replacement of local Neolithic ancestry in the Early Bronze Age. We also explore potential gene flows from Britain to Ireland during the Iron Age and Early Christian period.

OP05 From Siloed Cancer Data to Pan-European Discovery: Building Ireland's Foundations for the European Health Data Space

Prof. Aedin Culhane

University of Limerick, Ireland, Ireland. Limerick Digital Cancer Research Centre, Limerick, Ireland. CANDLE National Cancer Data Node, Limerick, Ireland

The European Health Data Space (EHDS) regulation, enacted in March 2025, is set to revolutionise health and genetic research by enabling secure, interoperable secondary access to health and genomic data across the EU. For the first time, all health data—including clinical records, genomics, and imaging—will be available for research, unlocking unprecedented opportunities for discovery and innovation. Sensitive health data will remain within national or institutional boundaries, while supporting cross-border research through standardised metadata catalogues and harmonised data access protocols.

Developing Ireland's research systems for the EHDS will enable Irish genetics researchers to participate in collaborative, high-impact research on vast EU datasets, while maintaining the highest standards of data security and patient privacy. Achieving an integrated health and genomics research ecosystem requires interoperability and the adoption of international standards[1].

This presentation will outline the key standards and systems forming the foundation for cancer genetic and genomics research in the EHDS, highlighting Ireland's strategic role in these developments. These include EU programs such as the 1+ Million Genomes (1+MG) Genomic Data Infrastructure (GDI), UNCAN-CONNECT, CANDLE[2] cancer data nodes, ELIXIR pan-European research infrastructure, and standards for clinical[3], genetics, and imaging data.

OP06 Investigating Genetic Links Between Sleep Disturbance and Neuropsychiatric Traits in Children: Insights from the Adolescent Brain Cognitive Development Study

Ms. Enya Nordon[1], Dr. Laura Fahey[2], Dr. Cathy Wyse[1], Prof. Lorna Lopez[1]

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Large-scale genome-wide association studies (GWAS) have identified numerous common variants linked to neurodevelopmental and neuropsychiatric conditions (NDPCs) such as ADHD, autism, bipolar disorder, major depressive disorder (MDD), and schizophrenia. Sleep traits, including chronotype and insomnia, also exhibit polygenic inheritance. Prior research has shown genetic correlations between these phenotypes; for instance, evening chronotype is genetically associated with schizophrenia and autism, while insomnia shares genetic risk with ADHD, bipolar disorder, and schizophrenia.

This study investigates the relationship between genetic liability for NDPCs and sleep/circadian traits in the Adolescent Brain Cognitive Development (ABCD) cohort, which includes genetic and behavioural data from

~11,800 children across 21 U.S. sites. After quality control, analyses included 4,289 unrelated individuals of European ancestry and over 10 million SNPs. Polygenic scores (PGSs) were generated using SBayesRC and summary statistics from the latest GWAS of autism, ADHD, schizophrenia, MDD, and bipolar disorder. Associations were tested between PGSs and sleep traits assessed via the Sleep Disturbance Scale for Children.

We found significant associations between NDPC-related PGSs and sleep disturbances. Notably, the ADHD PGS ($\beta = 4.26 \times 10^{6}$, R^2 = 0.42%, 95% CI [0.33%, 0.51%]) and the MDD PGS ($\beta = 9.82 \times 10^{6}$, R^2 = 0.62%, 95% CI [0.52%, 0.74%]) significantly predicted sleep disturbances in children ($p < 2 \times 10^{-16}$ for both).

These findings support shared genetic underpinnings between NDPCs and sleep traits. Ongoing work will expand to include additional sleep phenotypes and apply GWAS-by-subtraction to further investigate shared and distinct genetic contributions.

OP07 Incidental and Secondary findings of Cancer Predisposition Genes in Children Attending the Department of Clinical Genetics, CHI, Crumlin in the Republic of Ireland.

Dr. John Coleman[1], Ms. Sinead Whyte[1], Ms. Rebecca Redmond[1], Ms. Emma O' Donoghue[1], Mr. Eoin Hanney[1], Ms. Claire Giffney[1], Prof. Andrew Green[1], Dr. Noelle Cullinan[2], Dr. Lisa Bradley[1]

[1]Department of Clinical Genetics, Children's Health Ireland, Crumlin, Dublin, Ireland. [2]Department of Paediatric Oncology, National Children's Cancer Service, CHI, Crumlin, Dublin, Ireland

Introduction: With increased mainstreaming of genetic testing and improving technologies, there is additional detection/reporting of incidental (unexpected) and secondary (actively sought) findings (IF/SF), including cancer predisposition genes (CPGs), which can be challenging for clinicians and families.

Methods: We completed a service review of the paediatric genetics and haematology-oncology patients from July 2022 - March 2025. We reviewed patients (0-16) triaged as "cancer" subtype on our e-triage system or identified via our joint MDT and explored the burden of IF/SF.

Results: 277 referrals for CPG evaluation were identified. 5% (14/277) were referrals for IF/SF CPGs. 13/14 were incidental and 1/14 secondary (*BRCA1*). Referrals were from various specialities; General Paediatrics (6), Neurology (2), and one each from Cardiology, GP, Neonatology, Endocrinology, General Clinical Genetics and Respiratory. Array-CGH accounted for 78.6% of cases, with exome sequencing and panel testing generating 14.3% and 7.1% of cases respectively. Thirteen different CPGs were implicated. One of these cases has subsequently developed a related cancer. These 14 cases have generated 21 additional cascade appointments.

Limitations: Our study will not capture IF/SF CPGs dealt with during a general genetics appointment or non-referral of unrecognised IF/SF CPGs within mainstream testing reports.

Conclusion: IF/SF account for 5% of paediatric-cancer referrals. Significant workload and counselling challenge (21 cascaded to date). Difficulties estimating cancer risks (no FHx of cancer or CPG effects unknown). Autonomy of child 'right not to know' breached by SF of adult-onset CPG. Reason for referral/testing often 'lost' within unexpected CPG finding

OP08 A 10-year Audit in the Trends of Microarray Findings of the Regional Northern Ireland Clinical Genetics Service

Mr. Jack Courtney[1], Ms. Lucy O'Kane[1], Dr. Deirdre Donnelly[2]

[1]Ulster University, L'Derry, United Kingdom, [2]Northern Ireland Clinical Genetics Service, Belfast, United Kingdom.

The Northern Ireland Clinical Genetics service provides services to adults and children with a personal and/or a family history of various conditions. This Audit used artificial intelligence to process a large patient data set of microarray results (n ≈ 17,000) from 2013-2024, to standardise clinician patient summaries and standardise patients results to ISCN formatting; allowing for automated analysis of phenotype-phenotype and phenotype-genetic result co-occurrence. A further aim was to query use of Large Language Models (LLM) and Natural Language Processing (NLP) for bulk upload to large datasets.

Anonymised patient data (n=17,176) was processed with Python in Google-Colab in batches. OpenAI's LLM ChatGPT-3.5 Turbo-API produced cleaned phenotypes/results. This LLM was chosen to optimise for cost (<£1) and time constraints - along with batching patients in groups of 10. Phenotypes were then further mapped to 18 broader phenotype categories using ONTOLOGY SEARCH. As proof of concept, the NLP SapBERT mapped LLM outputs directly to the ~19,000 unique HPO terms. Missing data in columns was labelled as "unknown" to allowing filtering post-processing. Age at time of test was automatically calculated. A further python script was used to output visualisations of the dataset.

This audit provided a proof of concept within our limitations, for the potential use of LLMs and NLPs to process large data sets, allowing for bulk uploads to databases such as DECIPHER. Further work using larger parameter models such as GPT 4o could increase accuracy, and with other tools, allow direct spreadsheet to HPO mapping, then bulk upload.

OP09 Launching a Carrier Testing Study for Galactosaemia amongst the Irish Traveller Population

Ms. Aishling Whelan[1], Ms. Cathy Darcy[2], Prof. Michael Boyle[2], Dr. Catherine Clabby[1], Dr. Karen Flood[2], Ms. Fiona Hanrahan[2], Ms. Lynsey Kavanagh[3], Ms. Deborah Lambert[2], Dr. Jennifer McDaid[1], Dr. Trudi McDevitt[1], Ms. Valerie O'Leary[3], Prof. Sally Ann Lynch[1]

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There is a high incidence of classical galactosaemia amongst Irish Travellers (1 in 484). The protein in breast and formula milk can make affected neonates acutely ill. Since the 1980's, babies of Traveller women receive soy milk until results of a rapid Beutler test for galactosaemia are available. This has contributed to poor breastfeeding rates (2%) and causes stigmatisation on the post-natal wards. The majority of Traveller babies (483/484) do not have galactosaemia and are disadvantaged by this process.

Galactosaemia carrier testing for Traveller women can stratify the risk of galactosaemia: only those who are carriers remain at high risk and require a Beutler test. The Traveller GALT variant is known (c.563A>G p.(Gln188Arg)), and 1 in 11 Irish Travellers are carriers.
An 18 month project between the Department of Clinical Genetics, Children's Health Ireland; Pavee Point and the Rotunda Hospital was funded by The Children's Health Foundation to pilot antenatal galactosaemia carrier testing in Irish Traveller women. Women who are identified as non-carriers have the option to choose to breast feed from birth. Partners of women who are carriers are also offered carrier testing. To date 43 pregnant Irish Traveller women have been notified to the research mid-wife. 15/43 women have received carrier testing. 5/43 declined to participate. Efforts are underway to contact 15/43. There is consent to participate and awaiting blood sampling for additional 8/43. We describe the laboratory test validation; process and logistics involved in recruitment of participants; and outcomes following 6 months of carrier testing.

OP10 Expanding Somatic Variant Testing for Patients with Cancer in Ireland to align with EMA-approved Medications

Dr. Gráinne O'Mahoney[1], Mr. Brendan Reardon[1,2], Mr. Ciarán Haugh[3], Prof. Aedín Culhane[1]

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Delays in patient access to new cancer medicines is a growing concern. Most (81%) of new cancer medicines approved by the European Medicines Agency (EMA) in 2020-2022 were targeted therapies[1], necessitating somatic genomics testing. Quantification of patients affected is impacted by the absence of national cancer somatic variant data in Ireland.

The list of EMA-licensed oncology medications with genetic indications was previously extracted by manual review[2]. For each, the number of patients (2018-2022) meeting eligibility criteria, irrespective of variant status, was quantified in conjunction with the National Cancer Registry Ireland (NCRI). Staging, treatment and demographic variables were used to systematically refine patient eligibility at diagnosis. Mortality following treatment was used to infer refractory and recurrent disease. For each medication, international somatic variant data (AACR GENIE 17.0-public)[3] was used to estimate genomic variant prevalence within the indicated cancer type and age group.

By combining NCRI patient numbers and AACR GENIE[3] prevalence, we estimate the expected number of patients in Ireland eligible for an EMA-licensed molecularly-targeted therapy. We present a reference framework against which real world data could be used to identify distinct geographical and temporal patterns in cancer genomics. Finally, we present data to support expanding genomic testing to aid access to EMA-licensed oncology medications, clinical trial design and prioritisation of new medicines.

OP11 Exploring Canadian Genetic Counsellors' Perspectives and Experiences with Discussing Medical Assistance in Dying (MAiD)

Ms. Rebecca Candlish[1,2], Ms. Susan Creighton[2], Dr. Daryl Pullman[3], Dr. Alison M. Elliott[2,4,5]
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Through changes to Canada's eligibility criteria for Medical Assistance in Dying (MAiD) in 2021, Canada now has the most permissive assisted dying regime in the world. This study explores Canadian genetic counsellors' experiences, knowledge, and preparedness to discuss MAiD with their patients. Survey responses were collected from Canadian genetic counsellors (n = 44), followed by semi-structured interviews with 14 survey participants. Survey data were analysed using descriptive statistics, and interview transcripts were analysed using phronetic iterative analysis and interpretive description. Survey data reveal that genetic counsellors have discussed MAiD with patients referred for cancer, neurologic, metabolic, connective tissue, and cardiac indications (n = 18, 40.9%). While most thought that it was important for genetic counsellors to be prepared to discuss MAiD (n = 43, 97.7%), many were not familiar with the eligibility criteria (n = 27, 61.4%) and process for accessing MAiD in Canada (n = 29, 65.9%). Interview participants described discussions about MAiD that were initiated by themselves or their patients. Most participants felt prepared to explore a patient's thoughts about MAiD when the patient initiated the discussion, but did not feel well-prepared to share detailed information about MAiD. Participants were interested in education and professional guidance to assist them in preparing to discuss MAiD in the clinical setting. As genetic counsellors continue engaging in discussions about MAiD, it is critical that these sensitive conversations are approached with increased knowledge and awareness of MAiD legislation in their country of practice, the ethical issues surrounding MAiD, and relevant patient resources.

POSTER PRESENTATIONS

BASIC

P01 Linkage analysis of copy number variants in a Mexican American mood disorder pedigree cohort

Dr. Niamh Ryan[1], Dr. Cathal Ormond[1], Mr. Juan Peralta[2], Dr. Satish Kumar[2], Dr. Joanne E Curran[2], Dr. Elizabeth Heron[1], Prof. David Glahn[3,4], Prof. John Blangero[2], Prof. Aiden Corvin[1]

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Rare copy number variants (CNVs) have some of the highest estimated relative-risks among genetic variants contributing to mental illness. Many CNVs have been associated with multiple disorders and varying degrees of symptom severity. This study investigated CNVs in a cohort of Mexican-American pedigrees with a high load of mood and other psychiatric disorders, sequenced and phenotyped as part of the Genetics of Brain Structure and Function Study. Two-point linkage analysis was performed using SOLAR.

Among the top putatively-deleterious ultra-rare (MAF=0) CNVs were:
1. An 8Kb DEL on chr1 (LOD:2.5554) deleting the last exon, stop codon, and 3'UTR of *CD55,* a gene crucial for regulating the complement system and shown to be significantly elevated in a study of schizophrenia patients compared to healthy controls.
2. A 14Kb DUP (LOD:2.7673) on chr7 spanning *MUC3A* exons 3-11 and the 5'UTR and exons 1-3 of *MUC12*. Mucins play a role in the gut microbiome andsystem and shown to be significantly elevated in a study of schizophrenia patients compared to
3. A 3.2Kb DEL on chr18 (LOD:2.0324) disrupting 32 amino acids of *CDH19* and potentially generating a downstream frameshift. While cadherin-19 (*CDH19*) has not been associated with psychiatric illness, there is support for the role of cadherins in the pathophysiology of five major psychiatric disorders, including major depressive disorder.

These CNVs represent novel findings warranting further investigation into their potential role in psychiatric disorders. Next steps will include investigating their transcriptional and cellular effects using iPSC-derived neural stem cells available from this cohort.

P02 Investigating the impact of miRNA variants in pedigrees enriched for psychiatric illness

Mr. Brendan Hearn[1], Dr. Cathal Ormond[1], Dr. Lynn DeLisi[2], Dr. Elizabeth Heron[1], Dr. Niamh Ryan[1], Dr. Aiden Corvin[1]

[1]Trinity College of Dublin, Dublin, Ireland. [2]Harvard University, Cambridge, USA

Psychiatric disorders have been widely studied but the underlying biological mechanisms remain poorly understood. They are thought to result from a combination of environmental and genetic factors, including both common and rare variants. microRNAs (miRNAs) are a form of post-transcriptional regulation, binding to the messenger RNAs of dozens or hundreds of genes to prevent translation. miRNAs play a role in nervous system development and their dysregulation has been linked to several psychiatric disorders. In this study we investigated the potential impact of rare miRNA variants in pedigrees enriched for psychiatric illness.

We constructed a pipeline using miRbase, gnomAD, miRNASNP V3, and Gene Ontology

enrichment analysis to identify and analyse rare variants altering miRNAs in 26 psychiatric pedigrees. This process found two rare miRNA variants affecting miR-548as-5p and miR-4423-3p in one of the pedigrees, with nine of the eleven affected individuals carrying at least one variant. These variants alter both the secondary structure and the gene targets of the miRNAs. miR-548as-5p gained *RGMB* as a gene target, which is associated with nervous system development and has been linked to psychiatric disorders. miR-4423-3p lost 403 gene targets and gained 701, including multiple genes previously associated with psychiatric disorders. These differences in gene targets included the loss of two pathways related to synapse-regulation and gain of seven synapse/neurodevelopment pathways. These findings suggest that these rare variant miRNAs could play a role in the development of mental illness. Further research is needed to determine the extent to which these miRNAs impact gene expression.

P03 Single cell RNA Sequencing of iPSC-Generated Type 2 Alveolar Epithelial Cells Reveals Divergent Responses to Sex Hormones in a Pulmonary Fibrosis Model.

Ms. Jisha Jasmin[1,2], Dr. Anja Schweikert[3], Mr. Sahin Sarihan[1], Dr. Mari Ozaki[3], Prof. Gianpiero Cavalleri[1], Prof. Killian Hurley[3]

[1]Royal College of Surgeons in Ireland, Dublin, Ireland. [2]SFI Centre for Research Training in Genomics Data Science, Galway, Ireland. [3]Beaumont Hospital, Royal College of Surgeons in Ireland, Dublin, Ireland

O3 mouse study highlights a potential protective role of estrogen against PF, suggesting that sex hormones influence the development and progression of PF. Here we set out to detail sex hormone responses of alveolar type 2 epithelial cells to profibrotic exposure, using single cell RNA sequencing. We generated AT2 cells from induced pluripotent stem cells (iAT2) to examine the effects of sex hormones on gene expression using single-cell RNA sequencing. iAT2 cells were treated with estrogen and testosterone for 14 days, with subsequent profibrotic cocktail (PFC) exposure in the final 72 hours. Single live cells were encapsulated using a 10X-Genomics Core machine and RNA libraries were generated, followed by sequencing. scRNA-seq analysis was conducted using Seurat after identifying the highest-quality cells. Dimensionality reduction techniques were employed to visualise clustering, followed by cluster annotation and pathway enrichment analysis. Cluster annotation revealed that estrogen-treated cell clusters exhibited senescence markers following PFC-exposure, whereas testosterone-treated cell clusters demonstrated TGF-β activation and aberrant basaloid markers. RNA velocity indicated a transition towards aberrant basaloid cells from other clusters, including the TGF-β cluster. Overall, these analyses suggest that testosterone is linked to a potential transition to recognised profibrotic cell states after PFC-exposure. Our findings suggest distinct roles of sex hormones in modulating AT2 cells, offering insights into understanding PF and its treatment. However, additional laboratory validation is necessary to confirm these observations.

P04 Characterisation of diverse global ancestries among participants of the UK Biobank illustrates the immigration history of Great Britain in the 20th century

Ms. Fiona Pantring[1,2,3], Prof. Gianpiero Cavalleri[1,2,3], Dr. Edmund Gilbert[1,2]
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The UK Biobank (UKB) contains in-depth phenotype and genotype data for nearly 500,000 UK-based participants.
Studies leveraging the UKB typically focus on a subset of participants with homogenous European ancestry according to self-identification and genotype-based principal component analysis (i.e., “White British”). Here, we comprehensively characterise the remaining 78,573 UKB participants with diverse ancestries using population genetic approaches identifying communities that reflect the population history of the UK.

We developed a novel approach to characterise diverse ancestries in UKB by assigning individuals to one of eight primary continental-level ancestry clusters using machine learning and then identifying a total of 293 fine-scale ancestry communities within those clusters by applying community detection to a network of Identity-By-Descent sharing.

We find that the UKB is a repository of diverse ancestries primarily of European-, African-, and South Asian-like descent. Whilst capturing worldwide diversity, the 293 communities appear to reflect the immigration history of Great Britain and its Commonwealth in the 20th century and thus are likely less represented in other large global biobanks. Subsequently, notable communities that we identify include Afro-Caribbean-like ancestry, Ashkenazi Jewish-like ancestry as well as a diverse variety of communities with Indian- and Pakistani-like ancestry.

Our communities also facilitate novel findings of community-specific genetic risk factors. For example, in a community of Maltese-like

ancestry, we observe one of the highest global frequencies of the *MUC5B* risk variant for idiopathic pulmonary fibrosis. This work provides a framework for future studies of health-related genetic variation specific to otherwise understudied genetic communities.

P05 Exploring how to communicate genomics-based medicine in Ireland: Let's Chat Medicine - A public engagement initiative involving young people in designing creative graphics for complex themes

Dr. Maeve McCann, Ms. Anna Wedderburn, Ms. Emma Whooley, Dr. Jessica Ralston, Dr. Eadaoin McKiernan, Prof. Walter Kolch

Systems Biology Ireland, Dublin, Ireland

As biological research becomes more complex and technologically driven, a parallel challenge for researchers is maintaining public understanding. While it is difficult to communicate how genomics technologies work, doing so is crucial for patient/public trust and uptake in genomics informed healthcare and personalised medicine. As outlined in the core principles of the national genomics strategy for Ireland, public and patient involvement (PPI) in research and engagement strategies will be crucial to the overall success of any genomics based initiative at national or institute levels.

We present the current benefits, outputs and challenges of engaging in such a PPI initiative, specifically "Let's Chat Medicine" (LCM) at Systems Biology Ireland. LCM involves young people in designing communication outputs at a generally comprehensible level. To date, LCM has successfully completed two week-long programmes where approximately 40 teenagers gained first hand insight into the science of personalised medicine and subsequently created graphic and oral presentations which communicate core themes. This has proven to be a highly effective method for creating engaging and informative graphic content.

However, questions remain as to how such content can be effectively harnessed to inform the wider public on genomics-based personalised medicine and to what extent this would impact those who had no prior knowledge or trust in these practices. LCM is an informative case study for genomics researchers in Ireland wishing to engage the public in their research and is an ideal project to kick-start discussion of feasible PPI initiatives within the boundaries of existing research institutes.

P06 Leveraging haplotypes to increase genetic diagnoses in an Irish ADPKD cohort

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Background: Studies of some late-onset monogenic conditions have demonstrated common ancestral variant haplotypes are shared between seemingly unrelated individuals carrying the same pathogenic variant. Therefore, these shared variant haplotypes can be leveraged to infer putative carriers of disease-causing variants and connect different pedigrees into extended linked families.

Methods: Local identity-by-descent clusters (LICs) were identified across the PKD1 and PKD2 genes in 497 SNP-array genotypes from an Irish Autosomal Dominant Polycystic Kidney Disease (ADPKD) cohort (n=567). In parallel, pathogenic variants were identified in sequencing data from 279 samples from the same cohort. Using a novel LIC stratification algorithm, we (a) characterised kinship between carriers of the same ADPKD variant, (b) predicted carriers of pathogenic variants in the unanalysed individuals, and (c) reclassified variants of unknown significance (VUSs) using the American College of Medical Genetics and Genomics (ACMG) guidelines for population/cosegregation data.

Results: First, we identified 15 diagnostic ADPKD variant haplotypes in our cohort, each descended from one putative common ancestor. Second, we accurately predicted the presence of variants in 83.3% of previously unanalysed samples, including two from a haplotype cluster carrying a VUS. Finally, we increased the diagnostic yield of NGS by 1.3% by reclassifying a VUS as likely-pathogenic due to additional "population" evidence from haplotype data.

Conclusions: We highlight the clinical utility of haplotype-based methods in increasing the diagnostic yield of a cohort by predicting carriers of pathogenic variants and

reclassifying VUSs, therefore reducing both diagnostic timelines and associated costs.

P07 Novel Aptamer Development for Oesophageal Cancer

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Oesophageal cancer (OC) is a disease with a five-year survival rate of approximately 10-15%, often diagnosed at an advanced stage due to the lack of early symptoms, with Barrett's Oesophagus (BO) being the only known precursor. To address the need for novel diagnostic tools, this work explores the development of aptamers—short, single-stranded DNA molecules that fold into specific three-dimensional structures to bind targets with high affinity and specificity. The objective is to generate aptamers that can selectively recognise a biomarker distinguishing OC from BO and non-cancerous oesophageal cells, with potential application in early diagnosis. Aptamers were selected using the cell-Systematic Evolution of Ligands by EXponential enrichment (cell-SELEX) process, which involved iterative rounds of binding a DNA library to the cells, partitioning, and amplification to enrich oligonucleotide sequences that bind specifically to the surface of target cells. SELEX was carried out against an OC cell line, OE33, a BO cell line, QH, and a non-cancerous oesophageal cell line Het1A, to identify aptamers capable of binding to OC cells with minimal to no affinity for non-cancerous cells. The resulting aptamer pools underwent sequencing using Illumina-based Next Generation Sequencing (NGS) to identify and quantify enriched sequences. Sequence analysis will be conducted using Galaxy tools, including the FASTAptamer tool, to identify candidate aptamers and will involve ranking of sequences based on enrichment trends and structural prediction. The diagnostic potential of the top aptamer candidates will be further investigated for sensitivity, specificity and potential clinical use in the future.

P08 Green space, DNA methylation and mild cognitive impairment in NICOLA (Northern Ireland Cohort for the Longitudinal Study of Ageing): an epigenome-wide association study with Mendelian randomization

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Green spaces, areas of vegetation such as parks or greenways, are environmental features which have been suggested to be of benefit to cognitive health, reducing the risk of cognitive impairment. Methylation profiles have been evidenced to be differentially expressed in accordance with green space exposure. We aim to locate epigenetic markers which associate green space exposure to mild cognitive impairment outcomes, harnessing NICOLA, a cohort of adults aged >50).

We will use systemic blood sample DNA methylation profiles from a sub-set of the NICOLA cohort (n=1870). Samples were bisulfite sequenced using the EZDNAm Kit and the Illumina Infinium Methylation EPIC Bead Chip 800K Array was used to assess methylation. Two different metrics of green space exposure will be used in analysis, Normalised Difference Vegetation Index, and proximity to accessible green spaces such as parks within buffer zones (200m for primary analysis) of participants' residence. Participants were classified as being of normal cognition or mild cognitive impairment based on assessments of Mini Mental State Examination, Montreal Cognitive Assessment and subjective memory.

We will perform sequential epigenome-wide association studies on green space exposure and mild cognitive impairment respectively and compare statistically significant DNA methylation sites for concordance. We hypothesise that we may locate resilience markers of mild cognitive impairment from green space exposure. We additionally aim to perform causal analysis using a Mendelian randomization approach.

Identifying these resilience markers would provide an evidence base to promote the importance of high quality, accessible green space presence for both environmental and human cognitive benefit.

P09 Shared Genetic Variants Linking ALS, Sporadic FTD, and Cognitive Traits

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Background: Cognitive impairment affecting executive function, verbal fluency, and social cognition occurs in about 50% of ALS patients, with 15% meeting frontotemporal dementia (FTD) criteria. The genetic basis of cognitive decline in ALS remains unclear. This study explores shared genetic factors between ALS, sporadic FTD (sFTD), and cognitive traits to identify common biological pathways.

Methods: Using European ancestry GWAS data, we performed a multi-trait analysis (MTAG) on ALS, sFTD, and cognitive phenotypes. Shared loci were identified as lead MTAG SNPs ($p<5e-8$) with conjunctional false discovery rate (FDR) < 0.05. Local genetic correlations were assessed with LAVA, and colocalisation and fine-mapping were run using coloc. Gene mapping and functional annotation were performed using FUMA. Polygenic risk scores (PRS) for cognitive status in ALS were created using PRSice-2 and validated in an independent ALS cohort (AnswerALS).

Results: ALS and sFTD showed strong genetic overlap, with ALS negatively correlated to cognitive traits. Thirty shared genes, including *MEF2C, MOBP, MAPT, CRHR1, UNC13A, NSF, APOE,* and *EXOC4*, clustered in pathways of vesicle and membrane organisation. Most loci had negative correlations, except two with positive links to cognition. Fine-mapping highlighted variants such as rs2013478 (*CLCN3*) and rs429358 (*APOE*). The combined ALS+cognitive trait PRS improved prediction of ALS-FTD risk over ALS-only models, pending refinement with larger datasets.

Conclusion: Shared genetic factors in ALS, sFTD, and cognition involve brain-expressed genes linked to vesicle transport and membrane organisation. Identified variants provide targets for further study, and integrated PRS models hold promise for better FTD risk prediction in ALS.

P10 FOXP1 Dysregulation and Its Association with Schizophrenia and Cognitive Function

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FOXP1 (Forkhead-box protein P1) is a crucial transcription factor in neural development and is associated with schizophrenia (SCZ). FOXP1-regulated genes may contribute to genetic risk of SCZ and this may vary across different stages of neurodevelopment. We analyzed RNA-seq transcriptomic data from mouse and human models of FOXP1 loss-of-function across prenatal and postnatal developmental stages, including neural stem cells from embryonic mice (E14.5) and human brain organoids (equivalent to second trimester), and cortical tissues from different mouse postnatal stages P0, P7, and P47. P0 in mice corresponds to the third trimester in humans, while P7 and P47 represent early childhood and adolescence, respectively. Linkage disequilibrium score regression assessed if FOXP1-regulated genes were enriched for SCZ heritability. Gene-set enrichment analysis investigated if FOXP1-regulated genes were enriched for SCZ-associated genes reported as differentially expressed in single cortical cell studies. SynGO analysis mapped FOXP1-regulated genes to synaptic locations and functions. FOXP1-regulated genes were enriched for SCZ heritability, with significant results for E14.5, P7 and P47 but not P0. The P7 gene-set showed the strongest enrichment for SCZ-associated genes from single cortical cell studies. FOXP1-regulated genes at both P7 and P47 were involved in multiple synaptic functions and were mainly enriched within glutamatergic excitatory neurons, with P47 also showing enrichment within GABAergic inhibitory neurons. Prenatal FOXP1-regulated genes were enriched in progenitor cells and also mapped to the synapse. Genetic risk for SCZ within FOXP1-regulated genes follows a dynamic trajectory across developmental stages, showing strongest effects at a timepoints that map to early childhood.

P11 Evaluating Scientific Approaches To Newborn Screening (NBS) For SCN1A Related Disease With WGS – A Scoping Literature Review And Exploring Variants in Public Databases

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Introduction: *SCN1A* epilepsy is caused by various genetic mechanisms, causing disorders including Dravet Syndrome. This severe early-onset paediatric disorder is currently included on 13 international genomic NBS panels. *SCN1A* (GoF) epilepsy responds to high-dose sodium channel blockers, however several antiseizure medications can exaggerate seizures. We reviewed public literature and databases to explore variants reported and complete burden testing for S*CN1A,* considering NBS implications.

Method: A variant list was curated using public databases. ClinVar reported LP/P and conflicting pathogenicity *SCN1A* variants were reviewed. Variants without a clear paediatric phenotype and multigene deletions were excluded. GnomADv4.1 *SCN1A* variants were compared with ClinVar. Burden tests were completed using GeneBass.

Results: 2015 *SCN1A* variants were recorded LP/P within Clinvar. Variant types included missense (934), nonsense (306), frameshift (469), splice (161) and other/non-coding (145). SKAT-O burden tests did not show a significant association with epilepsy for either pLoFs (p=1) or missense variants in *SCN1A* (p=0.0578) in Genebass cohorts. The burden p-value was 0.851 for pLoF variants and 0.0344 for missense. 69 (3.4%) variants were in both ClinVar and gnomAD v4.1. Of these, 84% were congruous reports of pathogenicity, conflicting reports occurred in 7% and 9% unclassified.

Conclusion: *SCN1A* remains a candidate gene for NBS. Most pathogenic variants are causative of severe phenotypes and largely absent from healthy populations. Genebass pLOF value may suggest these variants are rare in their datasets, while the burden test for missense variants suggest an association with epilepsy. We plan to further explore *SCN1A* using the UK Biobank.

P12 Investigating the relationship between green and blue spaces and depression in older adults via DNA methylation using a mechanistic review approach

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Green and blue spaces (GBS), such as parks, trees, rivers and coastlines have been shown in research to reduce the risk of depression and improve depressive symptoms. However, the biological mechanisms underlying these positive changes remain poorly understood. There is evidence to suggest that changes in DNA methylation may be one of the mechanisms through which green spaces positively affect mental health. We explored the association between GBS, DNA methylation and depression in older adults using a mechanistic review approach, as depression in older adults is associated with negative health outcomes such as dementia.

We conducted our mechanistic review according to the World Cancer Research Fund/University of Bristol guidelines. A mechanistic review is a type of systematic review which investigates the association between an exposure and an outcome through a biological mechanism. A mechanistic review was chosen as we were unable to find any studies exploring DNA methylation related to GBS and depression. We conducted two searches: the environmentally focused search used terms such as “green space”, “blue space”, while the depression focused search used “DNA methylation” and “depression”. A narrative synthesis was conducted with discussion of potential biological pathways influenced by both green spaces and depression.

Our review included 4 studies from the environmentally focused search and 5 studies from the depression focused search. We found differential methylation in the RGS12 gene associated with both green space and depression. We found no papers investigating blue space related methylation changes, highlighting the importance of further research in this field.

P13 The Shared and Differential Genetic Risk Factors of Neurodegeneration

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Background: Neurodegenerative diseases comprise many complex pathologies that result in neuronal loss. Heterogeneous in nature, they often exhibit overlapping symptomatologies, protein aggregates, and comorbid psychiatric disorders, resulting in diagnostic difficulties for even experienced neurologists. Recent literature suggests overlapping genetic risk for these diseases, which could be core to the biology of neurodegeneration.

Material and Methods: This research aims to identify the shared genetic risk factors that contribute to nine neurodegenerative traits. We analysed summary statistics from their largest genome-wide association studies (GWAS) using LD-score regression (LDSC) and genomic structural equation modeling (GenomicSEM) to examine genetic correlations between traits and model their complex interrelatedness. To uncover shared SNPs between neurodegenerative disorders, we used multi-trait analysis of GWAS (MTAG) and conjunctional false discovery rate (conjFDR) analysis as complementary methods. Transcriptome-wide association studies (TWAS) identified links between gene expression and neurodegeneration across brain tissues.

Results: We identified genetic correlations and a shared latent genetic factor between several neurodegenerative traits. MTAG analyses revealed 100 novel risk loci significantly associated with our nine neurodegenerative traits, 18 of which were reinforced by conjFDR as shared between two or more neurodegenerative traits. These loci were enriched for differential expression in ontologies relevant to neurodegeneration (e.g. microglial cell activation, neuron death regulation).

Conclusion: Multi-trait analysis of neurodegenerative traits reveals shared genetic risk loci and improves our biological understanding of core neurodegenerative mechanisms. The research conducted in this abstract was jointly funded by Taighde Éireann – Research Ireland under grant number GOIPG/2024/5066, and the MND association under grant number 979-799.

P14 Participant-Centred Design of a Phenotypic Database and Long-Term Engagement Application for the Genome of Ireland

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The Genome of Ireland (GoI) project aims to establish the first reference genome representative of the population resident on the island of Ireland, through the recruitment of 1,200 participants. The GoI contributes to the Genome of Europe initiative, which seeks to create a European reference dataset of at least 100,000 whole genome sequences. Given the critical importance of structured and interoperable data sharing, we set out to develop a FAIR (Findable, Accessible, Interoperable, Reusable) proof-of-concept database and a participant-facing application to standardise phenotypic data capture and to support dynamic consent and longitudinal engagement.

We have created a bespoke and interoperable database for the GoI project in collaboration with the GoI Patient and Public Involvement (PPI) Steering Board. This database was developed using Research Electronic Data Capture (REDCap), a secure and GDPR-compliant web-based application. The database architecture was designed to align with the Global Alliance for Genomics and Health Beacon v2 model to ensure data standardisation for future deposition of the GoI dataset in the European Genomic Data Infrastructure. Furthermore, we have developed a participant-facing mobile application, MyCap, that will enable the communication of study updates, reconsenting and remote data capture. PPI co-design of the MyCap instance improved language and feature accessibility to enhance participant experience. However, the real-world applicability of these instances within the participant recruitment workflow has yet to be validated.

The REDCap and MyCap instances have been developed to facilitate secure data capture, dynamic consent and long-term engagement throughout the GoI project, supporting the advancement of genomic research.

P15 From Genes to Rhythms:Autism Polygenic Risk and Sleep-Circadian Timing of Adults in the UK Biobank Study

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Autism is a heterogeneous neurodevelopmental condition characterised by persistent deficits in social communication and interaction, as well as restricted, repetitive patterns of behaviour, interests or activities. Sleep difficulties in autism are one of the most frequent medical complaints in adulthood. Common genetic variations linked to autism have been found to overlap with those contributing to sleep traits significantly. The objective of this study is to investigate the correlation between polygenic scores for autism and sleep traits (chronotype, sleep quality and insomnia) in adults, using data from the UK Biobank.

The UK Biobank (UKB) is a longitudinal study of over 500,000 UK residents (aged 37 – 73 years, with a mean age of 55). A polygenic risk score is the weighted sum of alleles that quantify the effect of several genetic variants on an individual's phenotype. The discovery dataset is the summary statistics file from a genome-wide association study of autism conducted by the Psychiatric Genomics Consortium. In contrast, the target dataset comprises individual-level genotypes and phenotypes from participants in the UKB. The analysis includes 150,856 participants who are not of white British ancestry, contain chromosomal aneuploidies, have high SNP missingness, are related, and perform shift

work. The number of single nucleotide polymorphisms (SNPs) is 7,301,380 in the discovery dataset, while there are 6,436,171 SNPs in the target dataset. The MegaPRS tool is used for calculating polygenic risk scores, which reveal risk predictions and stratification of autism related to sleep problems and circadian rhythm disruption.

P16 Joint analysis of de-novo SNVs across trio genomic datasets for the discovery of novel dominant epilepsy genes

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The developmental and epileptic encephalopathies (DEEs) and “epilepsy plus” are characterised by refractory seizures and developmental issues. Both groups have been shown to have underlying monogenic aetiology, characterised by dominant *de novo* variants (DNVs) across a range of highly conserved genes associated with brain development and function. A significant proportion of people with these types of epilepsy do not receive a molecular diagnosis, despite appropriate and extensive genetic testing, suggesting there are yet to be identified genetic causes of these epilepsies. We set out to identify novel genes of DEEs and “epilepsy plus” by amalgamating affected child, unaffected parent ‘trio’ genetic datasets using whole-exome (WES) or whole-genome sequencing technologies (WGS). A bioinformatics workflow using GATK4.2.0 was used for the variant calling. DeNovoWEST was used as a statistical framework to test for a significant excess of DNVs at the genic level. Next-generation sequencing (NGS) data from a total of 3,308 trios and quads were included in the final analysis. We identified 55 known ‘OMIM/epilepsy’ genes enriched with qualifying DNVs in cases, at the exome-wide level ($P < 1.3 \times 10^{-6}$). Restricting the analysis to brain-expressed genes ($P < 4.6 \times 10^{-5}$), we identified 73 genes with a significant excess of DNVs, 71 of which were known epilepsy genes. Our results provide support for *RANGAP1 and EGR3* as emerging and novel epilepsy genes.

P17 Reclassification rates and patterns for genomic variant submissions in ClinVar

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Background: Accurate genomic variant interpretation in the clinic is essential, often forming the basis for major life-impacting decisions. The ACMG/AMP guidelines (Richards et al. 2015) together with databases such as ClinVar (Landrum et al. 2014), greatly assist interpretation. However, it is known that variant classifications do not always remain stable over time resulting in reclassifications, adding to the complexity of assessing risk for identified variants, potentially impacting treatment and care. Existing estimates of reclassification rates vary (3.6%-58.8% Walsh et al. 2024), often focusing on small datasets, specific phenotypes or individual cohorts. An understanding of the rates in a broader context is lacking.

Methods: Monthly archived XML files containing information on the ClinVar record submissions (and updates) for germline SNVs were downloaded and reclassified variants were identified.

Findings: We estimated that 9.90% of genomic SNV submissions to ClinVar between Jan 2013 and May 2021 were reclassified by May 2024. Of the ACMG/AMP categories, initial classification of Likely Pathogenic had the highest reclassification rate (15.25%) and Benign the lowest rate (1.59%). Although variants of uncertain significance account for the largest proportion of submissions to ClinVar, only 10.56% were reclassified. Broadly, most reclassifications were in the

expected directions (e.g., Benign to Likely Benign).

Significance: Through analysing a relatively large dataset, this research quantifies the extent of the variant reclassification problem in a broader context (across phenotypes, submitters, cohorts) providing critical insights into the rates and directions. This research highlights the need for greater awareness and consideration of the reclassification issue.

P18 Investigating differentially expressed genes for schizophrenia for association with cognitive function

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Schizophrenia is a common psychiatric disorder that affects ~1% of the population and is associated with poor cognitive function. Differentially expressed genes (DEGs) for schizophrenia have been identified from single cell gene expression studies in the cortex. These include several transcription factor genes but their contribution to cognitive function is unknown. This study aimed to identify important single nucleotide polymorphisms (SNPs) within DEGs that function as transcription factors and test these for association with different measures of cognitive function. Eleven genes were chosen by cross referencing 287 DEGs with 1,620 brain transcription factor genes from the ChEA3 database. SNPs were selected based on either their association with schizophrenia from genome-wide association studies (GWAS) or their identification as expression quantitative trait loci (eQTLs) in the GTEx, MetaBrain or SingleBrain databases. These significant SNPs were assessed using Plink and linear regression association was modelled for the cognitive phenotypes of intelligence (IQ), social cognition (SC) and working memory (WM). Seven SNPs, which mapped to 5 of the 11 genes, were selected to be analysed for each phenotype using a linear regression model. In *FOXO3,* rs2153960 was associated with all 3 phenotypes (IQ (p=0.0002), WM (p=0.007) and SC (p=0.04)). In *GATAD2B*, rs10127983 was associated with both IQ (p=0.0014) and WM (p=0.0062), whereas rs7541871 only associated with SC (p=0.012) in this gene. DEGs for schizophrenia from single cell gene expression studies include transcription factor genes. Common variation in several of these genes is associated with cognitive function but independent replication in larger cohorts is required.

P19 Evaluation of the Emedgene Variant Assessment Platform

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This study is a validation of Illumina's Emedgene variant assessment platform. It examines functionality, performance, and security / data protection features, to determine suitability as a tool supporting assessment of germline variant datasets generated by the Mater Misericordiae NGS Laboratory. Evaluation was conducted using 132 anonymised clinical cases covering a range of variant types and indications. Sixty-two cases were positive for clinically relevant variants previously reported by the Laboratory. An additional 70 negative cases were included. Sequencing was performed on the NextSeq2000 using the Twist Whole Exome capture kit.

Emedgene possesses an artificial intelligence (AI) variant prioritisation module developed to expedite variant interpretation. The AI module correctly prioritised pathogenic or likely pathogenic variants in all positive cases, with over 98% of variants categorised as 'most likely' candidates. Also, in 21 negative cases, the AI prioritised variants classified by the platform as [likely] pathogenic, potentially leading to novel clinically relevant findings. The aim was to assess whether the platform can assist, not replace, expert interpretation by clinical scientists. While the AI contributes to efficiency and consistency, final variant classifications will remain under expert review.

Security and privacy features were also reviewed. Emedgene is ISO 27001 certified, adheres to HIPAA and GDPR standards, role-based privilege and access controls, and audit logging. All data were processed within secure cloud environments within the EU to uphold privacy and data integrity.

These findings suggest that Emedgene may be a useful adjunct for clinical variant analysis, improving prioritisation speed while maintaining rigorous oversight by qualified professionals.

P20 Exploring repeat sequences in Epilepsy. An imputation analyses of short tandem repeats in UK Biobank.

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Short tandem repeats (STRs) are 2-6nt motifs representing 3% of the human genome and

possess mutation rates orders of magnitude higher than single nucleotide polymorphisms (SNPs). They represent a source of both common and rare variation acting in coding, transcriptional, and post-transcriptional regulation; This makes them prime candidates to explore missing additive heritability. Exploring their contribution to complex traits poses technical challenges but development of tools such as ExpansionHunter Denovo now facilitate their characterisation in whole genome sequence data.

STRs have been associated with a range of heritable neurological conditions such as autism and schizophrenia. Their contribution to additive heritability in Parkinsons was recently explored, representing 15% of the additive heritability captured. Epilepsy is a complex condition and in particular Genetic Generalised Epilepsy possesses a high SNP heritability. The most recent epilepsy GWAS identified 26 SNP loci, however the role of STRs was not explored in this research. Here we present an analysis of common STR variation in epilepsy with UK Biobank data.

We leverage genotype data of 200 participants with epilepsy in UK Biobank and impute common STR variants using Beagle and the recently published ensemblTR phased SNP-STR reference panel. We perform association testing using AssociaTR and a GCTA-COJO analysis to identify LD independent STR loci. We demonstrate how this approach can be used to improve snp based heritability scores, fine mapping approaches, and help characterise the underlying biology of epilepsy. Gene prioritisation techniques inclu de gene-set enrichment testing, transcriptomics intersection, and network-based analysis e.g. webgestalt & FUMA.

P21 Investigating the effects of schizophrenia risk transcription factor genes on cognitive ability

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Background: Schizophrenia is a common psychiatric disorder with an array of symptoms ranging from psychosis to cognitive impairment. Due to its polygenic nature, schizophrenia remains a disorder where the underlying biology remains to be fully elucidated. Single cell gene expression (scRNA-seq) studies in the cortex have provided evidence that several transcription factor genes contribute to schizophrenia biology but their contribution to cognitive ability is unknown.

Aims: The aim of this project was to investigate a set of 14 transcription factor genes for association with the cognitive domains of intelligence (IQ), social cognition (SC) and working memory (WM).

Methods: Fourteen transcription factor genes were selected for analysis based on a recent scRNA-seq study of schizophrenia. SNPs were prioritized for analysis based on either their association with schizophrenia from genome-wide association studies (GWAS) or their identification as expression quantitative trait loci (eQTLs) in the GTEx, MetaBrain or SingleBrain databases. SNPs were then tested using linear regression models in Plink in an Irish case/control psychosis dataset (N=1247) to determine the effects of the SNPs on IQ, SC and WM.

Results: Sixteen SNPs were chosen for analysis mapping 8 of the 14 genes. At *RORB*, rs500102 was associated with IQ (p=0.045), WM (p=0.05) and SC (0.0002). At *MYT1L*, rs13419191 was associated with IQ (p=0.001) and WM (p=0.008). At *SATB2*, rs1376591 was associated with IQ (p=0.04).

Discussion: Analyses indicate that transcription factor genes associated with schizophrenia also influence cognitive function, but independent replication in larger sample sizes is required.

P22 ELIXIR-Ireland and Bioconductor: Opportunities for Irish Genomics Research

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As Ireland scales up its national genomics infrastructure, alignment with international and European networks is key to maximising impact. Two such initiatives, ELIXIR and Bioconductor, offer complementary strengths: ELIXIR connects life science data resources across Europe, including training, interoperability, data and software standards, and collaboration, while Bioconductor provides a robust R-based ecosystem for genomics data analysis.

The ELIXIR-Ireland node, now led by the University of Limerick, brings together five national partners and supports strategic areas including cancer genomics, personalised medicine, microbiome science, and the national Genomic Data Infrastructure (GDI) supporting

the 1+Million Genomes initiative. It connects Irish-developed resources to the wider European ecosystem and ensures that national capabilities contribute to both health-focused and broader bioscience domains.

UL also plays a global leadership role in Bioconductor, leading international grants and projects focused on tool development, infrastructure, and training. This includes coordinating a global Bioconductor training programme and a train-the-trainer network with over 40 instructors [1], which recently delivered a course in Kenya in collaboration with African partners, reflecting our commitment to inclusive, globally connected capacity building.

We welcome engagement from researchers across Ireland interested in using or contributing to these initiatives. By aligning national research needs with international infrastructure, we aim to foster a more connected, reproducible, and impactful genomics research environment in Ireland.

CLINICAL

P23 Prevalence of BRCA1/2 Variants in Breast Cancer Cohort: Outcomes from a Nationwide Testing Program

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Background: Genetic testing in breast cancer (BC) detects pathogenic variants (PVs) responsible for inherited cancer syndromes, providing crucial insights for both risk evaluation and guiding treatment decisions. Poly (ADP-ribose) polymerase inhibitors (PARPi) have demonstrated efficacy in patients with germline *BRCA1/2* (*gBRCA1/2*) mutated BC (1, 2). This study examines the prevalence of g*BRCA1/2* PVs in HER2-negative advanced gBRCA1/2 mutated BC in an Irish nationwide cohort.

Methods: Patients were centrally referred to St. James's Hospital for genetic testing from referral hospitals nationwide. *gBRCA* testing was conducted using smMIP panel sequencing and MLPA for detecting large genomic rearrangements (LGR). Variant classification followed ACMG and ACGS guidelines, with CanVIG-UK specifications. Data was analysed using descriptive statistics. Ethical approval was obtained.

Results: Among the 538 patients referred from 24 referral centres, the majority were female (97.2% female) and the mean age was 60 years (range: 28–90). Most patients (82.7%) were classified as *BRCA1/2* wild-type, however *gBRCA1/2* PVs were identified in 28 patients (5.2%) — 12 with *BRCA1* (2.2%) and 16 with *BRCA2* (3.0%). The most common PV detected was BRCA1 c.5266dup, p.(Gln1756Profs*74), found in 3 patients. Five patients (0.9%) carried *BRCA2* variants of uncertain significance and one LGA was identified in this cohort.

Conclusion: This nationwide cohort study found a *gBRCA1/2* prevalence of 5.2% in patients with HER2-negative advanced BC, closely aligning with reported international rates of 5% - 10% (1, 3). As the largest study of its kind in Ireland, it highlights the value of region-specific data given geographic variation in *BRCA* mutation prevalence.

P24 Urgent Cancer Referrals to the Department of Clinical Genetics (DCG), CHI, Crumlin: A Service Review Project

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Introduction: Due to advances in genetic testing, the feasibility of obtaining genetic results in a timeframe compatible with influencing treatment decision is becoming an increasing reality. Early prioritisation within genetic services for those at risk of cancer predisposition genes (CPGs) creates significant workloads.

Methods: A retrospective service evaluation review (2024 inclusive), identified patients electronically triaged as "urgent cancer". Data was collected/analysed using excel.

Results: 75 urgent cancer referrals were identified. These included; 91% adult, 9% paediatric, 79% diagnostic and 21% predictive. Referrers included breast surgeons (60%), in-house cascade (21%), oncology (15%) and GP (4%).

Referral reasons included; surgical planning (55%), screening implications (25%), palliative (8%), severe condition (5%), medical management (4%) and pregnancy (3%). 69% of breast cancer referrals documented triple negative status.

Urgent testing initiated included: breast cancer (65%), Polyposis (3%) and bespoke (3%) panels, familial variant (26%), karyotype (1.5%) and single gene test (1.5%).

Germline genetic testing was completed in 83% of cases. Of those tested, 21% had an actionable CPG variant identified (11 different

genes), 3% VUS, 76% uninformative testing. The diagnostic yield for breast cancer was 15%. Median time from referral receipt to appointment was 15 days. Median time appointment to results disclosure was 32 days. 24% had results that potentially guided imminent medical/surgical intervention. For 71% of cases, testing provided utility for long-term surgical management. 18% had cascade implications.

Conclusion: Our study supports clinical utility for selected urgent CPG testing. In particular those triaged appeared at significant risk of CPGs with meaningful intervention.

P25 Cancer Genetic testing: uptake, outcomes and patient feedback in Cork University Hospital

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Between January and December 2023, a total of 200 patients availed of diagnostic cancer genetic testing via a pilot cancer genetic clinic in Cork University Hospital after pre-test counselling provided by a Genetic Counsellor/ Consultant Geneticist. Eligible patients were required to be over 18 years, have a diagnosis of cancer and meet the Cork University Hospital defined BRCA or Lynch test criteria. Patients eligible for BRCA testing were offered the choice of BRCA genes only or a breast cancer gene panel. Feedback surveys to access satisfaction and clinical utility of the service were distributed to patients and referring clinicians.

The median waiting time for a diagnostic appointment was 26 days. All BRCA eligible patients opted for the full breast cancer panel with no patient opting for BRCA1/BRCA2 only analysis. Pathogenic variants were identified in 15/200 (7.5%). The questionnaire was returned by 78/200 (39%) patients, all respondents indicated that they 'agree' or 'strongly agree' that they were pleased to have had a genetic test. 89% of responding patients noted the test result was helpful to clarify their risk of developing further cancer and 99% of patients noted the test result was helpful in refining familial risk. The clinician questionnaire was returned by 11/25 (44%) of referring clinicians; 100% of clinician respondents noted that this regional pathway was faster than external genetic testing routes in providing a result that informs clinical care. Successful integration of cancer genetic testing into a regional cancer centre is feasible and highly acceptable to patients and clinicians.

P26 Our search for meaning: Intricacies of variant classification, challenges to clinical management, and benefits of a collaborative multidisciplinary approach

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Pathogenic/likely pathogenic variants (PV/LPVs) in *BRCA1* and *BRCA2* are the most commonly detected causative variants following genetic testing in eligible individuals. Determining the clinical significance of a variant may be complex, and gene-specific guidelines evolved from the ACMG/AMP recommendations are available to help diagnostic laboratories with this process. The *BRCA1* and *BRCA2* genes are well characterised, and therefore variant interpretation is relatively straight forward.

Nevertheless >30% (>4000, *BRCA1*) and >50% (>10,000, *BRCA2*) of submissions to ClinVar are variants of uncertain significance (VUS). Only PV/LPVs are considered clinically actionable for options such as PARPi treatment and surgery for the patient; and predictive testing for family members. Clinical management of families with a VUS is therefore challenging, with decision-making relying on risk estimates based on personal and family history, rather than risk associated with a PV/LPV.

The process is further complicated when the classification of a variant changes over time as new evidence emerges. Changes at the LP-VUS threshold are the most significant, as these may result in a change to established clinical management. We report how recently published studies necessitated a change from LP to VUS for *BRCA2* splice variant c.631G>C p.? present in multiple Irish families managed between two Dublin centres. We demonstrate how collaborative efforts involving clinical and laboratory teams successfully generated new evidence in support of pathogenicity, which allowed reinstatement of LP for this variant. This in turn facilitated the continued availability of predictive testing, and accurate risk assessment for family members

P27 Diagnostic Testing for Cancer Predisposing Syndromes in an Irish Paediatric Cancer Cohort

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Introduction: Genetic testing is of increasing importance in paediatric cancer care. Cancer predisposing genes (CPGs) confer an elevated risk of cancer development with approximately 10% of childhood cancers attributable to underlying CPG variants.

Methods: We conducted a retrospective review of all paediatric cancer diagnostic testing from July 2022 to March 2025, identified through the clinical genetics services and paediatric cancer genetics MDT at CHI Crumlin.

Results: We identified 132 cases, representing all cancer subtypes; solid-organ tumours (77/132), central nervous system (40/132), leukaemia/myelodysplastic syndromes (13/132) and lymphomas (2/132).A total of 110/132 patients (83.3%) have completed genetic testing, 7/132(5.3%) declined or did not attend for testing, 5.3% did not meet criteria for genetic testing, 4.5% have results pending and 1.5% remain on the waiting list. Of those who underwent genetic testing, 41% (45/110) were confirmed to carry a disease-causing CPG, 49% had non-informative testing, 9% had a variant of uncertain significance reported, and 1% had an incidental finding. Those who received a germline genetic diagnosis were represented by 22 different CPGs (e.g. *PTCH1, DICER1, RB1, NF1, APC*). 117 subsequent cascade predictive testing appointments were generated to date, of whom 33 were identified pre-symptomatically to carry the disease-causing CPG and avail of surveillance protocols.

Conclusion: Our paediatric CPG detection rate is significantly higher than the expected frequency of CPGs in a childhood cancer cohort (41% V 10%), attributable to the current selective high-risk referral pathway. Resultant cascade testing and health surveillance of pre-symptomatic family members requires dedicated resources and funding.

P28 Predictive Testing For Cancer Predisposition Genes (CPGs) in a Paediatric Cohort

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Introduction: Germline pathogenic variants in cancer predisposing genes (CPGs) confer an elevated risk of cancer development. Predictive testing for CPGs may be appropriate for at-risk children for whom cancer surveillance protocols are recommended.

Methodology: We conducted a retrospective review of paediatric patients (0-16 years) from July 2022 – Feb 2025 referred for predictive testing through the department of clinical genetics and paediatric haematology/oncology at CHI Crumlin. Patients were identified by electronic referrals and MDT record lists.

Results: 131 patients (mean age 9.2) were referred for predictive testing of 27 different CPGs. 11 of these are pending assessment with upcoming appointments and 120/131 patients have been evaluated. 5 failed to attend. 3 referrals were dealt with by letter advice. Another 3 patients were recommended to defer appointments due to age testing criteria. 109 patients have attended for assessment.

Of those who have attended clinic, 95/109 (87.2%) have completed genetic testing. 2.8% declined testing, a clinical examination was offered in lieu of testing in 0.9%. Testing was performed in an alternate family member in 1.8%, 1.8% were not offered testing, 3.6% are awaiting sample collection and 1.8% have pending results. 95 patients underwent CPG testing, of whom 38 patients (35%) were confirmed with a CPG in 13 different CPG syndromes. All received genetic counselling and surveillance advice. The 4 most common CPGs confirmed were SDHB (10), APC (5), VHL (8) and TP53 (3).

Conclusion: We report high uptake of predictive testing for CPGs in the paediatric cohort, with only 2.7% declining testing.

P29 Development of a Patient information leaflet: A Quality Initiative by the NGS laboratory

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The Next Generation Sequencing (NGS) laboratory currently provides diagnostic genetic testing services to patients at Mater Misericordiae University Hospital (MMUH) and other hospitals in the Republic of Ireland. The laboratory holds accreditation to ISO 15189 standards. With the introduction of ISO 15189:2022, a new requirement, standard 4.3, focuses on patient-centred communication. This standard outlines how laboratories must ensure that patients are informed, respected, and involved in the diagnostic process where appropriate. To comply with this update, the laboratory initiated the development of a patient information leaflet to be provided to individuals undergoing genetic testing.

In preparation, the laboratory consulted with relevant stakeholders including Consultants, Nursing staff, and Genetic Counsellors to gather input related to laboratory queries and the overall genetic testing service. Additionally, guidance from the MMUH Quality team was sought to ensure that the language used in the leaflet was accessible, inclusive, and met best practices in patient communication.

The resulting patient information leaflet is designed to inform patients and their families from a laboratory perspective. It explains the purpose and nature of genetic testing, with a particular focus on NGS. The leaflet also addresses processes such as result reporting, data storage, and quality assurance, with an emphasis on maintaining transparency.

By developing this leaflet, the NGS laboratory has ensured alignment with the updated ISO 15189 standards, particularly the newly emphasised requirements around patient engagement and understanding. The leaflet also contributes to the laboratory's continued commitment to excellence and its standing as a trusted, accredited diagnostic service provider

P30 Implementation of ACMG SVC v4.0 Guidelines into a Diagnostic Laboratory

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The American College of Medical Genetics (ACMG) and Association for Molecular Pathology (AMP) guidelines, published in 2015, define a standardised approach for the interpretation and classification of variants. As genetic testing has advanced, so too has the need for a more refined system of evidence assessment. The upcoming iteration, referred to as SVC (Sequence Variant Classification) v4.0 moves from the previous semi-quantitative framework to a fully quantitative, points-based model. While many of the principals remain the same, the way in which evidence is categorised and combined will change with the newer version. The proposed guidelines have three broad categories; 1) Population evidence, 2) Clinical evidence (e.g. case:control data, phenotyped case counts, segregation) and 3) Molecular impact evidence (e.g. computational predictors, variant type), with decision trees to guide the user through the available evidence.

Implementation of SVC v4.0 in a diagnostic laboratory will likely encounter challenges. Here, we review some foreseeable challenges with implementing the switch to SVCv4.0; 1) training of personnel on the new model and categories, 2) validation of the new guidelines, 3) updates to local SOPs and documentation, 4) integration of the new points-based system into variant analysis pipelines and tertiary analysis platforms. For the validation, a set of previously classified variants (using 2015 guidelines) was performed and compared to the v4.0 classifications. Furthermore, as the guidelines aim to minimise subjectivity, we also assessed inter-analyst concordance within our laboratory. Here, we present a review and necessary validation of SVC v4.0 for implementation into a diagnostic laboratory.

P31 Silent Alleles: A Comparative Study of Rare Forms of Alpha-1 Antitrypsin Deficiency in Ireland

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Introduction: Alpha-1 antitrypsin deficiency (AATD) is an autosomal co-dominant condition caused by a spectrum of SERPINA1 gene mutations on chromosome 14 (14q32.1), resulting in insufficient circulating levels of alpha-1 antitrypsin (AAT). The degree of AATD confers varying risks of emphysema and liver disease[1].

Null alleles are a subgroup of rare SERPINA1 variations, which cause complete absence of AAT protein and confer the highest risk of pulmonary damage[1]. We will describe the Irish cohort of patients with six different Null variations and compare their clinical phenotypes to their more prevalent deficiency counterparts, MZ and ZZ.

Methods: Patients with Null mutations were identified via the National Targeted Detection Programme database. Clinical characteristics, spirometric, CT thorax and Fibroscan data were analysed. This cohort consists of a variety of genotypes including M/Null, Z/Null and the elusive Null/Null, allowing comparison across the groups. We performed cross comparison with MZ and ZZ (more common deficiency genotypes[2]), matched for age, sex and smoking status.

Results: Null variants confer a higher risk of emphysema, but conversely a lower risk of liver disease. The Irish population includes several ultra-rare variations, which are described. Each variant is mapped, allowing geographical visualisation of the prevalence of Null genotypes.

Conclusions: Early recognition of rare genotypes is key to disease prevention and is critical with the advent of exciting novel gene therapies on the horizon. The absence of government funding of existing treatments (which are shown to have significant benefit in this niche population[3]) remains a significant barrier in Ireland.

CLINICAL RESEARCH

P32 Model Process for Care Pathway Development for Rare Diseases

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Background: There is an existing major need for multidisciplinary care pathways (CPs) for rare diseases (RDs). In contrast to agreed best practice methodology for the appraisal and development of clinical practice guidelines, there is lack of an agreed definition and approach for CPs. Under the 'JARDIN' EU4Health current joint action, a multi-stakeholder group developed a model process for ERN CPs for adoption into national healthcare systems.

Material and Methods: A systematic review of existing CP development methodologies was completed. A 'model process' for the development of RD care pathways was agreed by comparing key activities identified in the systematic review, aligning common characteristics and identifying gaps. The model process was co-created and validated by a multi-stakeholder group of clinical experts, experts by lived experience, methodologists and health authorities.

Results: The model process comprises 5 phases with 18 steps: Planning, Scoping, Development, Implementation and Evaluation. This study focussed on the first 12 steps: Selection of Topics & Defining Outline Scope; Identification of Experts & Key Stakeholders; Governance & Planning; Defining Detailed Pathway Scope and Parameters; Gathering & Appraisal of Published Evidence; Mapping of Current Clinical Practices; Collecting Patient Needs; Triangulation of Patient Needs, Baseline Pathway & Published Evidence; Designing Ideal Care Pathway; Consensus on Evidence Gaps; Revising Care Pathway & Supporting Material; Approval & Publication.

Conclusion: The model process was co-created with a patient-centred approach by a multi-stakeholder group, to be published with a supporting toolkit, and piloted under 'JARDIN' in 2025 with development of lead ERN care pathways.

P33 Detecting MUC1 variable number tandem repeat variants using VNtyper in Irish renal patients

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Background: Autosomal dominant tubulointerstitial kidney disease MUC1 (ADTKD-MUC1) is a rare genetic kidney diseaese resulting from pathogenic variable number tandem repeats (VNTR) in the MUC1 gene. This VNTR is very challenging to detect by short-read next-generation sequencing (NGS). VNtyper is a bioinformatic tool designed to genotype *MUC1* VNTR from NGS data. Here, we analysed a large cohort of Irish kidney patients to validate VNtyper performance and investigate its ability to detect pathogenic *MUC1* VNTRs in other CKD patients.

Methods: Patients were recruited via Beaumont Hospital. Detection of pathogenic variants in *MUC1* VNTR was performed from NGS data of the patients using VNtyper. The performance of VNtyper was validated by testing samples from diagnosed ADTKD-MUC1 patients (n=6) whose pathogenic variants were identified previously by the Snapshot PCR method. We also used VNtype to conduct a systematic scan of 522 non-cystic and 366 cystic kidney disease patients, to detect pathogenic *MUC1* genotypes.

Results: VNtyper was able to detect pathogenic VNTRs in all six known ADTKD-MUC1 patients. Among the additional 522 CKD

patients screened by VNtyper, four had heterozygous pathogenic *MUC1* genotypes. Further, analysis in the 366 cystic kidney disease patients detected four pathogenic genotypes.

Conclusions: The results of this study support the use of VNtyper as a mechanism to detect pathogenic *MUC1* genotypes in kidney disease. Results also highlight a possible expansion of the *MUC1* phenotype to other kidney disorders, beyond ADTKD.

P34 Optimizing NMNAT genes for Gene-Independent NAD+ Augmentation Therapy in dry AMD

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We have investigated novel disease-independent gene therapies for dry age-related macular degeneration (AMD) using AAV-delivered optimised nicotinamide mononucleotide adenylyltransferase isoforms (*NMNAT2* and *NMNAT1).* AMD is a leading cause of blindness in the aging population in developed countries, thought to affect ~ 10% of people over the age of 65. NMNAT enzymes catalyze the final step of NAD^+ biosynthesis, a cofactor essential for metabolism, DNA repair, and mitochondrial function—processes disrupted in AMD. Reduced NAD^+ levels are linked to neurodegenerative conditions and age-related diseases, with *NMNAT1* and *NMNAT2* offering neuroprotective and anti-inflammatory benefits through modulation of SIRT1 and PARP signaling.

NMNAT2 and *NMNAT1* sequences were codon-optimizedand and CpG-depleted in order to minimize potential immune activation to unmethylated CpG motifs while maximizing protein expression. Optimized constructs were cloned into a CHOP AAV vector driven by the *CAG* promoter, widely used in ocular gene therapy. Restriction enzyme digestion and Sanger sequencing confirmed successful cloning.

Reduction in immunogenicity to CpGs was assessed using a HEK-DUAL™ hTLR9 reporter assay, which showed significantly reduced TLR9-mediated immune activation for the CpG-depleted *NMNAT2*. Results suggest reduced immunogenicity for *NMNAT1* as well. Increased expression of optimized constructs was confirmed using an NAD^+ fluorometric assay and western blotting. These results support further development of optimized *NMNAT* constructs as promising candidates for gene-independent therapy for dry AMD, potentially overcoming the limitations of current disease-targeted approaches.

P35 Anyone Can Do Exons

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The importance of intronic variants in gene function and disease is increasingly relevant, thereby pushing the move towards whole genome sequencing (WGS). However, the challenges associated with WGS (cost, data storage, extensive analyses requirement) makes it unattainable for many diagnostic laboratories. Therefore, we looked to develop novel gene panels that encompassed the exonic regions and intronic variants/regions of interest. Our study details an approach that incorporates pathogenic deep intronic variants, validated gene-disease associations, and optimised probe design.

An extensive review of literature was undertaken and variant data from ClinVar was extracted, focusing on pathogenic deep intronic variants that would escape conventional exon-based panels. These variants, which disrupt splicing, are critical for resolving previously undiagnosed genetic disorders.
Ensuring gene-disease validity was the next crucial step. We employed expert-curated resources, including PanelApp and ClinGen, to assess and prioritise genes based on robust clinical associations. This process not only refined our gene selection, but also provided confidence levels that are indispensable for precise clinical reporting. These rigorous evaluations minimise the inclusion of genes with limited evidence and reinforce the reliability of the panel.

The final element of our strategy involved optimizing probe design to capture challenging genomic regions, exemplified by the *RPGR* ORF15 region. Known for its low-complexity repetitive structure, *RPGR* ORF15 has been historically difficult to sequence. Through iterative probe design, we ensured that variants are more reliably detected.

In summary, our comprehensive approach, encompassing variant curation, validated gene selection, and technical refinements, demonstrates significant improvements over conventional gene panels.

P36 The Clinical Gap in AI-Driven Autism Genetics: A Review of Evidence and Implementation Barriers

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Background: Artificial intelligence and machine learning (AI/ML) are increasingly being applied in autism spectrum disorder (ASD) research[1], particularly in the analysis of genetic and epigenetic data[2]. These tools have shown research potential in identifying novel risk genes[2,3], biomarkers[4,5], and molecular subtypes[6]. However, their translation into clinical genetic practice remains uncertain. We assessed the literature on the application of AI/ML in ASD genetics, and evaluated the extent to which these tools have been validated, regulated, and integrated into clinical practice.

Methods: A comprehensive review of peer-reviewed literature was conducted, including original research and review articles, evaluating AI/ML applications in the genomic and epigenomic investigation of ASD. Data collected included study methodology, data type, model type and performance, validation and regulatory status and clinical application.

Results: AI/ML has been successfully employed in research settings to prioritise ASD risk genes, classify epigenetic profiles, and identify molecular subtypes. Models such as forecASD[7], ASiDentify[8], and deep learning-based methylation classifiers[4,5,9] have demonstrated high performance metrics. However, none of these tools have been externally validated in diverse clinical populations, nor have they received regulatory approval. Current diagnostic practice continues to rely on established technologies such as chromosomal microarray and exome/genome sequencing, interpreted through expert-curated frameworks.

Conclusions: While AI/ML have enhanced discoveries in ASD genetics research, they have not yet been adopted in clinical diagnostics. Ethical issues, interpretability, and generalisability challenge introduction to mainstream clinics. Future clinical utility of AI/ML depends on clinical validation, addressing ethical concerns, and assuring regulatory standards.

P37 A novel case of Shone complex and vascular malformation in Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome

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Introduction: Zhu-Tokita-Takenouchi-Kim (ZTTK) syndrome is a rare multisystem neurodevelopmental disorder caused by heterozygous variants in the SON gene, a key embryonic regulator of RNA splicing and gene expression. Clinical features include developmental delay, epilepsy, structural brain anomalies and variable dysmorphism. Shone complex is a rare congenital heart disease (CHD) comprising left-sided obstructive lesions including supravalvular mitral membrane, parachute mitral valve, subaortic stenosis and coarctation of the aorta. Its association with ZTTK syndrome has not been previously reported.

Case: We present a 4-year-old female with a confirmed diagnosis of ZTTK syndrome due to a de-novo pathogenic SON:c.4723_4729del, p.Arg1575Tyrfs*46 mutation. She presented neonatally with Shone complex and later epilepsy, global developmental delay and a facial capillary-venous malformation. At 4, she is non-verbal but is walking with an aid. She has distinctive facial features.

Methods: We performed a literature review using PubMed central, with articles including "ZTTK" or "ZTTK syndrome" for phenotype analysis.

Results: Developmental delay was very common (>90%), while CHD was less frequent (30%). No previously reported cases included Shone complex. Some cases involved immunological, endocrine and musculoskeletal abnormalities. Skin/vascular abnormalities were rarely documented.

Conclusion: This is the first reported case of Shone complex and facial capillary venous malformation in a patient with ZTTK syndrome. The underlying mechanism remains unclear but SON may be important in cardiac development. This may relate to abnormal splicing of other cardiac genes or mitochondrial dysfunction, with presentations of myocardial injuries and metabolic stoke. Future research and functional work may help establish a mechanism.

P38 Exploring the Genotype-Phenotype Relationship in Irish Cardiac Patients for *SCN5A* Variants

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SCN5A encodes for the sodium channel protein type 5 subunit alpha, a pore-forming component of a voltage-gated sodium channel. It is mainly expressed in cardiac muscle, and plays a role in cardiac impulse propagation. Variants in *SCN5A* are associated several

cardiac diseases such as Brugada syndrome, familial long QT syndrome, dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, with varying levels of supporting evidence. In a review of *SCN5A* variants identified in cardiac patients, the correlation between genotype and disease presentation was explored. Understanding this relationship allows for improved variant classification and interpretation. Other pleiotropic genes involved in cardiac disease, such as *TTN,* have shown the location of a variant influences disease presentation.

Pathogenic variants in *SCN5A* are often dominant, and there is evidence of haploinsufficiency being a mechanism of disease in Brugada syndrome. Some pathogenic variants were identified in multiple patients in the Irish population, such as c.362G>A, p.Arg121Gln. This variant is found in a cytoplasmic domain, close to the first transmembrane section of the protein. Clinical management of patients with *SCN5A* variants includes regular monitoring, lifestyle adjustments, and pharmacological treatments.

Higher throughput of genetic testing, especially next-generation sequencing will allow for the detection of new variants, including detection of copy number variants in the future. However, interpretation of these results will remain a challenge, particularly as *SCN5A* is associated with several cardiac diseases. Further research will be required to fully realise the potential of cardiac genetic testing and screening within Ireland.

P39 A Ten-Year Review of Cystic Fibrosis Carrier Testing in the Republic of Ireland: Implications for Reproductive Risk

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Background: Cascade carrier testing (CCT) is recommended for family members of those diagnosed with a recessive condition as they have an increased reproductive risk. Cystic fibrosis (CF) is the commonest recessive disorder for those of Irish ethnicity (1/19 carrier frequency). The true uptake and utility of CF-CCT for reproductive planning is unknown (1,2). Despite uncertainty, CF carrier testing is offered commercially to ethnically Irish couples for prenatal planning. We reviewed CF-CCT data in our laboratory to evaluate the number of high-risk couples identified and assess the benefit of carrier testing in a disorder with high prevalence.

Material and Methods: CF carrier tests from 2015-2024 were analysed (n=3010). Carrier tests performed for parents of an affected child, foetal echogenic bowel, assisted reproduction, or where family history was unknown were excluded (n=654). Data extracted from CF-CCT reports (n=2356) included ascertainment (family history), relatedness of proband, and post-test reproductive risk.

Results: The largest ascertainment for CCT (23.4%;n=705) was for abnormal newborn screening (NBS) in unaffected children. 27.5% (n=827) of CCT was done for a family history, a quarter of these for close relatives affected with CF (relatedness=1); the most distant CCT was for 6th degree relatives. Couples risk was given for 1011, and testing increased CF reproductive risk for 2.2% couples (n=22/1011).

Conclusion: Broadly implemented CF-CCT reveals an increase in reproductive risk for ~2 high-risk couples per year of testing. While CF-CCT is an effective screening tool, its relatively low yield raises questions about its impact on broader reproductive counselling strategies in Ireland.

P40 Elucidation of the genetic landscape of retinal ciliopathies in the Target 5000 cohort

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Background: Retinal ciliopathies (RCs) represent a group of conditions involving retinal degeneration. They are attributable to pathogenic variants in >100 genes required for ciliogenesis and function. Perturbation in cilia development and/or function causes a spectrum of clinical manifestations including vision loss, hearing impairment, renal pathology, polydactyly, and obesity amongst others. RCs can be syndromic and non-syndromic, depending on the gene and variant involved. To the best of our knowledge, this is the first study to characterise the genetic architecture of RCs in Ireland.

Materials and methods: Following informed consent, blood was obtained, DNA isolated and next-generation sequencing undertaken. Candidate variants were interpreted according to ACMG guidelines, confirmed by Sanger sequencing and phased where possible. Novel variants of uncertain significance were investigated by AI-powered AlphaFold, RNA-analysis and midigene functional assays.

Results: In total, >200 candidate variants were detected across 34 RC-associated genes in 345 participants. Notably, 45 variants were novel. The most common syndromic condition was Usher syndrome followed by Bardet-Biedl syndrome, whilst variants in RPGR represented the largest number of non-syndromic cases. In total, RCs accounted for ~20% of solved cases in this cohort. Two novel variants were found to perturb mRNA-splicing.

Conclusions: It is of paramount importance that patients and their families with RCs obtain a molecular diagnosis to inform management, decision-making and potential treatment. This study sheds light on the profile of RCs in Ireland. 45 novel variants were identified highlighting unique features of this patient cohort in Ireland and aiding the diagnostic process for future patients.

P41 Rare and polygenic risk for neuropsychiatric and neurologic disorders in ALS: associations with family history and clinical features

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Background: Neuropsychiatric (NP) and neurologic conditions often cluster in ALS kindreds, yet most ALS patients lack a known genetic cause. Exploring shared genetic risk across ALS, NP and neurologic disorders may reveal new disease mechanisms.

Methods: We analysed WGS and SNP-array data from the Irish ALS Register (WGS: n=264; PRS: n=601) to identify rare variants and calculate polygenic risk scores (PRS). ClinVar-pathogenic/likely-pathogenic NP (n=570) and neurologic (n=52116) variants were annotated using bcftools. NP and neurologic family history was quantified using weighted scores based on affected first-to third-degree relatives. PRS were computed using PLINK for five NP traits ($p<0.01$) and correlated to family history scores. Beaumont Behavioural Inventory (BBI) was correlated to family history. The same methodology will be applied to AnswerALS data, including available behavioural/cognitive data such as CNS Lability Scale.

Results: In Irish WGS data, 29 patients had pathogenic neurologic variants in genes including SPG7, SPG11, MPO, GBA1, SH3TC2, MFN2, FIG4, POLR3B, AMPD2, POLG, PLA2G6, and PRRK; 55.2% had family histories of neurodegeneration. Clinical data will be reported for each case. No ClinVar-significant NP variants were identified. PRS for traits such as bipolar disorder, OCD, and MDD significantly positively correlated with NP family history ($p=0.0009$-0.005). NP family history scores also correlated with BBI ($p=0.025$).

Conclusions: Neurologic rare variants were enriched in Irish ALS cases. Elevated polygenic risk for NP traits was associated with NP family history. Increased NP familial burden may predispose to behavioural changes in ALS. Comprehensive family histories may enhance genetic insights into ALS.

P42 Rare but Relevant: Improved detection of M_{malton} in Alpha-1 Antitrypsin Deficiency

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Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder that causes lung, liver, and skin disease. This is caused by a mutation of the SERPINA1 gene, which codes for alpha-1 antitrypsin (AAT), an important protease inhibitor. The most common harmful mutation is Z (Glu342Lys, rs28929474) (carried by 1 in 25 Irish people (1)). Rarer genotypes such as the M_{malton} variant can be difficult to elucidate due to the expertise required to interpret these more esoteric banding patterns. International guidelines advocate screening all chronic obstructive pulmonary disease (COPD), poorly-controlled asthma, and cryptogenic liver disease patients, and first-degree relatives of known AATD patients.

Methods: >25,000 individuals have been tested for AATD following WHO, American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines, in a national targeted detection programme (TDP). AAT quantification is performed by turbidimetry, while phenotyping conducted via isoelectric focusing. Careful

interpretation of discordant AAT levels and banding patterns indicate the presence of potential clinically significant variants. Indicating the need for an additional allele-specific genotyping assay.

Results: The rare Mmalton variants were detected in a number of these individuals who had discordant AAT levels and banding patterns. Family screening remains ongoing.

Conclusions: This technology will allow for the more accurate and rapid detection of rarer variants which would have otherwise been attributed with the healthy MM genotype. The advantages of which include lung and liver surveillance, family screening, smoking cessation, and specific treatments.

P43 Resolving the unsolved – investigation of 300 inherited retinal degeneration patients in the Target 5000 cohort.

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Whole Exome Sequencing (WES). Unlike panel sequencing methods that are limited to pre-selected genes, WES can be repeatedly interrogated with expanded gene panels. In the current study, analysis was initially undertaken with 250 known IRD-associated genes. Patients that remained genetically unresolved were subsequently analysed for disease-causing variants in >200 additional genes.

Methodology: Following informed consent, DNA was isolated, WES undertaken and analysed. WES was performed at BGI-Europe. Reads were aligned to the human reference genome (hg38), nucleotide and CNV calling were performed with the Genome Analysis Toolkit and CoNIFER 0.2.0, respectively. Variants were annotated using a bespoke in-house pipeline, confirmed by Sanger sequencing, phased where possible and interpreted according to ACMG guidelines.

Results: The panel of 250 known IRD-associated genes identified potential disease-causing variants in >50% of patients. Following interrogation with the expanded panel, additional candidate disease-causing variants were most commonly identified in genes associated with ocular atrophy, ocular albinism and retinal ciliopathies, reflecting the enrichment of these genes in the new panel. Patients that remained unresolved following this study are being prioritised for whole genome sequencing (WGS).

Conclusion: Our results highlight the importance of re-examining patient WES to provide genetic diagnoses for unsolved patients. Furthermore, it allows investigation of candidate genes to reveal new genotype-phenotype correlations. This approach will enable inclusion of additional genes in future gene panels thereby resolving additional patients.