27th Meeting of the Irish Society of Human Genetics

Thursday 19th September 2024
Royal College of Physicians Ireland, Dublin

PROGRAMME

09:00 Registration, tea/coffee, Poster viewing, visit Sponsors

09.50 Welcome

10:00 Keynote address I: Prof Aiden Corvin, Trinity College Dublin

10:45-11:45 Oral presentations (Basic) Plenary I

11:45 Tea & coffee & poster viewing

12:10 Keynote address II: Gene Hunting to New Treatments – The Complex Genetics of Amyotrophic Lateral Sclerosis, Prof Orla Hardiman, Trinity College Dublin

12:55-13:25 Student Summership talks, Plenary II

13:25-14:40 Lunch, Poster viewing, visit Sponsors

14:25 AGM

14:40 Keynote address III: Genomic insights into mechanisms and consequences of reproductive ageing and menopause, Prof Anna Murray, University of Exeter

15:25-16:25 Oral presentations (Clinical) Plenary III

16:25 Tea/coffee, Poster viewing & visit the Sponsors

16.50 Keynote address IV: What can zebrafish teach us about human genetics? Prof David Lyons, University of Edinburgh

17.35 Honorary Membership Presentation to Prof Michael Gill

17:50 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 Characterisation of diverse global ancestries within participants of the UK Biobank

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) is a large dataset containing in-depth phenotype and genotype data of 500,000 UK-based participants. To control for cryptic population genetic confounders, studies leveraging the UKB are typically restricted to a subset of the participants with homogenous European ancestry. By analysing the 78,573 UKB participants with non-UK-like ancestries using population genetic approaches, there is an opportunity to better understand the global genetic diversity in the UKB and enable their inclusion in disease association studies.

Here we characterise these diverse ancestries by identifying primary continental-like ancestry clusters and for the first time fine-scale communities. To determine continental ancestries, an individuals' ancestry proportions were estimated using the ADMIXTURE algorithm. The machine learning algorithm XGBoost was trained using ADMIXTURE results to assign each individual to one of eight continental-like ancestry clusters. These continental clusters were further divided 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 102 communities appear to reflect the immigration history of Great Britain and its Commonwealth in the 20th century and are likely less represented in other large global biobanks. Our communities also facilitate novel findings of

community-specific genetic risk factors, such as one of the highest worldwide frequencies of idiopathic pulmonary fibrosis risk variant rs35705950 in individuals of Maltese-like ancestry. Thus, this work provides a framework for future studies of health-related genetic variation specific to otherwise understudied genetic communities.

OP02 Genomic Insights into an Irish Hunter-Gatherer Community

Mr. Corey Alwell[1], Dr. Marion Dowd[2], Dr. Linda Fibiger[3], Dr. Lara Cassidy[1]

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The first continuous human occupation of Ireland began around ten thousand years ago, when hunter-gatherer populations from Europe made their way to Irish shores. These Mesolithic hunter-gatherers occupied the island before being replaced by incoming Neolithic farmer populations almost four thousand years later. Despite being the sole human settlers on the island for 40% of its occupation, extremely little is known about these people. Only two genomes of individuals from this Irish Mesolithic have been sequenced, and both these samples are from near the end of this era. Here, we present whole genome sequences for five novel Irish Mesolithic individuals from Killuragh Cave, bringing the total Irish dataset from two to seven genomes and containing likely the oldest Irish genome ever sequenced. The individuals buried in Killuragh present identical-by-decent (IBD) segments and allele sharing inflated beyond background, suggesting these people are all from the same community and thus making this the first Irish Mesolithic community identified. In the European context, the Irish Mesolithic individuals are of Western Hunter-Gatherer ancestry, which was prevalent across Europe from fourteen thousand years ago. Defining European genomic clusters using the Leiden algorithm (an approach not yet applied to ancient DNA), we find the Irish genomes cluster most closely with other North-Western European samples. Finally, analyses of Runs-of-Homozygosity (RoH) show that the Irish genomes present some of the greatest degrees of RoH identified in any pre-Neolithic population, reflective of their extended period of island isolation.

OP03 Analysis of blood-based DNA Methylation signatures and disease progression in Inflammatory bowel diseases patients

Mr. Trevor Doherty[1,2], Dr. Edel McDermott[3,4], Prof. Hugh Mulcahy[3,4], Prof. Sarah Jane Delany[5], Dr. Therese Murphy[1]

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Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders with a dysregulated immune response partly influenced by environmental factors. DNA methylation (DNAm), a key epigenetic mechanism, is implicated in the etiology of complex diseases, including IBD. Epigenetic clocks, which use DNAm patterns to estimate biological aging, have been increasingly linked to various health and disease states. Previous studies have associated DNAm with IBD and Horvath's first-generation epigenetic clock, DNAmAge, with IBD subtypes.

In a discovery IBD cohort (n=149) with 8-year follow-up data, we explored the relationship between DNAm variation, second and third-generation epigenetic clocks, and IBD clinicopathological outcomes, including disease subtype, activity, and recurrence. One CpG site was significantly differentially methylated (Benjamini Hochberg adjusted p-value < 0.05) in patients with clinical recurrence of disease over the long term (i.e., after the first year of study) compared to non-recurrence (no treatment escalation after 8 years). Next, we assessed DNAm aging signatures and IBD outcomes using logistic regression. Significant associations were found between epigenetic clocks (GrimAge, GrimAge2, and DunedinPACE) and IBD subtypes (Crohn's disease/ulcerative colitis (CD/UC)) (p=6e-4, p=1.9e-3, and p=6e-4, respectively). CD patients exhibited epigenetic age acceleration (defined as the discrepancy between predicted age, as determined by DNA methylation patterns, and chronological age) compared to controls. These associations were replicated in two independent IBD cohorts (GSE87648 (n=377) and GSE112611 (n=238)).

Taken together, these findings suggest that blood-based DNAm signatures could serve as biomarkers for detecting, monitoring, and classifying IBD subtypes.

OP04 FOXP1 Dysregulation and its Association with Schizophrenia and Cognitive Function

Ms. Deema Ali[1], Prof. Derek Morris[2]

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Rare mutations in FOXP1 (Forkhead-box protein P1), a transcription factor crucial for cortical neural development, cause FOXP1 syndrome, characterized by developmental delays, intellectual disability, with or without autistic features. Common SNPs in the gene are associated with schizophrenia and cognitive function. This study explores FOXP1's contribution in these conditions using RNA-seq data from FOXP1 knockout animal models, including cortical neural stem cells from embryonic mice and cortical tissues from different postnatal stages (P0, P7, P47).

We performed pairwise comparisons and time-course expression analysis on the RNA-seq data from these stages. Linkage disequilibrium score regression was used to determine if differentially expressed genes (termed gene-sets) were enriched for heritability related to schizophrenia and cognitive function. Cell type enrichment and gene ontology analyses identified affected cell types, brain regions, and biological mechanisms impacted by FOXP1 knockout.

Our findings show that FOXP1 gene-sets across all stages are enriched for SNP-based heritability related to educational attainment (EA) and/or intelligence. Most FOXP1 gene-sets are enriched for schizophrenia heritability, with the highest enrichment at the P7 stage. Gene-sets from P7 and P47 exhibit significant enrichment in excitatory glutamatergic neurons in the frontal and posterior cortex. FOXP1 influences neurogenesis and synaptic signalling, with P7 and P47 showing a particular association with ion transport and G protein-coupled receptor signalling. Time-course analysis identified 1,128 significant genes across stages, enriched for schizophrenia and EA heritability and involved in similar biological processes. Overall, FOXP1 disruption affects genes linked to schizophrenia risk and cognitive function, revealing diverse biological pathways in their aetiology.

OP05 Non-invasive testing of hospitalised patients identifies novel actionable targets against SARS-CoV-2 - withdrawn

Ms. Laura Freeman[1], Dr. Joseph McLaughlin[2], Dr. Darren McDaid[2], Dr. Seodhna M. Lynch[2], Dr. Andrew English[2,3], Mr. Jonathon McLaughlin[2], Dr. Maurice O'Kane[4], Dr. Martin Kelly[4], Dr. Manav Bhavsar[4], Dr. Victoria McGilligan[2], Dr. Priyank Shukla[2], Dr. Shu-Dong Zhang[2], Dr. Elaine K. Murray[2], Dr. Taranjit Singh Rai[2], Prof. Anthony J. Bjourson[2], Dr. David S. Gibson[2], Dr. Rachelle E. Irwin[1], Prof. Colum Walsh[1,5]

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OP06 Exploring the limits of short-read Whole Genome Sequencing (WGS) by investigating samples from three population cohorts

Ruth McNulty[1,2], Dr Niamh Ryan[2]

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The human genome contains "dark" gene regions that cannot be adequately assembled or aligned using standard NGS short-read sequencing (SRS) technologies, preventing researchers from identifying variants within these regions that may be relevant to human disease. While it is estimated that between 10-15% of the genome is dark, or inaccessible to SRS, variability between samples has not been explored. Furthermore, as the human reference genome is known to be biased towards individuals with European ancestry, it is unknown how variable dark-regions may be across individuals from different population backgrounds. The Neuropsychiatric Genetics Research (NGR) group at TCD have generated whole genome SRS data for more than thirty ethnically-diverse pedigrees with a high load of psychiatric illness.

This project aimed to quantify the amount of dark-regions present in whole genome SRS data for 57 individuals sequenced by the NGR group, representing three different pedigree population cohorts:

1. European: 23 individuals from a Swedish mono-zygotic twin study of psychosis.
2. Costa Rican: 16 distantly related individuals from a Tourette syndrome study.
3. Pakistani: 18 individuals from two pedigrees with a range of psychiatric disorders

The stability of dark-regions was investigated by quantifying the pair-wise sharing of dark-regions between: i. related individuals; ii. individuals from within the same population cohort; and iii. across population cohorts.

This analysis found substantial variability in the overlap of dark-regions across all pair-wise comparisons, including between identical twins. This suggests that issues such as sequencing quality and batch effects may impact dark-regions more than genomic ancestry.

OP07 Comparing the Rare disease diagnostic journey in the Republic of Ireland to the rest of Europe, how do we compare?

Ms. Ceri Arnott[1], Ms. Vicky MrcGrath[2], Dr. Alana Ms. Cliona Carroll[4], Dr. James O'Byrne[4], Prof Sally Ann Lynch[1,5]

[1]University College Dublin, [2]Rare Disease Ireland, [3]NRDO, MMUH, [4]Metabolic Dept MMUH, [5]Children's Health Ireland, Crumlin, Dublin

1st Project. In 2022 (March-June), EURORDIS (a global non-profit alliance of rare disease patient organisations) commissioned a global patient survey. The survey was conducted through the Rare Barometer programme, which enables high-quality, secure data collection and analysis. This survey contained 50 questions to explore experiences of Patients Living with a Rare Disease (PLWRD) as they sought a diagnosis. Global data was analysed and published by EURORDIS in 2024. The Irish data (from 105 participants) was returned to Rare Diseases Ireland (RDI), the national alliance for rare disease patient organisations in Ireland, to enable country specific analysis. We interrogated the Irish patient data and compared to European patient responses via univariate descriptive analysis. The findings were collated and will be published through RDI's dedicated Rare Reality webpage (https://rdi.ie/rare-reality/) and distributed to key stakeholders across policy, HSE leadership and media. This is timely as a new National Rare Disease Strategy and implementation plan will be published in 2024, so our data will act as a benchmark to measure future progress against.

2nd Project. Through a previous Adelaide Health Foundation grant, a survey of adult metabolic patient attending the Mater Hospital (MMUH) was performed to gather data on patient access to genetic counselling services. The data suggested most patients were unaware that they had had genetic testing and had limited understanding of the genetics of their condition. The second project involved analysing the responses and preparing a manuscript of the findings of this research study for submission to a peer review journal.

OP08 Using CRISPR to create ciliopathy models in C. Elegans

Ms Glazier Ventura, Dr Karen Lange

University College Dublin

Primary cilia are antenna-like organelles that are found on almost all human cells. They play important roles in developmental signalling pathways (eg. Shh, Wnt) and sensing the environment. Cilia dysfunction causes rare genetic disorders, called ciliopathies, which affect most body tissues and organs. Primary cilia are highly conserved in *C. elegans* (a microscopic roundworm) and we can use worms to study ciliopathies. TMEM237/JBTS-14 is a ciliary protein that is localised to the base of the cilia in a region called the transition zone. Mutations in this gene cause a neurodevelopmental ciliopathy called Joubert Syndrome. Fluorescent tagging of endogenous proteins allows us to quantify protein levels at the ciliary transition zone and determine how patient mutations affect protein localisation. We used CRISPR genome editing in *C. elegans* to knock-in an N-terminal mScarlet tag at the *jbts-14* gene. Microscopy confirmed the correct localisation of the mScarlet::JBTS-14 protein at the transition zone. Sanger sequencing was performed to confirm the correct DNA sequence was inserted into the worm genome. A dye filling assay, which quantifies cilia integrity, found that the fluorescent mScarlet tag did not affect the function of JBTS-14. These new mScarlet::JBTS-14 worms will be used in future experiments to model ciliopathies.

OP09 A clinical evaluation of GLA variants of uncertain significance

Ms. Cliona Carroll, Dr. Loai Shakerdi, Dr. Robert O'Byrne, Ms. Alison Sheerin, Ms. Jessica Ivory, Mr. Kevin Jon Ilagan, Ms. Aya Ibrahim, Dr. James J O'Byrne

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Fabry disease is caused by pathogenic variants in the X-linked GLA gene that produces a deficiency of the Lysosomal enzyme α-Galactosidase A. Deficiency of α-Galactosidase A results in the inability of cells to catabolize glycosphingolipids, and these glycosphingolipids, progressively accumulate in the lysosomes within a number of organs, resulting in the multi-system disease.

Diagnosis of Fabry disease can be confirmed by demonstrating reduced enzyme activity, accumulation of GB3 substrate or by identification of lysosomal inclusion bodies in tissue biopsy specimens. However, a diagnosis cannot rest solely on these biochemical tests, because enzyme levels are often normal in females, and substrate levels can be normal in patients with a mild or attenuated forms of Fabry disease. For this reason, many patients have a diagnosis that has relied on genetic testing.

The National Centre for Inherited Metabolic disorders, Mater Hospital in Ireland, currently has over 100 individuals with a diagnosis of Fabry disease, and many of these diagnoses were made on the basis of a pathogenic variant being identified in the GLA gene.

The classification of the GLA variants D131Y, A143T, R118C have, in recent times, been downgraded to VOUS or "risk allele". In this study, we scrutinised the phenotype of patients attending NCIMD with one of these variants, to examine how their phenotype and family history compares with that of patients with classic Fabry disease. We discuss clinical management of these patients, in this evolving

genomic landscape, including the complexity of Genetic counselling in the context of this new diagnostic uncertainty.

OP10 Catalogue of inherited autosomal recessive disorders found amongst the Roma population of Europe

Dr. Shauna Quinn[1], Dr. Ioana Streata[2], Dr. Aoibhinn Walsh[3], Dr. Kathleen Gorman[4], Dr. Ellen Crushell[5], Prof. Andrew Green[6], Dr. Janna Kenny[6], Dr. Anca Lelia Riza[7], Prof. Sally Ann Lynch[8]

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Background: The Roma population are an endogamous, genetically isolated, minority population who migrated from North-Western India to Europe from the 10th Century. Approximately 10-12 million Romani people reside in segregated settlements in Europe, North America and China. In addition to endogamy, they also practice consanguinity. This results in higher frequencies of rare autosomal recessive disorders, some of which are unique to the Roma population. Some disorders result from founder variants, others within a wider clan and some are private variants.

Objectives: Clinicians with experience in managing and diagnosing rare diseases have developed a comprehensive catalogue of autosomal recessive inherited disorders found in the Roma population. Our aim is that this catalogue will aid rapid diagnosis and highlight the differentials to consider.

Methods: We performed a detailed literature search to identify relevant publications and variants described in patients whose ethnicity was described as Roma. In addition, we interrogated data from clinicians in Europe to collect additional unpublished variants, yet to be reported in the medical literature. We mapped these disorders to their European country of origin.

Results: We identified 83 distinct autosomal recessive disorders, manifesting as 85 distinct phenotypes and 104 pathogenic disease variants, including published and unpublished findings in the Roma population.

Conclusion: We assembled a catalogue of inherited autosomal recessive disorders, one pseudo-autosomal disorder and 104 pathogenic variants found in the Roma population. We hope this will assist the medical community to make prompt diagnoses and consider targeted genetic approaches to facilitate timely and cost-effective investigations in this population.

OP11 Direct to Consumer Genetic testing; the experience of two Clinical Genetics services in the Republic of Ireland

Ms. Emma O'Donoghue[1], Ms. Cliona Carroll[2,1], Ms. Rebecca Redmond[1], Ms. Claire Giffney[1], Dr. James J O'Byrne[2], Dr. Robert O'Byrne[2], Dr. Laoi Shakerdi[2], Prof. Sally Ann Lynch[1], Prof. Andrew Green[1]

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The rising accessibility of Direct-to-consumer (DTC) genetic and genomic tests has meant that many clinical services are increasingly receiving referrals for interpretation of DTC-identified genetic risks. A number of reports have indicated significant false positive rates from DTCGTs, which raises concerns about their clinical utility.

The Department of Clinical Genetics in CHI at Crumlin and The National Centre for Inherited Metabolic Diseases in the Mater Hospital are two publicly-funded services that have observed an increase in DTC-related referrals in recent years. We have completed a pre-screen to identify suitable cases for review, and here we present the outcome of the first ten cases, five from each centre.

Each service had different procedures for triaging these referrals. Two of 10 referrals were not accepted to service. Of those that were accepted, 4 were offered a confirmatory genetic test and 5 were offered supportive biochemical testing. At the time of writing this abstract, 2 cases remain on a waiting list. Of the 6 referrals accepted to service, 5 had their result negated, while 1 had their result confirmed.

DCT-related referrals raise ethical concerns about the impact on the equity and distributive justice of the resources of publicly-funded clinical genetics services. Further ongoing review of such referrals will help to quantify the impact of DTCGT on our Clinical Genetics services and contribute to the knowledge base needed to inform policies for managing DTC-related referrals.

OP12 DRAGENv4.0 increases the accuracy and utility of the Genomics England Rare Disease Bioinformatics Pipeline applied in the NHS Genomic Medicine Service

Mr. Gabriel Aldam[1], Dr. Mark Doherty[1], Dr. Liam Abrahams[1], Mr. Kevin Savage[1], Dr. Susan Walker[1], Dr. Javier Lopez[1], Dr. Eva Serra[1], Dr. Catherine Whibley[1], Dr. Rachael Mein[2], Dr. Augusto Rendon[1], Dr. Ellen Thomas[1], Dr. Dalia Kasperaviciute[1], Dr. Jamie Ellingford[1]

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Genomics England partners with National Health Service (NHS) England to provide clinical whole-genome testing for individuals with rare disease and cancer, through the NHS Genomic Medicine Service (GMS). DRAGEN software is central to the Genomics England Rare Disease Bioinformatics Pipeline applied in the NHS GMS (RD-Pipeline). DRAGEN is used for short-read sequencing alignment and variant detection, including single-nucleotide variants (SNVs), copy-number variants (CNVs) and short-tandem repeats (STRs).

Since its inception, the RD-Pipeline has utilised DRAGENv3.2. DRAGENv4.0 has enhanced capabilities, including improved de novo variant detection, improved variant detection for some known disease genes, CNV inheritance determination, targeted-callers (e.g. GBA, SMN1, SMN2) and STR improvements (an additional 39 loci and complex loci resolution).

Upgrading the RD-Pipeline from DRAGENv3.2 to DRAGENv4.0 required extensive validation, including calibration of variant detection performance metrics for standard reference samples, and processing of >9000 genomes for assessment against standard-of-care methodologies and regeneration of internal allele frequencies.

Across all assessed metrics, DRAGENv4.0 improves or remains consistent with DRAGENv3.2. For example, there is improved detection of high-confidence SNVs (99.63%,95%CI:99.55-99.7%, 0.4% improvement), INDELs (99.71%,95%CI:99.31-99.95%, 0.48% improvement) and pathogenic STRs (sensitivity:100%,95%CI:92.9-100%, 4.2% improvement; specificity:99.7%,95%CI:99.2-100%, 0.1% improvement). Coverage is improved, with several known disease genes increasing from 0% to 100% coding-region coverage at >20X coverage. Whilst the sensitivity for known pathogenic CNVs was unchanged (97.95%, 95%CI: 96.09–99.29%), there is increased utility in determining inherited/de novo CNVs.

In summary, the integration of DRAGENv4.0 within the RD-pipeline enables increased precision and increased diagnostic yield for individuals receiving genomic testing through the GMS.

OP13 Genotype-phenotype correlations in IFT140-related retinal dystrophy in a cohort of Irish patients.

Ms. Anna Rose Ridgeway[1], Dr. Laura Finnegan[1], Dr. Matthew Carrigan[1], Dr. Laura Whelan[1], Dr. Adrian Dockery[2], Ms. Giuliana Silvestri[3], Prof. David Keegan[2], Ms. Emma Duignan[4,5], Dr. Paul Kenna[5,4,1], Prof. Jane Farrar[1]

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Introduction: The *IFT140* gene encodes the Intraflagellar Transport A protein (IFT-A). IFT-A is essential for retrograde intraflagellar transport and import of proteins into primary cilia. Pathogenic variants in *IFT140* are associated with a spectrum of ciliopathies including non-syndromic Retinitis Pigmentosa, autosomal dominant Polycystic Kidney disease and Short-Rib Polydactyly syndromes. The purpose of this study was to investigate the NM_014714.4:c.903-5T>G variant by midigene functional analysis and investigate genotype-phenotype correlations.

Methods: Following consent, blood was collected and DNA isolated. Patients were sequenced by target capture NGS and whole exome sequencing. Candidate variants in *IFT140* were interpreted according to ACMG guidelines and confirmed by Sanger sequencing. The variant of uncertain significance, NM_014714.4:c.903-5T>G, was investigated as a potential splice-altering variant. Midigene plasmids were constructed and transfected into HEK293T cells. 48 hours post-transfection, mRNA was harvested, and wildtype and mutant transcripts analysed by RT-PCR, gel electrophoresis and Sanger sequencing.

Results: Six candidate variants were identified in seven different pedigrees of which NM_014714.4:c.903-5T>G and c.(810+1_811-1)_(1652+1_1653-1)del are novel-IRD variants. Interestingly, the NM_014714.3:c.903-5T>G variant causes exon eight skipping and was present in all seven pedigrees suggesting it may be enriched in the Irish population.

Conclusions: Recent evidence has highlighted that aberrant splicing plays an important role in the pathogenesis of several retinal ciliopathies. However,

it is essential to conduct functional studies to verify splicing defects thereby upgrading the classification of novel variants. In this study, the mutational and phenotypic spectrum of *IFT140*-related retinal dystrophy has been interrogated.

POSTER PRESENTATIONS

BASIC

P01 Cardiovascular Pharmacogenomics for Primary Care

Ms. Walaa Hefny[1], Dr. Suzanne Drury[2]

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Background: Pharmacogenomics (PGx) has emerged as a promising approach to improve the effectiveness and safety of Cardiovascular (CV) drug therapies. We have investigated CV PGx in primary healthcare to gain insights into its potential impact and successful integration.

Methods: We conducted a literature review to identify the most relevant and up-to-date information on PGx variants related to CV drugs, their clinical implications and the evidence supporting their implementation in primary care settings. By critically analysing the available data, this research seeks to elucidate the potential benefits and challenges of incorporating PGx into routine care. We designed a PGx panel test consulting CPIC guidelines and PharmGKB and also proposed a report for returning the results incorporating insights from two case reports.

Results: The literature review of 19 PGx implementation programs in primary care identified Clopidogrel, Warfarin, and Statins as the most commonly used CV drugs. It emphasised the importance of translating DNA sequences to genotypes using PCR, enabling therapeutic recommendations for drug/gene pairs with CPIC level 1A evidence and utilising Electronic Healthcare Records (EHR) for easier interpretation.

The clinical landscape has shifted from reactive single-gene assays to pre-emptive panel testing. Based on this, we designed a PGx panel test with six genes and twelve variants, proposing a workflow for clinical PGx testing.

We also developed a report for returning PGx results aiding Warfarin dosage calculation, drug substitution and dosage adjustments.

Conclusion: This research highlighted the potential of PGx in improving care quality, reducing adverse drug reactions, and lowering healthcare costs.

P02 Joint analysis of NGS data from over 2,000 epilepsy trios, to determine diagnostic yield of de-novo copy-number variants and discovery of novel disease loci.

Ms. Hamidah Ghani[1,2,3], Dr. German Demidov[4], Dr. Marie T Greally[1,3,5], Ms. Maire White[1], Prof. Peter Widdess-Walsh[6], Dr. Eavan McGovern[1,6], Dr. Michael Doyle[1,6], Dr. Patrick Moloney[7], Dr. Daniel Costello[8], Prof. Brian Sweeney[8], Dr. Mary O' Regan[9], Prof. David Webb[9], Prof. Colin Doherty[3,10,11], Prof. Norman Delanty[1,3,6], Prof. Stephan Ossowski[4], Dr. Susan Byrne[3,9], Dr. Katherine Benson[1,3], Prof. Gianpiero L. Cavalleri[1,2,3]

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The epilepsies with co-morbid intellectual disability/developmental delay (ID/DD) and developmental and epileptic encephalopathies (DEE) are characterized by refractory seizures and developmental issues. A significant proportion of people with these types of epilepsy do not receive a molecular diagnosis, suggesting yet-to-be-identified genetic causes. Our objectives were to determine the diagnostic yield of *de novo*, autosomal copy-number variants (CNVs) for epilepsy with ID/DD and DEE and to identify novel causal loci.

We assembled over 2,000 epilepsy trios with exome or whole genome sequencing data (WES/WGS), that met specific HPO terms. We used ClinCNV to call autosomal, germline CNVs. We detected 58 *de novo* CNVs in 57/2,009 affected individuals. 47/58 *de novo* CNVs satisfied ACMG/ClinGen criteria for likely pathogenic (LP) or pathogenic (P) status. Most *de novo* CNVs detected were rare, recurrent established pathogenic CNVs. The size of *de novo* CNVs ranged from 100kb to 15.7Mb. 11 cases (0.5% of the cohort) carried large *de novo* CNVs (>200kb) of uncertain clinical significance (VUS), including a 0.9Mb duplication at 1q21, and a 1Mb deletion at 2q37.2 encompassing *AGAP1, GBX2,* and *IQCA1*. We demonstrate a diagnostic yield for *de novo* CNVs in epilepsy with ID/DD and DEE of 2.8% and point to potential novel epilepsy loci. This work highlights the

importance of comprehensive CNVs screening in specific forms of epilepsy and the practicalities of calling CNVs from NGS data.

P03 The impact of donor and recipient polygenic burden on kidney transplant outcome

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Much of the variation in kidney transplant outcomes is still unexplained. We hypothesise that donor and recipient polygenic burden for traits related to kidney function, as well as a combination of donor and recipient polygenic burdens, may influence graft function post-transplant.

We assembled a cohort of 6,060 living and deceased kidney donor-recipient pairs. We calculated polygenic risk scores (PRS) for kidney function related traits including hypertension, estimated glomerular filtration rate (eGFR), and intracranial aneurysm (IA) in both kidney donors and recipients. Donor and recipient PRS were discretized into high (top 10%), intermediate (middle 80%), and low (bottom 10%) burden. We investigated the association between donor PRS, recipient PRS, and combined donor and recipient PRS, and graft survival as well as recipient eGFR at 1 and 5 years post-transplant.

A standard deviation increase in donor PRS for hypertension, IA, and low eGFR was associated with reductions in recipient eGFR at 1 year of 0.80, 0.75, and 1.29 mL/min/1.73m^2 (p=0.001, 0.002, 0.02 respectively). For a recipient with high PRS burden for low eGFR, their eGFR at 1 year post-transplant is 51 mL/min/1.73m2 with a high burden donor and 57 mL/min/1.73m^2 with a low burden donor.

Much of the risk of having a high PRS burden recipient can be mitigated by having a low or intermediate PRS burden donor. These findings could play an important role in improving living donor transplant allocation decisions in the future.

P04 How sleep polygenic components interact with family income affecting sleep duration among children: evidence from The 2004 Pelotas Birth Cohort (Brazil)

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In a recent study, we identified that polygenic components associated with sleep episodes, observed in a European sample, partly explain for accelerometer-measured sleep duration among Brazilian adolescents. Poverty-related factors, including inadequate living conditions and limited healthcare access, impact sleep and overall health. The specific interaction between poverty and polygenic components affecting sleep duration in Brazilian adolescents remains unclear.

We investigated how family income interacts with polygenic scores for sleep episodes (sleep-PGS) to influence sleep duration among Brazilian children. Data were drawn from the 2004 Pelotas Birth Cohort, with sleep duration assessed at 11-year follow-up using ActiGraph accelerometers, and family income (R$, Brazilian money) reported at 24 months (n=2,976).

Linear regression models, adjusted for sex and the first 10 principal components of genetic ancestry, were used to test the interaction between sleep-PGS and family income, and to assess sleep-PGS effects on sleep duration across family income tertile groups.

We found positive association between sleep-PGS and sleep duration (Beta =2.30, SE=0.92, p=0.011). The interaction between sleep-PGS and income was statistically significant (Beta =-0.0012; SE=0.0010, p=0.066). Individuals from lower-income households showed higher effect of sleep-PGS on sleep duration (Beta for 1st tertile=4.18, SE=1.71, p=0.015, N=1041), while no significant effect was observed among those from middle or high-income households (Beta for 2nd tertile=1.10, SE=1.86, p=0.552, N=932; Beta for 3rd tertile=1.09, SE=1.65, p=0.509, N=1003).

These findings underscore the interaction between sleep-PGS and family income affecting sleep duration, emphasizing the stronger influence of genetic predisposition on sleep duration among Brazilian children from lower-income backgrounds.

P05 Multi-omic Sequencing Reveals Distinctive Gene Expression and DNA Methylation Alterations as Potential Predictors of Primary Sclerosing Cholangitis Development in Treatment-naïve Paediatric Ulcerative Colitis

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Background: Primary sclerosing cholangitis (PSC) is a progressive cholestatic disease, with up to 80% of patients also having ulcerative colitis (PSC-UC), complicating diagnosis and increasing cancer risk. Although inflammation and microbial dysbiosis are implicated in PSC-UC pathogenesis, the precise molecular regulators remain unclear.

Methods: We employed methyl-capture sequencing and mRNA sequencing on colonic mucosal biopsies from the DOCHAS study (GEN-193/11) to identify transcriptomic and epigenetic differences among treatment-naïve paediatric UC (n=10), PSC-UC (n=10), and healthy controls (n=10). Additionally, the epiTOC2 molecular clock was used to explore the epigenetic age of the patients.

Results: In PSC-UC relative to UC, 9 genes were upregulated (ADMTS14, PNCK, NLRP3, SLC6A19, DLL1, FCGR2C, KLHL17, APOB, EHBP1L1) and 5 were downregulated (SLC37A2, SLC14A2, RPL27, RPS25, SLC38A4). These genes are regulated by transcriptional regulators (pro-caspases, IL7RA) and transcription factors (AR, p53, JUND, CEBPA). Differential methylation analysis revealed 22 differentially methylated regions (DMRs) between PSC-UC and UC, with 5 hypermethylated and 8 hypomethylated DMRs predominantly localized in gene promoter regions. Notably, DMRs were enriched for the transcription factor ASCL1, suggesting altered methylation impacts its binding site in PSC-UC.

Conclusion: This study provides novel insights into the transcriptional and epigenetic differences between treatment-naïve paediatric PSC-UC and UC, highlighting the role of transcription factors and DNA methylation in disease phenotype. Further investigation in larger cohorts is warranted to assess these molecular differences as potential diagnostic or therapeutic targets.

P06 Diagnostic Yield of Familial Pulmonary Fibrosis in an Irish Cohort; an Update

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Idiopathic pulmonary fibrosis (IPF) is a fatal, progressive, irreversible lung disease. When IPF occurs across first-degree relatives, it is termed familial pulmonary fibrosis. We set out to calculate diagnostic yield of genomic testing in pulmonary fibrosis, stratified by familial and idiopathic cases with the ultimate goal of cataloguing the genetic landscape of pulmonary fibrosis disease-causing variation in Ireland. To date, we recruited 67 patients (27 IPF, 40 FPF) via respiratory clinics at Beaumont Hospital, Dublin. Whole exome sequencing data was generated from blood-derived DNA and was processed using a GATK-V4.2 pipeline for the SNV analysis while CNVs were identified using ClinCNV, the output was converted to VCF files followed by annotation using VEPP. Pathogenicity assessment was conducted following the American College of Medical Genetics and Genomics guidelines. We identified a known pathogenic variant *RTEL1* [RTEL1: NM_001283009:c.C2920T] in three individuals from one FPF family and a pathogenic variant in *ZCCHC8* gene [ZCCHC8: NM_017612.5:c.557C>T] in another FPF case. We also identified two distinct pathogenic variants in *PARN*, [PARN: NM_002582.4:c.388+5G>T and PARN:NM_002582.4:c.991_1005+18del respectively]. No disease-causing variants were identified in IPF dataset. Variants of unknown significance were identified in *RTEL1*, *SFTPA1*, *NAF1* and *ZCCHC8,* in both the FPF and IPF datasets. Analysis of CNVs identified one event in *CSF2RA* from a patient with CTD-ILD [CSF2RA: NM_172245.4:g.1282703_1309589dup], which classified as VUS. These results overall indicate a diagnostic yield in the Irish population 12.12% for FPF of and 0% IPF. Both diagnostic rates are in line with observations in the literature from other regions.

P07 Optimising imputation and IBD segment retrieval in ancient genomes

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Ancient DNA has revolutionised the study of genetic variation and population movements over time. However, significant gaps in ancient genetic data, alongside geographic and temporal variations, hinder fine-scale characterisation of genomic structure and relatedness between individuals and/or archaeological sites. In this study, we implemented the imputation pipeline proposed by Hui et al. (2020), involving a two-step approach: (1) Conducting genotype imputation on individual ancient samples using the GLIMPSE software with the 1000 Genomes Project reference panel. (2) Constructing a multi-individual dataset of confident genotype calls from GLIMPSE for input into Beagle5, enabling a second round of imputation and phasing to improve genotype accuracy and minimise missing data. To benchmark our imputation pipeline, we downsampled high-coverage ancient genomes, including shotgun sequences and 1240k target enrichment data. We investigated each step of the pipeline testing different filter thresholds, including genotype posterior probability after the imputation steps. Besides the missingness, as heterozygote sites pose challenges for imputation, we prioritise heterozygote sensitivity as our primary metric for assessing imputation quality. Our findings highlight that a second round of imputation enhances the quality of imputed genotypes for both shotgun sequences and SNP capture samples. Moreover, we evaluate the performance of the second imputation with the identification of Identity-By-Descent (IBD) shared fragments between individuals using refinedIBD software, including long fragments, by examining known parent-offspring pairs. In conclusion, this study sheds light on improving ancient DNA analysis methodologies offering insights into population genetics and evolutionary dynamics.

P08 Insights into the variant haplotype landscape of polycystic kidney disease in Ireland

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Background: Autosomal Dominant Polycystic Kidney Diseases (ADPKD) is primarily caused by pathogenic mutations in PKD1 and PKD2 genes which have a diagnostic yield of 71-83%. Studies have reported unrelated individuals carrying the same pathogenic variant often shared a haplotype across the variant locus, inferring inheritance from a recent common ancestor. Haplotype-based prediction can therefore be leveraged to confirm suspected cases of ADPKD. In our study, we set out to identify haplotypes across disease-causing variants shared within a cohort of PKD patients recruited from four Irish renal clinics.

Methods: Using ACMG guidelines, pathogenic variants were identified in whole-exome sequencing (WES; n=280) data. We then used DRIVE on phased genotype data (n=484) to identify clusters of shared haplotypes over PKD1 and PKD2 variant loci. We developed a stratification algorithm to identify unsequenced individuals within the clusters who likely carry a known pathogenic variant based on haplotype match across the relevant gene.

Results: We identified 17 putative carriers of diagnostic variants in PKD1 and 1 carrier in PKD2. The status of two unsequenced carriers of a PKD1 variant and one unsequenced PKD2 carrier were confirmed using WES. The carrier status of the other samples will be confirmed either using WES or Sanger sequencing.

Conclusions: We developed a stratification algorithm to identify putative carriers of a diagnostic variant based on haplotype match across the relevant gene. This method could accelerate clinical genetic diagnosis and therefore reduce time-to-diagnosis and its associated costs.

P09 Exploring the Genetic Underpinnings of Cognition in ALS through Multi-Trait GWAS Analysis

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Background: Approximately 50% of individuals diagnosed with amyotrophic lateral sclerosis (ALS) experience cognitive impairment. Better genetic understanding of cognitive decline in ALS can improve prediction and future treatment options. Here we aim to explore the shared genetic architecture between ALS and cognitive traits and elucidate potential underlying biological mechanisms.

Methods: We conducted multi-trait analysis of GWAS (MTAG) using the latest European ancestry GWAS data for ALS (n=138,086) and cognitive traits, including cognitive performance (CP) (n=257,828),

executive function (TMTB; n = 78,547, Tower; n=11,263 - from UK Biobank), fluid intelligence (VNR; n=171,304), and visual-declarative memory (Memory; n=331,679). Shared loci between ALS and cognitive traits were validated using the conjunctional false discovery rate (conjFDR) method. Finally, we assessed prediction of extreme ALS Cognitive Behavioural Screen cognitive scores (CBS-Cog<11; consistent with FTD) using Polygenic Risk Scores (PRS) built from GWAS summary statistics for ALS, and ALS boosted by cognitive GWAS (ALS-cog) in independent data from AnswerALS.

Results: ALS was significantly genetically correlated with cognitive traits: CP (r=-0.19, p=4.85E-06), VNR (r=-0.2, p=2.74E-06). MTAG analysis of ALS with CP identified new hits in NEGR1, *CLCN3*, MEF2C, *EXOC4*, TSNARE1, and *EFL1/SAXO2* genes. conjFDR supported results for MEF2C, *EXOC4* and EFL1/SAXO2. Biological annotation implicated gene-sets related to Mecp2-mediated gene activation. ALS and ALS-cog - PRS showed significant FTD risk prediction (Nagelkerke-R2) of 0.033 (p=0.029) and 0.053 (p=0.009) in ALS patients.

Conclusions: Our results reveal global genetic overlap between ALS and cognitive traits and 7 novel shared risk genes. We highlight the potential for improving cognitive risk stratification in ALS patients using polygenic risk scores.

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P10 The Shared and Differential Genetic Risk Factors of Neurodegeneration

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Background: Neurodegenerative diseases comprise a large number of 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.

Methods: This research aims to identify the shared genetic risk factors that contribute to nine neurodegenerative traits, namely Alzheimer's Disease, Amyotrophic Lateral Sclerosis, Creutzfeldt-Jakob Disease, Frontotemporal Dementia, Lewy-body Dementia, Multiple Sclerosis, Neuromyelitis Optica, Parkinson's Disease, and Vascular Dementia. We analysed summary statistics from their largest genome-wide association studies (GWAS) using LD-score regression (LDSC) and genomic structural equation modelling (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. Gene ontology analysis was run on positionally mapped genes from significant loci using FUMA.

Results: We identified genetic correlations and a shared latent genetic factor between several neurodegenerative traits. MTAG analyses revealed 152 novel risk loci significantly associated with our nine neurodegenerative traits. ConjFDR identified 56 risk loci shared between two or more neurodegenerative traits. These loci were enriched for differential expression in the basal ganglia and several gene ontologies relevant to neurodegeneration (e.g. neurotransmitter secretion and neuron projection).

Conclusion: Multi-trait analysis of neurodegenerative traits reveals shared genetic risk loci and improves our biological understanding of core neurodegenerative mechanisms.

P11 Investigating the correlation of autism polygenic score with sleep traits of adults in the UK Biobank

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Autism is a lifelong neurodevelopmental condition characterised by impaired social interaction, restricted interests, and stereotypical behaviours. Common genetic variation linked to autism has been found to overlap with genetic variation contributing to sleep traits significantly. Most of the autistic people (90%) experience sleep problems. My project will investigate the genetic association between autism and sleep-related traits by polygenic risk score (PRS) analysis. PRS estimates an individual's genetic risk for a disease or trait by summing up the effects of many common variants linked to the condition.

The correlation of an autism polygenic score with sleep traits (duration, chronotype, insomnia, nap during the day, snoring, daytime sleeping) of adults in the UK Biobank (UKB) is investigated. UK Biobank is a population-based database of ~502,160 participants (37-73 years/ mean age- 55 years). The discovery dataset is a summary statistics file from a genome-wide association study of autism, while the target data is individual-level genotype and phenotype data from UKB. Our analysis includes 290,956 UKB research participants by removing those not being of white British ancestry, containing chromosomal aneuploidies, having a high SNP missingness, being

relatedness and performing shift work. Single nucleotide polymorphisms (SNPs) are excluded on imputation information score <0.7, proportion of missing genotypes >0.02, minor allele frequency < 0.005 and Hardy-Weinberg equilibrium p-value < $1x10^{-6}$. Generation of PRS is performed by the MegaPRS tool. These research findings will be beneficial in understanding sleep problems in autistic people for psychiatrists, clinicians and researchers, and they will positively impact the individualised treatment for these problems.

P12 Genetic Risk for Neurodevelopmental and Neuropsychiatric Conditions: Impact on Sleep and Circadian Rhythms in the Adolescent Brain Cognitive Development Study

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Genome-wide association studies (GWAS) have linked numerous common genetic variants to neurodevelopmental and neuropsychiatric conditions (NDPCs), as well as sleep-related phenotypes. These findings indicate a polygenic nature for these traits, with significant genetic correlations reported between NDPCs and sleep phenotypes. For example, a morning chronotype negatively correlates with schizophrenia and autism, while insomnia shows positive genetic correlations with ADHD, bipolar disorder, and schizophrenia.

The aim of our study is to investigate how genetic risk for NDPCs contributes to sleep and circadian rhythm disruptions in the Adolescent Brain Cognitive Development (ABCD) study, a biobank of over 10,000 children in the United States.

Our analysis was restricted to 4,289 unrelated European participants. Single nucleotide polymorphisms (SNPs) were filtered based on minor allele frequency >0.01, Hardy Weinberg equilibrium p-value >1x10-6 and imputation r2 >0.3, resulting in 10,475,741 SNPs. Using SBayesRC and summary statistics from the largest GWAS of autism, ADHD, schizophrenia, bipolar disorder and major depressive disorder, we created PGSs for each individual. We then test the association of these PGSs with scores on the Sleep Disturbance Scale for Children and the Munich Chronotype Questionnaire.

Our findings reveal that NDPC PGSs associate with sleep disturbances and chronotype. For example, an ADHD PGS was found to predict sleep disturbances in children (R2=0.002; P=0.003).

These results will provide insights into the shared genetic variation between NDPCs, sleep and circadian disruptions. Future analyses will extend to non-European ancestries and interrogate genome-wide genetic correlations using the methods, GWAS-by-subtraction and factor analysis.

P13 Development and Validation of a NGS Germline Variant Calling Workflow

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A variant calling workflow describes the directed sequence of data transformation and filtration steps required to produce a set of variant calls from an individual's sequence data. In a diagnostic setting, these variant calls are investigated for their contribution to the individual's clinical phenotype. Validation is therefore an essential prerequisite to establish the reliability and accuracy of the variant calls produced by the workflow. Here we describe development and validation of a germline variant calling workflow, using sequence data generated from external reference and internal clinical material.

Workflow development followed best-practice guidelines published by the Broad Institute (MIT, Harvard). The workflow was implemented as a Python package that controlled flow of data between BWA, GATK, Picard, and other bioinformatics applications.

The validation process comprises two major components, analytical validity and analytical performance. Analytical validity is an assessment of the overall ability of the workflow to produce an accurate callset, made through direct comparison with an independently verified reference callset, producing measures of assay *sensitivity* and *precision*. Assessment was performed following best-practice guidelines published by the Global Alliance for Genomic Health (GA4GH), on callsets produced from Genome in a Bottle standardised genomic reference material (RM8398/NA12878). Analytical performance is an assessment of the workflow's *accuracy*, in this context being the ability to detect specific variants of clinical significance relevant to the assay's intended use. Assessment was made on callsets produced from a cohort of previously sequenced clinical samples, with at least one known variant of clinical significance, verified using Sanger sequencing.

P14 Investigating the impact of dark regions of the genome on genomic research

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Background: Genome-wide association studies (GWAS) have identified thousands of regions associated with diseases/traits, but have struggled to

pinpoint biologically relevant variants and genes for the majority of these loci. Similarly, while rare deleterious variants have been identified from short-read sequencing (SRS) data, candidate risk-variants remain unidentified for many cohorts. Regions of the genome that are inaccessible, or “dark”, to SRS may contribute to this. While dark regions are known to affect over 2,500 genes, their impact on genomic research remains largely unexplored. To address this, we investigated the presence of dark regions in data from three genomics study designs: 1. *Fine-mapping GWAS data*; 2. *WES data from rare variant association studies (RVAS);* and 3. *WGS data from a pedigree sequencing project.*

Results:
1. GWAS loci for eight diseases/traits were found to contain 90bp-1.3Mb of dark sequence. Moreover, GWAS genes overlapping dark regions were enriched for biologically-relevant GO terms.
2. Candidate genes from RVASs for Schizophrenia and Autism Spectrum Disorder were identified that overlap dark regions, including genes with supporting-evidence from other study designs, such as *SHANK3* and *C4B*.
3. Dark regions in WGS data for individuals from ancestrally diverse pedigrees were variable across samples and found to impact candidate psychiatric genes located on haplotypes co-segregating with illness.

Conclusion: This study highlights the negative consequences of dark regions on gene discovery across a range of disease and study types. Dark regions may therefore be preventing researchers from identifying genetic variants relevant to human disease and contributing to missing heritability.

P15 The Complex Genetic Interplay between Autism and Sleep - The Role of Rare Genetic Variation

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Background: Sleep disturbances are a highly prevalent and a debilitating symptom of neurodevelopmental conditions such as autism. Research suggests genetic variation contributes to the link between these two phenotypes. Rare genetic variants include single nucleotide variants in addition to large structural variants such as copy number variants and tandem repeats. Many of these variant types have been associated with autism and to a lesser extent, with sleep-related phenotypes.

Objective: This rapid review aims to investigate the contribution of all types of rare genetic variation to autism and sleep-related phenotypes.

Method: A systematic search was conducted in PubMed, Web of Science and the Cochrane Library for studies published since 1990. Keywords included “Autism Spectrum Disorder”, “Sleep", "Circadian”, “Gene”, “Whole Genome Sequencing” and “Whole Exome Sequencing”. The resulting 2,027 studies underwent title and abstract screening using Covidence software and specified inclusion criteria including restriction to studies of human populations, participants with a confirmed autism diagnosis, studies performing genetic investigations and those investigating sleep-related phenotypes. Full text screening of 213 publications further reduced the number of publications to only those that investigated rare genetic variation. Data extraction and synthesis will capture information regarding specific genes and genetic variants identified across studies. Preferred Reporting Items for Systematic Review and Meta Analysis (PRISMA) guidelines were followed.

Conclusion: This rapid review will provide a detailed summary and synthesis of the existing literature and contribute to the understanding of the genetic link between autism and sleep-related phenotypes.

P16 Epigenetic Effects of MTHFR 677 genotype and riboflavin supplementation in hypertension using isogenic induced pluripotent stem cells

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Genetic variants contribute to blood pressure variability. MTHFR is essential for generating S-adenosyl methionine (SAM), the universal donor for methylation reactions. A single nucleotide polymorphism, (*MTHFR* C677T), in the gene encoding MTHFR results in reduced enzyme activity, and is associated blood pressure variation. Homozygosity for this polymorphism is associated with higher risk of hypertension. Supplementation with riboflavin, the MTHFR co-factor, results in lower blood pressure in individuals with the TT genotype. We generated induced pluripotent stem cells (iPSCs) from individuals heterozygous for *MTHFR* to create isogenic lines (CC/TT) using gene editing, and examine phenotypic and epigenetic effects of riboflavin on vascular smooth muscle cell (VSMC) differentiation. Fibroblasts from *MTHFR* 677CT donors have been reprogrammed into iPSCs using a non-integrating Sendai virus. Pluripotency and optimisation of VSMC differentiation were verified using qRT-PCR, immunostaining and flow cytometry.

CRISPR-Cas9 targeted one allele to produce homozygous iPSCs. Morphology of three iPSC lines from each donor resembled that of human embryonic stem cells. *OCT4, SOX2* and *NANOG* in generated iPSC were highly expressed at mRNA and protein levels. Significant expression of mesoderm, early and mature VSMC markers was confirmed by immunocytochemistry, qRT-PCR and flow cytometry. Functionality of iPSC-derived VSMCs was confirmed by a contractile assay. Six iPSC lines were successfully derived from two *MTHFR* 677 heterozygous carriers and fully characterised. Differentiation protocol for iPSC-derived VSMCs was successfully established. This will elucidate the biological significance of this MTHFR SNP in hypertension pharmacogenomics to advance patient care and provide a valuable resource for future initiatives.

P17 Genome of Ireland: partnering to plan a public Irish genome sequencing initiative.

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The Genome of Ireland project (GoI) aims to establish a unique Irish genomic cohort, representative of the Irish population. As the Irish element of the Genome of Europe (GoE) at least 1200 participants (reflecting the 1.2% Ireland makes up of the European population, factored by the target size of the larger GoE project (n=100,000)) will be sequenced. GoI will be delivered through five work-packages (WPs) that align with the aims and objectives of the pan-European effort and national considerations. The WPs will 1) provide structured coordination and robust project governance, 2) involve the Irish public across the project lifecycle, 3) incorporate ethical, legal and social considerations throughout the project design, 4) implement a comprehensive, efficient and inclusive recruitment process and 5) provide findable, accessible, interoperable and reusable (FAIR) whole genome sequence data from a representative cohort of individuals living on the island of Ireland. The resulting GoI dataset will constitute a combination of short/long-read sequence data and include telomere to telomere assemblies in individuals of Irish-like ancestry. In terms of use, a reference of Irish whole-genome sequences will facilitate distinction between rare/neutral variation that is specific to Ireland and pathogenic disease-causing variation. It will also provide a high-definition reference of Irish genomic diversity for research uses globally. GoI will be highly relevant to Ireland's involvement in the European Health Data Space (EHDS) and will help Ireland benefit from the 1+ Million Genomes (1MG) initiative, in terms of research funding and equity in access to personalised medicine.

P18 Homozygous deletion in CDH3 identified within a consanguineous Irish pedigree

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The objective of this study is to highlight the genetic causes underlying disease in a consanguineous Irish family with a macular degeneration (MD) and congenital hair loss. A homozygous deletion of two exons was identified within the *CDH3* gene.

Once informed consent was obtained, three affected siblings and their unaffected mother were recruited. The proband and affected siblings present with similar ocular phenotypes displaying early childhood macular disturbances, with a dark choroidal appearance reminiscent of Stargardt phenotypes, as well as congenital fragile hair and alopecia.

The proband underwent targeted single-molecule molecular inversion probe (smMIPs) sequencing of exons and selected intronic regions of 105 inherited MD and age-related MD-associated genes. A homozygous deletion within *CDH3* was identified, leading to the deletion of exons 12 and 13. Breakpoint analysis was undertaken to determine the exact location of the deletion, as well as confirmational Sanger sequencing of family members.

Previous literature has linked *CDH3* with Hypotrichosis with juvenile macular dystrophy (HJMD) and ectodermal dysplasia, ectrodactyly and macular dystrophy (EEM), as the gene encodes the P-cadherin molecule which is expressed in the retinal pigment epithelium and hair follicles. These two syndromes have significant clinical and phenotypic overlap, and can often go misdiagnosed. To the best of our knowledge, this is the second case ever recorded to have a deletion homozygously within this region of *CDH3*. While highlighting this interesting case, we have been able to place emphasis on the importance of interrogating the genetic causes of macular degenerations in Ireland.

P19 Accurate environmental UV data for a genome-wide gene-environment interaction study of vitamin D status

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Vitamin D status (25-hydroxyvitamin-D [25OHD]) is a partially heritable trait, with varying heritability estimates depending on whether it is measured in summer or winter. More so than most outcomes, vitamin D status is largely influenced by a single environmental factor – sun exposure. Recent genome-wide association studies (GWAS) have identified over 140 variants linked to vitamin D status. However, interaction effects remain largely unobserved is such studies, which used a dichotomized summer/winter season variable as a proxy of environmental exposure.

We used an exact measure of ambient UV from satellite weather data to approximate sun exposure for each UK Biobank participant, based on place of residence and date of blood sampling. Participant UV dose was adjusted for cloud cover and other key factors and accounted for accumulation and decay of vitamin D in the body. We performed a genome-wide joint test of marginal and interaction effects in 25OHD in 338,977 White British individuals, adjusting for other key covariates.

We identified over 160 novel independent variants significantly associated with 25OHD concentration – doubling the number of previously known loci. Functional annotation of these variants supports vitamin D involvement in metabolic pathways and hormone and skin phenotypes, and identifies novel genes linked to 25OHD. From the GWAS results, we identify a SNP-heritability gradient of 25OHD positively associated with ambient UV.

Our findings provide new insights into the biology of vitamin D status. These results illustrate the advantage of accounting for interactions and using accurate environmental exposure measures in genetic studies of complex traits.

P20 Archaic ancestry inference in imputed ancient human genomes

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A little over a decade ago, studies showed that when Anatomically Modern Humans expanded into Eurasia, they interbred with Archaic Humans (Neanderthal and Denisovan). This discovery redefined the origin of humans and opened new research directions to study the impact of archaic introgression in human evolution. Up to now, the majority of archaic introgression studies have focused on contemporary individual genomic data, revealing that non-African populations harbour varying levels of Neanderthal and Denisovan ancestry. Despite recent advances in identifying and quantifying archaic introgression in humans, little is known about the evolution of archaic variants within modern human populations after the introgression event (40,000 years ago). Archaic variation continued to evolve within humans and was likely shaped by a population's unique demographic history as well as natural selection. While ancient DNA offers the potential to address this scientific gap, its poor quality has hindered the exploration of ancient genomes.

Here, we investigate the feasibility of using imputation to enhance global and local archaic ancestry inference in ancient genomes. We downsampled 20 high-coverage genomes, representing individuals from diverse temporal and geographical contexts, to 0.0625X, 0.5X, 1X and 2X. Following the imputation of downsampled genomes, we compared them with high-coverage genomes to assess global and local archaic ancestry inference, using also archaic reference genomes to ascertain the inferred introgressed segments origin. We unveil the significant capacity to infer archaic ancestry in imputed ancient genomes. Notably, local ancestry inference in imputed genomes outperforms that of the original high-coverage genomes.

P21 Demographic History of the Armenian Population

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The Armenians, a population historically inhabiting the area of the Armenian highlands, are recognized as one of the ancient populations in Western Asia. We conducted the first whole-genome study of Armenians and deciphered their fine-scale population structure and complex demographic history. We also investigated the most debated questions on their genetic origins and, particularly, the formation of its population of Sasun. We failed to find support for Herodotus` suggestions that Armenians originated in the Balkans; rather, they show a high degree of genetic continuity up to the Late Bronze Age, with a subsequent influx from a source linked to Levantine Early Farmers during, or just after the Late Bronze Age, indicating that this period has been marked by large-scale migrations in the whole region. We demonstrated that the Armenian populations from western, central, and eastern parts of the highlands are relatively homogeneous. Additionally, we found that the Sasun, an Armenian population in the south that had been argued to receive the major genetic contribution from Assyrians, instead has its slightly divergent genetic profile from a bottleneck occurred in the recent past.

P22 The (AB)C of Finding Short Tandem Repeats (STRs) in Short Read Sequencing (SRS) data: A Rapid Review of STR Search Tools and Approaches for Study Design

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Short tandem repeats (STRs) are defined by their short 2-6 bp long motifs. Both expansions and deletions of these motifs contribute to pathology in multiple conditions e.g. Fragile-X. These loci act by a range of functional mechanisms such as expression loci (eQTL), where they are estimated to contribute 10-15% of gene expression cis heritability and are linked with several complex traits e.g. autism, chronotype, and schizophrenia.

STRs are systematically obscured in short read sequencing data. Development of novel STR search tools promises improved characterisation and diagnostic reach but there is limited guidance on current or best practice.

A rapid review with quantitative and qualitative appraisal will help understand and inform on study designs. This review guides protocol development by clarifying on limitations/thresholds e.g. sample size or enrichment approaches based on a meta-analysis of existing publications.

A comprehensive search using the National Collaborating Centre for Methods and Tools (NCCMT) guidelines, and the Pubmed, Embase, and Web of Science databases using keywords for short tandem repeats and other repeat structures e.g. alu elements, and short read sequencing specifically yielded over 3,000 hits. Following a two-step screening of title/abstract, and full text by two independent researcher's results are synthesised quantitatively by meta-analysis and qualitatively by the reporting guidelines of synthesis without meta-analysis (SWiM) to reveal important considerations for study design. Extracted information includes tool usage; prioritisation strategies; statistical power; and STR contribution to heritability. Preliminary findings highlight several STR analyses approaches in existing research with varying levels of success and power.

P23 The genetic contribution to variation in aortic distensibility - withdrawn

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P24 *FOXP2* and Beyond: Shared Genetic Variation Between Autism, ADHD, Bipolar Disorder, Schizophrenia and Sleep-Related Phenotypes Uncovered Through Post-GWAS Analysis

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Understanding the genetic basis of neurodevelopmental and neuropsychiatric conditions, and their relationship with sleep phenotypes, is crucial for advancing individualised treatments. This study investigated the genetic relationships among four key conditions—autism spectrum disorder, attention-deficit/hyperactivity disorder (ADHD), bipolar disorder and schizophrenia (SCZ)—and two sleep-related phenotypes: morningness chronotype and insomnia. We utilised the FUMA (Functional Mapping and Annotation) platform to perform post-GWAS (Genome-Wide Association Study) analysis, leveraging the largest GWAS summary statistics available for each phenotype to identify overlapping genes and biological pathways.

Our results revealed statistically significant overlap in key genes and biological pathways. Notably, the *FOXP2* gene was identified as enriched for common genetic variation associated with the three phenotypes: ADHD, morningness chronotype and insomnia. The *TCF4* gene was also shared across three phenotypes: SCZ, morningness chronotype and insomnia. The *MFHAS1* and *MACROD2* genes were enriched in common genetic variation associated with both autism and morningness chronotype.

Further analysis of overlapping gene sets identified that the gene ontology biological pathway related to cognition and the gene ontology cellular component related to synapses are significantly enriched in both autism and sleep-related phenotypes.

These insights underscore the genetic underpinnings connecting sleep with neurodevelopmental and neuropsychiatric conditions. Our research provides valuable information for researchers aiming to understand the biological basis of these conditions. Ultimately, these findings have the potential to inform more effective, personalised treatment strategies for individuals affected by these complex conditions.

P25 Genome-wide association analysis of social participation and occupational engagement in the UK Biobank

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Psychosis is a leading cause of disability worldwide. Although generally characterised by hallucinations and/or delusions, individuals with psychosis are also subject to deficits in social participation (SP) and occupational function (OF), otherwise known as psychosocial disability (PD). While several environmental and cognitive factors have been identified as predictors of PD, the biological contribution to PD remains unclear. Here we sought to identify genetic determinants of variability in SP and OF in the UK Biobank (UKB). SP (N=360,431) was defined as a summed index of responses from frequency of friend and family visits and leisure/social activity questionnaires from UKB. OF was derived from individual employment status response (N=360,438). Mixed-linear-model genome-wide association (GWA) analysis was conducted on all phenotypes using fastGWA.

GWA analysis of SP and OF phenotypes revealed a total of 13 and 2 independent loci respectively. Gene-based FUMA analysis of SP indicated 16 significant gene-phenotype associations at a Bonferroni correction threshold (p < 2.62e-6). The top genes identified for SP include GBE1 (p = 8.88e-13), CSE1L (p = 1.52e-10), and CDH7 (p = 7.90e-09). Tissue expression analysis revealed that amygdalar, cerebellar, frontal lobular, hippocampal, and basal ganglion were the tissues most specific to the implicated genes in SP. Our findings propose that SP has a stronger genetic component than OF in a healthy population. Of the tissues implicated in this analysis, both the amygdala and frontal lobe have been linked to social behaviours in previous neuroimaging research. Overall, we identify genetic loci and tissue types with possible roles in PD.

P26 Novel Early Diagnostic Epigenetic Panel Development for Oesophageal Cancer

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Oesophageal cancer (OC) is a common cancer with a five-year survival rate of approximately 10-15%. The high mortality is primarily due to the absence of early clinical symptoms, leading to late-stage detection. Barrett's Oesophagus (BO) affects the cellular lining of the oesophagus and is a precursor to OC. The molecular changes underlying the transition from BO to OC remain poorly understood, making the search for molecular novel OC diagnostics a significant research focus. Recently, epigenetic mechanisms, defined as the study of mitotically heritable alterations in gene expression that are not causes by changes in a DNA sequence, have been identified as dysregulated in OC. The epigenetic phenomenon, DNA methylation (DNAm), being the most widely understood and studied in the context of OC. Potential candidate genes for a DNAm panel for BO and early OC detection were identified from the literature. A methylation specific qPCR (MS qPCR) multi-gene assay will be designed and optimised to create a new DNAm panel for the detection of OC. Nucleic acids for the development of this assay have been derived from OC (OE33 and SKGT4), and BO (GO and QH) cell lines, and will be compared to normal oesophageal cells (Het1A cells) to evaluate specificity of our DNAm panel in OC cells compared to normal oesophageal cells. The diagnostic potential of this DNAm panel will be further investigated for potential clinical use in the future by evaluating the sensitivity and specificity of the multi-gene MS qPCR panel in a patient cohort with BO and OC.

CLINICAL

P27 Clinical genetics, management and outcome of head and neck paragangliomas (HNPGLs): A single centre retrospective study covering 23 years

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Objective: Head and neck paragangliomas (HNPGLs) are rare neural crest-derived tumours. Definitive management pathways for HNPGLs are not clearly defined. We did a retrospective study of HNPGLs to analyse genetic subtypes and outcomes of different treatment modalities over 23 years.

Methods: Data were obtained from The NI Electronic Care Record (NIECR) and a prospectively maintained HNPGL database (January 2011 - December 2023).

Results: 87 patients were identified; 50 females: 37 males, mean age 52.3 ± 14.2 (range 17-91 years). 58.6% of patients had carotid body tumours, 25.2% glomus vagal tumours, 6.8% middle ear tumours, 2.2% in the parapharyngeal space and 1.1% in the sphenoid sinus. 5.7% of patients had multifocal disease. Mean tumour size was 3.2 ± 1.4 cm (range 0.5-6.9 cm). Variants identified included SDHD (41.3%), SDHB (12.6%), SDHC (2.2%), and SDHA (1.1%). Treatment modalities included surgery 51.7%, radiotherapy in 14.9% , observation in 28.7%, and somatostatin analogue therapy in 4.5%. Factors associated with a significantly higher risk of recurrence included age >60 ($p = .04$), tumour size >2cm ($p = .03$), positive SDHx variants ($p = .01$), and vagal and jugular tumours ($p = .04$).

Conclusion: The majority of patients had surgical intervention and achieved disease stability. Carefully selected asymptomatic or medically unfit patients can be safely observed provided lifelong surveillance is maintained. recognition of SDHx subtype is important for long term follow-up strategies to prevent recurrence. Establishment of a UK and Ireland national HNPGL registry would help delineate optimal management strategies and improve long term outcome in these rare patients.

P28 An audit exploring differences in the rate of identification of variants of unknown significance between singleton whole exome sequencing and trio whole exome sequencing

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Whole exome sequencing (WES) is a technique utilised to identify variants of genes in individuals with unexplained symptoms such as intellectual disability, developmental delay, and dysmorphic features. Two approaches have come to the forefront of WES techniques; singleton WES (sWES) and trio WES (tWES). sWES involves sequencing only the DNA from the affected individual, whilst tWES involves sequencing the DNA from both parents as well. Duo WES (dWES) utilises DNA from only one parent. The variants identified may be categorised, by ACMG guidelines, as likely benign/benign, likely pathogenic/pathogenic, or as variants of uncertain significance (VUS). The most benefit to both patients and clinicians comes with identification of variants as benign or pathogenic as a diagnosis may then be made or excluded, whilst a VUS leaves a great deal of uncertainty.

The purpose of this audit is therefore to identify any difference in the rates of VUS identification amongst sWES, dWES, and tWES amongst Belfast Health and Social Care Trust (BHSCT) patients. 266 pre-natal or post-natal cases tested across a 9-month period in 2023 with singleton, duo or trio WES. Percentage values of pathogenic and VUS cases were calculated by using the total number of cases within a test modality and their respective VUS/Pathogenic cases. The results showed a VUS versus pathogenic rate in sWES as 37% versus 21%, dWES as 20% versus 20%, and trio as 5% versus 20% respectively. This suggests a higher diagnostic utility for tWES over other modalities.

P29 Prevalence of somatic and germline *BRCA1/2* Pathogenic Variants in an Irish Ovarian Cancer Cohort

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Background: Ireland launched national mainstreamed *BRCA* testing for advanced/recurrent high-grade serous/endometrioid ovarian cancer (OC) in 2020. We aim to characterise test outcome.

Methods: Jan 1, 2020 – Dec 31, 2023, pts without prior g*BRCA* testing referred for tumor *BRCA* and/or g*BRCA* were included with ethical approval. Variants were classified per ACMG guidelines. Data on age, test result were summarised using descriptive statistics (Python (v.3.8) and scipy (v1.10.1)).

Results: 292/535 pts, median age 65 yrs (range 27–88), underwent dual testing, identifying *gBRCA* and sBRCA PV rates of 8.9% (26/292) and 8.9% (26/292) respectively. Among pts with *gBRCA* tests (n=455/535), 8.4% (38/455) and 0.02% (7/455) had a PV and variant of uncertain significance (VUS). 36% (163/455) of those did not undergo somatic tests. Three somatic VUS were identified. (2 *BRCA1*, 1 *BRCA2*). Pts with g*BRCA1/2* PV were younger (median age 58.0 vs 66.5yrs, $p <0.01$). A Northern European founder PV was identified in 6 pts (*BRCA1*c.5266dupC); *BRCA1*c.1175_1214del was

identified in 4pts and *BRCA2*c.4398_4402del in 4pts, residing in the south and east respectively.

Conclusion: Lower *gBRCA1/2* rates may be due to selection bias given exclusion of pt with known g*BRCA* PV. This real world cohort that has *sBRCA1/2* PV rate higher than expected based on international data (~5%) consistent with prior report from a UK real world population. Our analysis identified recurrent PVs, contributing to knowledge of the variant landscape in Ireland.

P30 Review of Cleft Lip/Palate Genetic Testing Pathway in Northern Ireland

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In 2017 a pathway was implemented in the Northern Ireland Regional Genetics Service to offer genetic testing to patients born with a cleft lip and/or palate. A microarray was recommended for all those presenting to the regional multidisciplinary cleft clinic with a cleft lip and/or palate . For those who returned a normal result, it was recommended to refer for genetics assessment if dysmorphic features, development delay or a family history of an affected first degree relative were present. We assessed the utility of our pathway from initiation in 2017 until 2024. We reviewed our numbers tested on a yearly basis, diagnostic yield from array and types of diagnosis returned. Consideration was given to recurrent and incidental findings returned.

P31 Variant Classification: A comparative review of the Bayesian point system

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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. These guidelines have been further refined in subsequent years by updates and recommendations from ACMG/AMP, the ClinGen Sequence Variant Interpretation (SVI) working group, The Association for Clinical Genomic Science (ACGS) and The Cancer Variant Interpretation Group UK (CanVIG-UK). In 2020, Tavtigian *et al* developed a scaled point system to the ACMG/AMP guidelines based on a quantitative Bayesian formulation to further assist with variant classification.

We undertook a review of the variant classification using the points system compared to the standard classification by Richards *et al*. The classification of 50 variants was reviewed, ten variants for each classification: Pathogenic, Likely Pathogenic, Variant of Uncertain Significance (VUS), Likely benign and Benign.

Variant classification remained unchanged in 47/50 variants, giving a concordance rate of 94%. One variant that was previously classified as Pathogenic (≥2 strong pieces of evidence), was reclassified as likely pathogenic following review. The variant scored 9 points, a score of ≥10 is required to reach Pathogenic by Tavtigian *et al*. One benign variant and one VUS were reclassified as likely benign following review. The points system proved useful in fine tuning variants on the VUS scale, providing more information regarding the probability of a variant being pathogenic/benign. Further investigation is needed to review the implications of switching to a points-based system and how this might impact the clinical significance of variants.

P32 Establishing a Genetic Counsellor Clinic in an Inherited Cardiac Conditions (ICC) Clinic

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Inherited Cardiac Conditions (ICCs) account for a large number of sudden cardiac deaths in Ireland. For those diagnosed with or at risk of an ICC, it is recommended that they are referred to a specialised ICC clinic. The clinic combines clinical and genetic testing to diagnosis, evaluate and manage patients and families affected with ICCs.

The Family Heart Screening Clinic (FHSC) was established in the Mater Misericordiae University Hospital (MMUH) in 2007. The team comprised Consultant Cardiologists, a nurse specialist and cardiac physiologists. In 2015, the Next Generation Sequencing lab opened in MMUH and began accepting samples for genetic testing for ICCs in 2020. Subsequently, the FHSC experienced an increase in the number of referrals requesting genotyping for patients.

With an increasing demand for genetic testing, a Genetic Counsellor (GC) joined the team in 2023. From June 2023 to February 2024, 205 patients were removed from the waiting list for the GC clinic. Of this, 22 did not attend and 21 did not require genetic testing. Of those who had genetic testing, 137 had diagnostic testing on a gene panel and 28 had

predictive testing for a single familial pathogenic or likely pathogenic variant.

This study outlines the establishment of the GC role within the FHSC. It will outline the triage process within the clinic, demonstrating how patients' needs are efficiently and appropriately met. It highlights the benefit of a GC role in an ICC clinic, which includes reducing the waiting list and the further development of a multidisciplinary team.

P33 Irish Pathogenic Variants in the *TTN* Gene and Their Clinical Implications

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The *TTN* gene, encoding the protein titin, is critical for the structural integrity and elasticity of cardiac and skeletal muscle. Titin spans half of the sarcomere, with distinct regions: The Z-disc, I-band, A-band, and M-band. *TTN*, encoding the largest human protein critical for muscle contraction and sarcomere structure, is implicated in about 25% of dilated cardiomyopathy (DCM) cases.

Pathogenic variants in *TTN*, particularly truncating variants (TTNtv), are predominantly linked to cardiomyopathies such as DCM and arrhythmogenic right ventricular cardiomyopathy. TTNtv often result in haploinsufficiency and impaired sarcomere function. Some pathogenic variants were identified in multiple patients in the Irish population, such as c.88812delC,p.(Val29606*) in the A-band, which truncates titin and disrupts sarcomere integrity, and c.11791C>T,p.(Gln3931*) in the I-band, leading to premature protein termination. Variants in the M-band were also identified and reported with the caveat that variants in this region may be also associated with recessive inherited conditions. Missense variants were only reported in a small number of cases.

The location of *TTN* variants influences disease severity; A-band mutations are often associated with more severe cardiac phenotypes. Clinical management includes regular monitoring, lifestyle changes, and pharmacological treatments. Advances in next-generation sequencing (NGS) have improved the identification of *TTN* variants, enhancing diagnostic accuracy and enabling personalised therapy. Despite progress, challenges remain in interpreting variants of uncertain significance, particularly missense variants and variants in the M-band. Future research should elucidate the molecular mechanisms underlying *TTN*-related diseases and develop targeted therapies, considering the functional diversity of titin's bands and isoforms.

P34 A survey of patient's expectations and knowledge of the clinical genetics service and their appointments with the service

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The clinical genetics service in CHI Crumlin accepts referrals for adults and children from around the country for investigation and management of genetic and genomic conditions and counselling around inheritance risk. A patient feedback survey was undertaken with the aim of evaluating patient's expectations and preparedness for an appointment with clinical genetics. A secondary aim was to determine patient preference for receiving information about appointments with the service.

Methods: The feedback survey was conducted over four weeks from 26th February 2024 to 25th March 2024. It was administered via a QR code to the survey on the Qualtrics survey platform, with an option of a paper copy. Data was analysed using descriptive statistics.

Results: 29 people responded to the survey, some respondents did not answer all questions, responses are presented as a percentage of those who answered the question. 27%(n=7) didn't know who they would be seeing at the appointment. 62%(n=16) gathered information on their family tree in advance. 46%(n=12) said they felt prepared or very prepared for their appointment. 56 %(n=10) indicated a preference for receiving information about appointments with the service via an information leaflet with their appointment letter. 41%(n=12) respondents provided suggestions for other families attending an appointment at the department, a number recommending doing some research on the family tree in advance.

Conclusion: The responses indicate that there are gaps in patients' knowledge and expectations of appointments with the service. In response to the feedback a patient information leaflet is being created.

P35 Still waiting to be seen? Family History information by Questionnaire (FHQ) improves triage efficiency and waiting lists

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Introduction: Cancer is a common condition of which 5-10% may have a genetic basis. Increasing demand for under-resourced genetic services necessitates that only high-risk patients are triaged to the waiting list (w/l). At DCG, consultants triage cancer referrals (~1 in 4 of all referrals). Urgent referrals or those meeting testing criteria independent of FHx move directly to the w/l. For the remainder a patient-completed Family History Questionnaire (FHQ) is obtained for assessment.

Methods: We performed a retrospective consecutive review of FHQs to determine outcomes, w/l impact and whether additional information in FHQ impacted management.

Results: Between December 2023-February 2024 inclusive, 289 total cancer referrals were received, 217 were placed directly on the w/l, 72 FHQs were sent and 55 FHQs were returned. All returned FHQs provided additional information compared to the referral letter. Further information (eg. histology, genetic results) to complete evaluation was obtained for 43.6% (n=24). Personalised risk assessment was performed in 29.1% (n=16). Genetic testing was indicated for 43.6% (n=24) but was not indicated for 56.4% (n=31) of consultees, who could be dealt with by letter with personalised advice. A living affected relative was identified for testing in 16.1% (n=5/24) of these.

Conclusion: The cancer FHQ is an effective way of managing a cancer genetic w/l ensuring that only high-risk cases are seen in the cancer genetics clinic, keeping the w/l as short as possible. A Family History Co-ordinator would be a welcome addition to our service to manage the FHQ pathway and ensure its effectiveness.

P36 A Review of Cases Presented at a Clinical Genetics Dysmorphology Meeting

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The Clinical Genetics Dysmorphology Meeting is a weekly multidisciplinary meeting which was established for non-geneticist clinicians to present urgent patient cases for advice about genetic testing from consultant clinical geneticists. Cases are accepted from wide ranging medical subspecialties. The primary aim of this meeting is to support and guide genetic testing decisions for non-geneticist clinicians. The aim of this review study was to investigate referrals to this meeting, to get an overview of the outcomes of the cases presented , to ascertain the impact of the meeting and identify areas for improvement.

Methods: Retrospective review of cases from the meeting over a six-month period from September 2023 to February 2024 was carried out. Data was analysed using descriptive statistics. Reviewed data included case demographics, genetic test advice and results, and patient pathway after presentation at the meeting.

Results: 42 patient cases were presented over 6 months (mean = 2 cases/meeting; range = 0–4 cases). Cases were presented by 9 medical subspecialties. 67% of cases were presented by neonatology (n=28), 17% were presented by general paediatrics (n=7). A single genetic test was advised in 76% of cases (n=32), with more than one genetic test advised for 12% (n=5). Testing advice improved diagnostic yield in 28% of cases (n=12) where genetic testing has been completed (missing data).

Conclusion: The results indicate that the meeting assists non-geneticist clinicians with the selection and ordering of appropriate genetic testing and leads to a more efficient and timely diagnosis for over a quarter of cases presented.

P37 Where does risk occur in Clinical Genetics and is it changing over time?

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In 2022 we presented results of a 6-week audit to identify where risk occurs in Clinical Genetics. A number of controls were introduced to ameliorate some of the risks observed since.

We re-audited in Jan-Feb 2024 and noted 57 events, (previous audit n=55). Controlling risk as an everyday activity accounts for ~11% of all referrals. The combined number of red and amber risk factors was 82% in Audit 1 and 87% for Audit 2. However, we noted a reduction in the number of serious nature events recorded eg no secondary finding referrals on repeat suggesting mainstream education is working. There were still 6 pregnancies on the waiting list over 6 weeks despite waiting times having reduced to ~18 months. A common risk is report transmission to the correct clinician from laboratories. This was particularly evident where an add on test was requested by a new clinician (e.g. Genetics) but the initial test organised by a mainstream clinician. In 5 instances, clinicians counselled families without being aware of additional genetic tests having been organised by another mainstream clinician. Duplication of testing remains commonplace (3) and there is still evidence of the wrong test being ordered

(2). There were 4 data breaches, 2 internal and 2 external.

A fit for purpose laboratory information management system would control many of the laboratory processing errors noted. A centralised laboratory service would wasteful reduce duplication events and facilitate access to reports; avoiding not having critical information to hand when counselling families.

P38 The complex nature of genetic Intellectual disability

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We reviewed families seen in 2023 whose phenotype fit within the ERN-ITHACA (European Reference Network for Rare Malformation Syndromes, Intellectual and Other Neurodevelopmental Disorders) umbrella. The DDD (UK Developmental Disorder's project) cites 2388 genes implicated in Intellectual disability (ID) confirming the heterogenous nature of ID. Our study's aim was to identify the number and complexity of disorders over a 12-month period with a view to collaborating within the ILIAD ERN ITHACA registry to facilitate research.

497 patients from 437 families were seen; 190 were reported as having mild ID, 49 number moderate and 28 severe. The age ranged from 0 to 75 years old. 3 were confirmed deceased. A total of 233 (47%) had a confirmed diagnosis; 35% had a chromosomal anomaly (large or small microdeletion/duplication); the rest having single gene disorders with 115 being autosomal dominant and 11 X linked. A total of 20% of cases had a Variant of Unknown Significance (VUS) with the diagnosis remaining unconfirmed.

82 of diagnoses were due to de novo events. A small number of disorders were seen in more than one unrelated family (BWS, Neurofibromatosis type 1, Bardet-Biedl, Alstrom syndrome and IMAGe). The genes logged mirror the findings of the DDD project where the following (mostly de novo) ID genes were found NF1, ANKRD11, ARID1B, KMT2A, DDX3X, MECP2, ADNP etc.).

Particularly challenging cases included counselling families with a VUS and also inherited ID, present in 29 families, as there are often multiple genetic mechanisms at play due to assortative mating.

P39 Sapopterin (Kuvan®) trial reveals a natural protein tolerance in two adults with Phenylketonuria

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Management of PKU has historically involved adherence to a low-protein diet and use of synthetic protein supplements. Tetrahydrobiopterin (BH4), and its pharmaceutical formulation Sapropterin hydrochloride (Kuvan®) is a genotype specific therapy which aims to improve dietary tolerance for protein by enhancing catabolism of blood Phenylalanine (Phe).

In March 2023, the Adult National Centre for Inherited Metabolic disorders (NCIMD) in the Mater Hospital, began delivery of Kuvan® to individuals with a diagnosis of PKU who had a genotype that was predicted to be BH4 responsive. To date NCIMD, Mater has entered 17 adult patients with PKU into the program during which their protein intake was maximised during a preparatory phase. Surprisingly, 2/17 patients who entered this phase, had their natural protein intake liberalised and were successfully weaned off their synthetic protein, and without the need for Kuvan®.

These two patients had been diagnosed with PKU on newborn screening and based on biochemical tests, were determined to have the classical phenotype. Later, genotyping revealed that both patients had one allele that is associated with mild PKU.

We compare the genotype of these patients with those who did not tolerate protein liberalisation to see whether this response can be explained by genotype alone or whether it is a multi-factorial phenomenon. The unexpected tolerance for a normal diet also raises the discussion about whether all patients shown to have at least one allele associated with mild PKU, should have their protein tolerance challenged.

P40 The Needle and the damage done; why are systems errors allowed occur in Irish laboratories but controls within NHS laboratories help prevent patient harm?

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Most patients don't care which laboratory tests their blood samples. It is the HSE's responsibility to ensure laboratories observe best practice. However, because patient representatives don't advocate for laboratories, they are not a priority.

Genetic tests are complex, requiring specialised staff to determine appropriate test selection depending on circumstances. Services are centralised in Northern Ireland, dispatch staff send all samples to one genetics laboratory. Controls are in place on receipt of samples to avoid harm. The NHS just has to ensure supporting one specialised service, optimising safety.

In the Republic, each individual dispatch laboratory must identify accredited testing laboratories (mostly international) themselves. Dispatch to multiple laboratories occurs increasing clinical risk. A risk assessment submitted to the HSE in 2010 identified risk but no ameliorative action resulted.

We recently counselled a family with numerous antenatal losses whose child died from renal agenesis; a small 22q11 pathogenic deletion was identified by laboratory A. Parental samples were sent to laboratory B without the test report. Standard FISH tests showed normal parental results and the family were reassured. The couple had a recurrence, their next baby has unilateral renal agenesis and a cleft palate. Subsequent appropriate testing revealed a paternal deletion.

The devastation to this family is huge. In addition to their trauma, there is trauma to the local team trying to process what went wrong. Fundamentally, this is a systems error and will recur until centralisation is brought in within the HSE. This harm would not have occurred in Northern Ireland.

P41 The impact of copy number variants in diagnosis and severity of autosomal dominant polycystic kidney disease

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by cyst development and kidney enlargement, leading to progressive kidney failure. Mutations in *PKD1* or *PKD2* cause most cases, but some remain genetically unresolved and have variation in disease severity.

Here, we assessed the contribution of copy number variants (CNVs) in 1) unresolved diagnoses and 2) disease severity.

Methods: Using ClinCNV, CNVs in cystic kidney genes were identified from targeted next-generation sequencing (NGS) of 378 ADPKD patients. CNVs were validated from array comparative genomic hybridization (aCGH) of 5 samples and multiplex ligation-dependent probe amplification (MLPA) of 50 samples. Regression models assessed the association of CNVs with age at kidney failure, height-adjusted total kidney volume, and liver cysts as clinical outcomes.

Results: Disease-causing CNVs were identified in 13 individuals across 7 families, increasing the diagnostic yield from 89.2% to 92.4%. ClinCNV detected *PKD1/PKD2* CNVs with 100% specificity and 60.00% sensitivity compared to MLPA; aCGH data indicated 83% sensitivity for regions with sufficient probe coverage.

After filtering, 9.7% (36/371 individuals) had an additional non-diagnostic cystic kidney gene CNV; 21 individuals had a pathogenic PKD variant alongside a non-diagnostic CNV. These CNVs showed no impact on the clinical outcomes tested, likely from low sample size of individuals with an additional CNV.

Conclusions: ClinCNV effectively identifies disease-causing CNVs in ADPKD, suggesting its utility when initial NGS analysis is inconclusive. Additional non-diagnostic CNVs do not appear to impact severity of ADPKD. This study underscores the importance of bioinformatic tools in repurposing NGS for diagnostics in ADPKD.

P42 Modifiable risk factors for cancer among people with lynch syndrome: an international, cross-sectional survey

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Lynch syndrome (Ls) is the most common cause of hereditary colorectal and endometrial cancer. Lifestyle modification may provide an opportunity for adjunctive cancer prevention. We aimed to characterise modifiable risk factors in people with Lynch syndrome and compare with international guidelines for cancer prevention.

Methods: A cross-sectional study was carried out. Following public and patient involvement, the survey was disseminated through patient advocacy groups and social media. Self-reported demographic and health behaviours were collected in April 2023. We undertook comparison of adherence to guidelines from the World Cancer Research Fund (WCRF) 9

lifestyle recommendations. Median adherence scores, as a surrogate for lifestyle risk, were calculated and compared between groups.

Results: 156 Ls individuals participated from 13 countries. Median age 51; 54% were cancer survivors. Mean BMI was 26.7, mean weekly duration of moderate /vigorous physical activity was 90 min. Median weekly consumption of ethanol was 60 g, 3% reported current smoking. Adherence to WCRF recommendations for cancer prevention ranged from 9 to 73%, with all but one recommendation having < 50% adherence. Median adherence score was 2.5 out of 7. There was no significant association between median adherence scores and age ($p = 0.27$), sex ($p = 0.31$), or cancer history ($p = 0.75$).

Conclusions: We have characterised the modifiable risk profile of people living with Lynch syndrome, outlining targets for intervention based on lifestyle guidelines for the general population. As evidence supporting the relevance of modifiable factors in Lynch syndrome emerges, behavioural modification may prove an impactful means of cancer prevention.

P43 Data collection survey investigating barriers to predictive testing - withdrawn

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P44 Update on the CINDI registry and EpiFUN study

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Introduction: In paediatric neurology we see children with rare neurogenetic conditions. This study has two aims i) set up a registry for children with known neurogenetic conditions, and ii) develop a research diagnostic pathway for children who have not had a diagnosis made using current clinical standard of care testing.

Materials and methods: The CINDI (Collaboration In geNomic Disorders in Ireland) is a cloud-based register (REDCap) to record patients with/and without a diagnosis so that patients and their families can be contacted should a research study, clinical trial or precision medicine become available. Patients without a diagnosis join the EpiFUN study. The UNSOlved Neurology (UNiSON) research clinic integrates deep phenotyping and reanalysis of repatriated exome data. A diagnostic prescription is formulated which directs investigations (bioinformatic re-analysis, long read sequencing, optical genome mapping, transcriptomic analysis/functional work). A multidisciplinary team meeting discusses outputs from the multi-omic pipeline. In addition, the pipeline allows linking in with international efforts to make a diagnosis (RD CAT/ERDERA). Ethics approval:CHI REC approval GEN 739-19.

Results: Recruitment to the CINDI registry began in September 2023. 60 children have been recruited to date; 42 with a known diagnosis of whom two have been recruited to trials. 8 children without a diagnosis have attended the UNiSON clinic and diagnostic work is ongoing.

Conclusions: The CINDI register allows for diagnosed patients to be recruited to future research studies, clinical trials or for precision medicines. Children presenting without a genetic diagnosis have access to a research diagnostic pathway.

P45 Genomic resequencing of unresolved patients with polycystic kidney disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease, caused primarily by pathogenic variants in *PKD1* and *PKD2*. Due to sequence context of *PKD1*, commonly used techniques such as Targeted Sequencing (TS) tends to have poor capture efficiency. Here we examine whether Whole Exome Sequencing (WES) provides higher capture rates for *PKD1* and increases diagnostic yield in patients without a genetic diagnosis following appropriate TS.

Methods: PKD patients were recruited via the Inherited Kidney Disease Clinic at Beaumont Hospital, following negative results from TS. Raw genomic data were regenerated using WES and then reanalysed using a GATK4-based bioinformatics pipeline. Variant pathogenicity was determined using guidelines from the American College of Medical Genetics and Genomics and was used to calculate the diagnostic yield.

Results: 30 patients with ADPKD were included in the study. Likely pathogenic or pathogenic variants were noted in seven patients and the diagnostic yield was 23% (7/30). Four individuals carried likely pathogenic variants in *PKD1*. Two individuals carried likely pathogenic truncating variants in *PRKCSH*. One individual carried a pathogenic missense variant in *COL4A1*.

Conclusions: WES in patients without a genetic diagnosis following TS led to the identification of diagnostic variants in 23% of patients tested, with most of the novel detections being made in *PKD1*. These findings suggest that WES outperforms TS as a diagnostic tool for ADPKD, primarily due to improved detected across *PKD1*.

P46 The Mater Misericordiae University Hospital's Sudden Arrhythmic Death Syndrome (SADS) Biobank

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Sudden cardiac death (SCD) is the most prevalent cause of death in Western countries. In Europe, 5–8% of SCD cases have no evidence of any structural cardiac defect or coronary disease at autopsy. SCD profoundly affects the overall grief for the affected families and communities. Sudden Arrhythmic Death Syndrome (SADS) is a disorder that can be prevented if detected early on, and is identified when sudden death remains unexplained even after post mortem examination. The Mater Misericordiae University Hospital's (MMUH) Next Generation Sequencing (NGS) Laboratory hosts a SADS Biobank which retains samples for genetic testing. The main goal of the project is reviewing the genetic variation detection rates in samples analysed through the bio bank after a SCD. It aims to illustrate the potential benefits of this resource for family members' primary prevention. Family members of SADS victims attend the MMUH Family Heart Screening (FHS) Clinic, either on their own initiative or as a result of a recommendation following a post-mortem, and are offered screening tests for inheritable cardiac illnesses. Consent for genetic testing is considered by the family. Since the founding of the Bio-bank in January 2015, 497 samples have been received. 136 probands have undergone genetic testing after individual consent was obtained. 93 were tested through the MMUH FHS clinic for which we have clinical information. Results of samples received for molecular autopsy have been retrospectively analysed; diagnostic rate and phenotype data will be presented highlighting this important resource to families and our understanding of SCD.

P47 The importance of being counted: Increasing visibility of rare diseases in Irish health information systems

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Rare Diseases (RDs) cannot be reliably identified using any of the available generic coding terminologies. People living with a RD (PLWRD) are not currently optimally visible in Irish health information systems (HISs). Approximately 83% of RDs cannot be distinguished from non-RDs.

To improve visibility of RDs and provide interoperable RD health data, the use of RD coding nomenclature ORPHAcode is considered best practice in EU member states. The EU Orphanet Data for RDs (OD4RD2) Joint Action aims to support the implementation of ORPHAcodes in the European Reference Networks (ERNs) across EU Member States. Ireland is a member of 18 of the 24 ERNs.

The National Rare Diseases Office conducted a survey of the 18 Irish ERN clinical lead and co-lead sites about their current status with regards to the direct and indirect use of ORPHAcodes to provide epidemiological RD data to ERN coordinators; and barriers to usage.

Of the 18 Irish ERNs, 16 completed the survey. Of these, 4 ERN sites are currently using ORPHAcodes directly for ERN reporting. Reasons for not using ORPHAcodes included: unavailable in hospital IT platforms; lack of institutional awareness of the importance of ORPHAcodes; lack of training/support; additional workload; and lack of electronic health records.

Results reflect the current lack of awareness and support for ORPHAcodes in Irish HISs. National policy for the optimisation of RD coding is critically required. OD4RD2 is a timely and important initiative to support this process and ensure PLWRD have accurate and equitable representation in Irish health data

P48 Aspirin use and cancer surveillance among people with Lynch syndrome: an international, cross-sectional survey

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Background: Lynch syndrome is the most common cause of hereditary colorectal and endometrial cancer. Guideline recommendations regarding cancer surveillance and use of aspirin for colorectal cancer prevention vary internationally.

Methods: An international, cross-sectional study was carried out utilizing survey methodology. Following public and patient involvement (PPI), the survey was disseminated through patient advocacy groups and by social media. Self-reported demographic and health behaviours were collected in April 2023. Proportions between groups were compared using a X^2 test.

Results: 156 individuals with Lynch syndrome participated from 13 countries. The median age was 51, and 54% (n=88) were cancer survivors. Self-reported pathogenic variants included MSH2 (n=54), MSH6 (n=39) MLH1 (n=38), PMS2 (n=17) and EPCAM (n=4). Among participants, 46% (72/156) reported regular aspirin use. Regular aspirin use for chemoprevention was more frequent in those with a previous diagnosis of cancer (52% vs. 36%, $X^2 = 4.15$, $p = 0.04$) and residents in Europe compared to North America (50% vs. 33%, $X^2 = 4.01$, $p = 0.04$), but there was no significant difference in those older than 50 years old, compared to younger participants (48% vs. 44%, $X^2 = 0.24$, $p = 0.62$). Extra-colonic cancer surveillance was more frequent among participants residing in North America compared to European countries (65% vs. 41%, $X^2 = 8.1$, $p < 0.001$).

Conclusions: We have highlighted international variation in self-reported use of aspirin and methods of cancer surveillance between individuals with Lynch syndrome. Emerging clinical trial evidence, including the CAPP3 trial, along with consideration of family history and gene specific data, are needed to guide more individualised recommendations for cancer surveillance and prevention