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Oral presentations

OP01. (Abstract published https://doi.org/10.1038/s41398-020-0752-7)

OP02. The clinical significance of amyotrophic lateral sclerosis and frontotemporal dementia associated genetic variation: a comprehensive, uniform analysis of three decades of genetics research

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We present JournALS, a web application designed to assess the clinical significance of all previously reported amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD)-associated variants. ALS is a devastating motor neuron disease. Next-generation sequencing led to a deluge of reported rare variants in ALS-associated genes; explaining at most, 70% of familial and 15% of sporadic cases. However, many reported variants are likely to represent non-pathogenic rare variation. The difficulty of interpreting the clinical significance of rare variants is exacerbated in ALS and FTD due to genetic heterogeneity, late age of onset, incomplete penetrance and a high proportion of sporadic cases. However, many reported variants are likely to represent non-pathogenic rare variation. The difficulty of interpreting the clinical significance of rare variants is exacerbated in ALS and FTD due to genetic heterogeneity, late age of onset, incomplete penetrance and a high proportion of sporadic cases. An extensive literature review identified 861 relevant studies, documenting 2,725 reported variants in 336 genes. Patient phenotype data and variant information such as zygosity and de novo status were gathered. 438 pedigrees exhibiting segregation were documented. Variants in the 336 genes identified in the literature were extracted from publicly available, ALS-specific, genomics datasets, creating a final database of 1.4 million variants. Leveraging large-scale genomics resources such as gnomAD in conjunction with the American College of Medical Genetics variant classification guidelines, we have uniformly assessed all variants for pathogenicity, penetrance, prevalence, and phenotypic and geographic heterogeneity. Pathogenic and likely pathogenic variants are identified in 12 genes. 10% of variants are classified as benign or likely benign; and greater than 89% remain variants of uncertain significance. All supporting evidence and analyses are provided in an easily accessible format. As gene-based therapies are currently enrolling patients, identifying pathogenic variants is now essential.

OP03. Dissecting the sex-dependent genetic architecture of amyotrophic lateral sclerosis

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Amyotrophic lateral sclerosis (ALS) is a late-onset neurodegenerative disease characterised by progressive loss of upper and lower motor neurons. Sex plays an observable role in ALS disease risk and heritability, with higher overall risk in males and higher rates of mother to daughter transmission. However, the extent that sex affects the genetic architecture of ALS is currently understudied. To address this we reanalysed genetic data from a published ALS GWAS (N = 36,052), accounting for gene by sex interactions. We ran GREML analysis of ALS heritability fitting sex as an interaction term, observing significant evidence of gene by sex interactions (p = 0.0087) that account for ~1/3rd of total SNP heritability. We further dissected sex effects by running GWAS on male-specific (N = 18,732) and female-specific (N = 17,322) data subsets. We estimated global and regional heritability using LD-score regression and Heritability Estimation from Summary Statistics (HESS) on these sex-specific GWAS, observing higher heritability in females ($h^2 = 0.087; SE = 0.029$) than males ($h^2 = 0.0023; SE = 0.0288$), alongside greater polygenicity in females. Finally, we ran a sex-specific association scan identifying variants significant at a 5% FDR in one sex and above nominal significance in the other (p > 0.05). Our scan identified several known (MOBP, C9orf72, SARM1, UNC13A) and novel (PIP5K1B, ATP8A2, PCDH9, RNASE9, OTUD7A, ITPIPL2, UNK, FB1) loci harbouring SNPs associated with ALS in only one sex. The majority of sex-specific novel loci were strongly expressed in the brain (GTEx) consistent with known ALS aetiology.

OP04. Investigating the genetics of cognitive resilience in healthy ageing using the UK Biobank

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Cognitive resilience is the ability to withstand the negative effects of stress on cognitive functioning during aging. The polygenic contribution to cognitive resilience requires large data sets for analysis. In addition, longitudinal data is needed to identify individual differences in cognitive performance over time. The UK Biobank (500,000 participants > 40 years of age) offers the potential to advance research on the genetics and biology of cognitive resilience.

**Methods:** We created a longitudinal cognitive resilience phenotype by combining reaction time (RT; a measure of processing speed representing cognitive ability at present) with the phenotype of education years (EY; representing cognitive ability in the past). Using Genomics SEM (structured equation modelling), we performed GWAS-by-subtraction which allowed us to subtract the genetics of EY from the genetics of changes in cognitive ability over time to leave the genetics of resilience.

**Results:** This analysis identified 8 genetic loci containing 13 independent genome-wide significant SNPs and 95 genes that were associated with resilience. These genes were specifically expressed in multiple regions in the brain but not in other tissues. Gene ontology analysis showed that biological pathways related to synaptic organisation and modification of post synaptic structures were enriched for genes associated with resilience. LD score regression shows that the genetics of resilience was positively correlated with the genetics of white matter volume in the brain.

**Conclusion:** This first GWAS of cognitive resilience, employing novel Genomics SEM, identifies that genes that function at the synapse and/or influence white matter volume as contributors to variance in resilience in an older population.

**OP06. AVV-mediated gene replacement therapy in cell culture models of an inherited retinal degeneration**

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RP2 is a ubiquitously expressed protein thought to be involved in ciliary trafficking of lipid-modified proteins. Mutations in RP2 are responsible for approximately 15% of X-Linked Retinitis Pigmentosa (XLRP) cases, with those affected experiencing a severe, early-onset form of inherited retinal degeneration.

**Background:**

Primary human dermal fibroblast lines with two naturally occurring RP2 null mutations, R120X and N142fs, were established and compared to five unaffected control fibroblast lines. R120X and N142fs fibroblasts exhibited reduced RP2 mRNA expression and a complete lack of RP2 protein, indicating nonsense-mediated decay of both mutant transcripts. High titre AAV vectors were generated in multiple serotypes and their tropisms were evaluated in fibroblast cultures and murine photoreceptors. Transduction of RP2 null fibroblasts with AAV-RP2 successfully restored RP2 expression.

**Results:**

R120X fibroblasts were then reprogrammed into induced pluripotent stem cells and, alongside an additional CRISPR-Cas9 gene-edited RP2 knockout line (RP2 KO), were differentiated into retinal organoids. R120X and RP2 KO organoids underwent a significantly higher level of apoptosis at day 150 (D150) of differentiation when compared to controls, followed by reduced rhodopsin expression and thinning of the outer nuclear layer (ONL) by D180. AAV-mediated overexpression of RP2 in RP2 KO organoids was successful in ameliorating the rod degeneration phenotype, as evidenced by increased rhodopsin expression and ONL thickness. Additionally, in vivo tolerance of RP2 overexpression was evaluated in the context of wild-type murine photoreceptors after subretinal AAV delivery.

**OP07. A NRXN1 deletion phenotype: characterization of cognition and brain structure**

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**Background:**

NRXN1 deletions are one of many rare copy number variants (CNVs) associated with neurodevelopmental and neuropsychiatric disorders (NDDs). NDDs are characterized by cognitive impairments, behavioural difficulties, and atypical brain development. However, NDDs are highly heterogeneous, both phenotypically and etiologically. This study aimed to characterize cognition and brain structure in a NRXN1 deletion cohort.

21 NRXN1 deletion cases and 21 age- and gender-matched controls (age range = 9–53 years) were recruited. Participants completed a battery of computer-based tasks (http://www.cambridgecognition.com/) which measured attention, executive function and social cognition.
Data were analysed using Cox regression analyses. MRI scans, including high resolution T1-weighted anatomical scans and diffusion tensor imaging (DTI) data were also acquired. Data were analysed to examine differences grey and white matter structural architecture between NRXN1 deletion cases and controls. NRXN1 deletions were associated with poorer executive function and social cognition, but not with attention. No effect of group on white matter structure was found, however, a group-by-age interaction was observed in the genu of the corpus callosum, a major white matter tract. Preliminary analysis showed no group differences in grey matter. Characterization of the impact of CNVs such as NRXN1 deletions on cognition and brain development will help to better understand their clinical implications. As part of an international autism clinical trials consortium, our research is investigating biomarkers of rare genetic conditions and patient stratification approaches.

OP08. Isodisomy screen of Irish rare disorder cohort identifies a novel TMCO1 variant and maternal isodisomy of chromosome 1 in a patient with cerebrofaciothoracic dysplasia

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The prevalence of uniparental disomy is estimated to be 1 in 2,000 births, with approximately one quarter of these representing uniparental isodisomy (UPiD) events. As a person with UPiD possesses two identical chromosomes from a single parent, this inheritance anomaly has the potential to unmask pathogenic recessive variants. A UPiD screen using genotype data from 119 trios with rare disorders was performed to identify large runs of homozygosity (ROH) of uniparental origin. Subsequently, whole genome sequencing (WGS) analysis was performed to identify pathogenic variants within these ROH. This analysis established one instance of maternal isodisomy of chromosome 1 in a child with craniofacial dysmorphism, skeletal anomalies and intellectual disability. WGS of this proband revealed a novel pathogenic homozygous frameshift variant p.(Glu110Valfs*20) in the TMCO1 gene on chromosome 1. Truncating loss-of-function variants in TMCO1 are associated with cerebrofaciothoracic dysplasia, which is consistent with the proband’s phenotype. To the best of our knowledge this is the first case of cerebrofaciothoracic dysplasia associated with UPiD 1. We also identified one instance of UPiD 2 in our cohort, but no variant of clinical significance was identified at this time by WGS analysis. The overall prevalence of UPiD in our small cohort was 1 in 60 births, suggesting that UPiD may be found at a higher frequency in rare disease cohorts than in the general population. Our study demonstrates that UPiD screening may be used to improve diagnostic yields by isolating regions of the genome where a rare inheritance error has unmasked pathogenic variants.

OP09. The prevalence of morbidities & cancers in a large cohort of adults and children with Down syndrome

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Down syndrome (DS) is associated with the development of multiple morbidities throughout the life-course. However, there is limited existing literature on the prevalence of these morbidities. Existing studies tend to have small sample sizes, focus on the adult population and rarely provide a comparison group. Using a large linked UK dataset we aimed to determine the prevalence of morbidities and cancers in adults and children with DS. This matched retrospective cohort study utilised linked electronic health record data from Clinical Practice Research Datalink (CPRD), Hospital Episode Statistics (HES), the Cancer Registry and the Office for National Statistics (ONS), April 1997-February 2016. Each individual with DS was matched ≥4 controls. Prevalence and adjusted odds ratios were calculated for 31 morbidities and 24 cancers. 4,648 individuals with DS (32,920 person yrs) and 23,238 controls (236,883 person yrs) were included in the study. Individuals with DS had a significantly higher prevalence of almost all of the morbidities examined. Notably they had lower recorded rates of anxiety and depression. Individuals with DS had a significantly higher prevalence of leukaemia and testicular cancer. Conversely they had a lower prevalence of breast, lung, ovarian, prostate and uterine cancers, but significance was lost after adjustment for confounders. Our findings support many aspects of current practice in DS health surveillance, however we also identified a number of common morbidities, which are amenable to screening and therapy, that are not traditionally included. Our findings provide support for the expansion of health surveillance for individuals with DS to include these morbidities.

OP10. Genomic diagnostics in adults and children with severe epilepsy: an update from FutureNeuro

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Introduction: The diagnostic value of genomic testing in epilepsy is well established in the paediatric setting, but relatively poorly understood in adults. It can be difficult to clinically diagnose childhood-onset epilepsy syndromes in adult patients due to continuing development of the patient’s phenotype. Aim: Compare diagnostic yields of genomic testing in adults and children with severe forms of epilepsy, and integrate results into the clinical care pathway using eHealth technologies.

Methods: Patients were recruited through referral centres across Ireland. Whole-exome sequencing libraries (Roche SeqCap) were sequenced on Illumina NextSeq, via a research pipeline. Copy-number variants were detected using array-CGH. A custom bioinformatics pipeline was used to analyse exome data. Patients without molecular diagnosis were reanalysed using Congenica(v2.4). Pathogenicity was assigned using American College of Medical Genetics and Genomics guidelines and discussed at a multidisciplinary team meeting, conducted online during COVID restrictions. Pathogenic variants were confirmed using an accredited service provider.

Results: At submission, 138 trios were recruited and 125 trios have completed genomic testing. 89% of patients had co-morbid...
intellectual disability. A diagnostic rate of 30% was obtained; 29% in adults and 34% in children. Variants were identified in 26 genes including three unrelated patients with diagnostic CHD2 variants. In total, 69% of pathogenic variants were denovo. Copy-number variants were identified in two patients.

Conclusion: Genomic testing has similar utility in adult and paediatric cohorts of people with epilepsy and ID. A genetic diagnosis brings an end to the ‘diagnostic odyssey’, and may inform prognosis or highlight alternative treatment options.

OP11. Fabry disease: the Republic of Ireland experience

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Introduction: Fabry disease (FD) is an X-linked, lysosomal storage disorder caused by pathogenic variants in GLA gene which leads to glycosphingolipid substrate accumulation in multiple organs. A number of therapies have become available for FD including a chaperone therapy that is genotype specific and other novel therapies are in development. As personalised medicine is now a reality for this rare disease a review of patients with FD in ROI was performed.

Aim: To perform a complete review of adult patients with FD in the ROI.

Methods: Complete ascertainment was achieved of all diagnosed patients (>18 years) with FD in ROI by studying those attending the National Centre for Inherited Metabolic Disorders-Adult Service from 2013–June 2020. Data on demographics, phenotypes, genotypes, primary critical organ complications, sentinel events, treatments and their outcomes were collected. Statistical analysis was performed using SPSS Version 25.0.

Results: Demographics: N = 79 [32/79 (40.5%) males, 47/79 (59.5%) females] representing 26 families.

Diagnosis: 13/79 (16.4%) were index cases, 66/79 (83.6%) diagnosed from cascade screening (83.8%). Phenotype: 33/64 (51.6%) classic, 31/64 (49.4%) later-onset phenotype. Genotype: 18 different genotypes identified, N215S was the most common variant.

Treatment outcomes: Significant clinical improvement was noted in patients on treatment with regards to acroparathesia, gastrointestinal disturbances, cardiac manifestations and quality of life.

Conclusion: This is first review of patients with FD in ROI and elucidates FD phenotypes, genotypes and response to therapies. FD disease phenotype. As Tulp1 is mainly expressed in photoreceptors, we developed a Tulp1 supplementation therapy targeting these cells in Tulp1-/- mice. We utilised subretinal AA V2/5 delivery and rhodopsin-kinase promoter (GRK1P) driving an optimised Tulp1 cDNA construct. Expression of Tulp1 mRNA and protein were assessed by qPCR, western blot, immunocytochemistry and visual function by electroretinography (ERG) in Tulp1-/- and wt mice. Bioinformatic analysis of retinal cell type specific expression datasets and predicted TULP1 interactors was also performed. In spite of Tulp1 supplementation providing similar to wild type levels of Tulp1-/- photoreceptors at p20, no substantial structural and functional rescue of the Tulp1-/- retina was found. TULP1 was detected in both the outer and inner retina in wt mice. Bioinformatic analysis indicated Tulp1 expression in retinal progenitor, photoreceptor and non-photoreceptor cells; predicted TULP1 interactors differed in various retinal cell types. Our results indicate that Tulp1 supplementation targeted to photoreceptors may not be sufficient to provide robust benefit in Tulp1-/- mice. Expression of Tulp1 extends to multiple retinal cell types from early age, as such, lack of Tulp1 may also lead to primary degeneration of non-photoreceptor cells, which may not be repaired by targeting photoreceptors only. These findings highlight potential hurdles in the development of treatments for TULP1-linked IRDs.

P02. Tulp1 expression and supplementation in the mouse retina

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Biallelic mutations in the tubby like protein 1 gene (TULP1) are causative of some forms of inherited retinal degenerations (IRDs) in humans; a mouse knock-out model (Tulp1-/-) is characterized by a similar disease phenotype. As Tulp1 is mainly expressed in photoreceptors, we developed a Tulp1 supplementation therapy targeting these cells in Tulp1-/- mice. We utilised subretinal AA V2/5 delivery and rhodopsin-kinase promoter (GRK1P) driving an optimised Tulp1 cDNA construct. Expression of Tulp1 mRNA and protein were assessed by qPCR, western blot, immunocytochemistry and visual function by electroretinography (ERG) in Tulp1-/- and wt mice. Bioinformatic analysis of retinal cell type specific expression datasets and predicted TULP1 interactors was also performed. In spite of Tulp1 supplementation providing similar to wild type levels of Tulp1-/- photoreceptors at p20, no substantial structural and functional rescue of the Tulp1-/- retina was found. TULP1 was detected in both the outer and inner retina in wt mice. Bioinformatic analysis indicated Tulp1 expression in retinal progenitor, photoreceptor and non-photoreceptor cells; predicted TULP1 interactors differed in various retinal cell types. Our results indicate that Tulp1 supplementation targeted to photoreceptors may not be sufficient to provide robust benefit in Tulp1-/- mice. Expression of Tulp1 extends to multiple retinal cell types from early age, as such, lack of Tulp1 may also lead to primary degeneration of non-photoreceptor cells, which may not be repaired by targeting photoreceptors only. These findings highlight potential hurdles in the development of treatments for TULP1-linked IRDs.

P03. A review of the cognitive impact of neuropsychiatric risk associated copy number variants

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Copy number variants (CNVs) are genomic regions over 1 kb in size, deleted or duplicated in comparison to a reference genome. Many rare CNVs are implicated as pathogenic, conferring risk for
P04. Investigating OPA1 isoforms as gene therapy interventions for mitochondrial dysfunction

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allowing for personalised interventions.

Overall rare CNV burden is not associated with cognitive ability in the general population. However, rare deletion burden exerts more deleterious cognitive effects. Unaffected carriers of neurodevelopmental risk-associated variants perform cognitively between the level of non-carriers and individuals with schizophrenia. Genotype accounts for only a small proportion of variance in cognitive phenotypes. Various CNVs are associated with domain specific impairments, including language impairment in 16p11.2 deletion, and reading and mathematical difficulties in 15q11.2 deletion. In 22q11.2 deletion, influence of COMT genotype varies with age. Met carriers reportedly exhibit superior pre-frontal cognitive functioning in childhood, with greater degrees of cognitive impairment observed longitudinally compared to Val carriers. Understanding the cognitive impact of CNVs is useful to clinicians in counselling patients, with identification of specific educational needs allowing for personalised interventions.

P05. (Abstract Withdrawn).

P06. Transplant recipient genetic risk scores of Membranous Glomerulonephritis are significantly associated with adverse kidney graft outcome

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Membranous Glomerulonephritis (MN) is a rare cause of End-Stage-Renal-Disease, characterised by autoimmune antibodies directed towards podocyte antigens. The common genetic architecture of MN has recently been dissected in a genome-wide-association (GWAS) of 3,782 cases and 9,038 controls, demonstrating that four loci (NFKB1, IRF1, PLA2R1, HLA) account for nearly one-third of disease risk (Xie et al., 2020). Despite this strong genetic component, it is unclear how genetic risk of MN impacts graft survival in kidney transplants given the high rates of graft failure in recipients with MN. Motivated by these recent GWAS results, we sought to test if common genetic risk scores (GRS) of MN were associated with poorer graft survival in 1,774 British/Irish kidney transplant recipient-donor pairs with SNP-microarray genotypes. We calculated and compared two normalised GRS; the first quantified the weighted dosage effects of the top 6 SNPs independently associated with MN, the second quantified the genome-wide dosage of all markers with a significance lower than 0.01. We confirm that the trait’s structured genetic architecture leads to strong discriminative power of MN GRS in identifying cases from controls, especially the 6-SNP score. Furthermore, we demonstrate that both recipient and donor 6 SNP GRS are strongly associated with risk of acute rejection within the first 12 months of transplant (Recipient – OR: 1.44, adj.p.value: 8e-5; Donor: OR: 1.33, adj.p.value: 0.026), but not time-to-graft-failure. Our results have implications for the risk management of antibody-mediated kidney pathologies in kidney transplantations. Future work includes investigating if GRS of similar traits likewise impact graft survival.

P07. Identifying genetic predictors of severe cutaneous adverse drug reactions

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Background: Cutaneous adverse drug reactions (cADRs) range from mild rash to more severe reactions such as hypersensitivity syndrome (HSS), stevens-johnson syndrome/toxic epidermal necrolysis (SJS/TEN). These reactions affect approximately 3% of people prescribed aromatic anti-convulsants such as carbamazepine, phenytoin and lamotrigine. Genetic biomarkers, HLA-A*31:01, HLA-B*15:02 and CYP2C9*3, have diagnostic value in predicting cADR-risk, yet these markers do not have complete prognostic sensitivity and specificity. We hypothesize that additional pharmacogenomic biomarkers for severe AED-induced skin can be detected through increased study sizes, facilitated by large consortia.

Methods: Severe cADR cases (n=87) were obtained from the EpiPGX consortium and the Canadian Pharmacogenomics Network for Drug Safety (CPNDs) and matched drug-tolerant controls of European-descent (n=198). The anti-epileptic drugs that triggered these cADRs were carbamazepine (n=34), lamotrigine (n=34), phenytoin (n=15) and oxcarbamazepine (n=4). We first conducted a genome wide study (GWAS) of all cases in the dataset, here we employed the model score with 5 covariates to control for population structure. Individual GWAS were conducted for each drug, employing the model em.

Results: Preliminary analyses show replication of the HLA-A*31:01/carbonamazine and CYP2C9*3/phenytoin cADR associations. As expected, the HLA-B*15:02 allele was not observed in our European patients. Analyses are ongoing.

Conclusion: In conclusion, we present one of the largest collections of severe cADRs caused by AEDs in European-ancestral patients assembled to date. We were able to replicate some previously reported genetic predictors of cADRs. An opportunity presents for meta-analysis of these and previously published results. We also plan to expore the role of rare genetic variants in these conditions.

P09. Enrichment of a deep intronic ABCA4 variant in Irish Stargardt disease patients

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Purpose: The Target 5000 study aims to provide clinical assessment and genotyping services to those affected by an inherited retinal degeneration in Ireland. 22% of probands present with a clinical diagnosis of Stargardt Disease (STGD1), a recessively inherited form of macular dystrophy caused by variants in the ABCA4 gene. ABCA4 c.4539 +2028C>T is a pathogenic deep intronic variant that results in aberrant splicing. This study aims to determine the number of STGD1 patients who possess the ABCA4 c.4539 +2028C>T variant in Ireland.

Approach: Participants are clinically examined by Target 5000 affiliated ophthalmologists. Patient samples are provided to a laboratory in Trinity College Dublin once informed consent is given. Patients undergo either target capture next generation sequencing of ABCA4 or single-molecule molecular inversion probe-based sequencing of the entire gene as well as 40 kb of flanking sequence.

Results: Through continued and retrospective analyses of the Target 5000 STGD1 cohort, 16 individuals across 14 pedigrees carry ABCA4 c.4539 +2028C>T and another pathogenic variant. Furthermore, one individual is homozygous for the variant. Globally, only 15 other incidences have been reported across five studies in the literature indicating that this variant is highly enriched in the Irish population.

Conclusions: DNA sequence analyses have shown that ABCA4 c.4539 +2028C>T is potentially enriched in the Irish STGD1 cohort. The number of individuals found to carry ABCA4 c.4539 +2028C>T highlights the significant role of intronic variants in STGD1 in Ireland. As therapies designed to modulate aberrant splicing progress in clinical trial, the identification of causal intronic variants has become a diagnostic imperative.
PCa. Transforming growth factor β (TGF-β) signalling is also an important regulator of EMT, but the relationship between miR-21 and TGF-β remains poorly understood. Therefore, this project will investigate the role of miR-21 in TGF-β-induced EMT.

**Methods:** Bioinformatics analysis was carried out to identify miR-21 target genes that are associated with EMT in PCa. PCa cells were treated with TGF-β1 for 72 h and miR-21 expression was quantified by real-time qPCR. In silico analysis of The Cancer Genome Atlas (TCGA) datasets was performed to explore clinical relevance of miR-21 and target gene expression in PCa.

**Results:** Bioinformatics analysis identified EMT-related genes SPRY2, TGFBR3, FERM2, FOXO1 and EPHA4 as putative targets of miR-21. Increased miR-21 expression was observed in TGF-β1 treated cells compared to untreated. TCGA analysis revealed significant inverse correlations between these genes and miR-21 expression in a PCA dataset (p<0.05). High miR-21 and low SPRY2, TGFBR3 and FOXO1 expressions in PCa patients could be unfavourable for disease-free survival.

**Conclusion:** Results generated to date suggest that TGF-β and miR-21 can contribute to PCa progression through the regulation of key EMT-related genes. Further investigation of how these interactions affect cell behaviour will improve our understanding of PCa pathology, with potential for identifying biomarkers which can improve prognostic and therapeutic approaches in this disease.

**P12. (Abstract published https://doi.org/10.1038/s41431-019-0494-2).**

**P13. AAV-ophNdil: a promising treatment strategy for Leber Hereditary Optic Neuropathy (LHON)**

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LHON is a debilitating mitochondrial-inherited eye disorder affecting 1/30,000 – 1/50,000 individuals, predominantly young adult males. It is characterised by rapid, painless loss of central vision in one eye, typically followed by loss of vision in the second eye within months. LHON is caused by mutations in one of the mtDNA-encoded subunits of NADH:ubiquinone oxidoreductase complex (complex I). A gene therapy approach to replace the ND4 subunit in affected individuals is showing great promise in clinical trials. However, over 25% of patients harbour mutations in other subunits and therefore will not benefit from this approach. Furthermore, the rapid onset of LHON vision loss and the difficulties in diagnosis due to commonality of symptoms with other disorders would enable a mutation-independent treatment, such as that described here, to be applied to all LHON patients and potentially, those with other disorders where mitochondrial dysfunction is involved.

The therapy under development uses a nuclear yeast gene, NADH-quinone oxidoreductase (Ndil), that encodes a single subunit complex I equivalent and is therefore mutation independent. AAV2/2-ophNdil, a codon optimised Ndil, significantly protected retinal ganglion cells (RGCs; p<0.01) in a rotenone-induced murine model of LHON. RGCs are the cells primarily affected in LHON and are critical for vision. Here we explored whether the observed RGC rescue was sufficient to preserve mouse vision. Indeed, retinal function was significantly greater in AAV2/2-ophNdil treated mice, as assessed by optokinetics (OKR; p<0.001). Furthermore, measurement of the photopic negative response (PhNR), a direct measure of RGC function, also demonstrated significant improvement (p<0.01).

**P14. Unravelling the role of the Dihydrofolate reductase 2 gene through examination of the human proteome**

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The dihydrofolate reductase gene family consist of five highly homologous genes that are found to be dispersed across the human genome. The Dihydrofolate reductase (DHFR) gene is the most well-known gene of this family as it encodes a key enzyme involved in One-Carbon Metabolism (OCM). This ubiquitously expressed enzyme initially reduces dietary folic acid to dihydrofolate (DHF) and subsequently breaks down DHF into the active form of folate, tetrahydrofolate (THF) in the cytoplasm and nucleus. THF supplies one-carbon groups that are required during multiple cellular reactions, such as purine / thymidylate synthesis and methylation. This supply is particularly important during early embryonic development. It is reported that mature mRNA belonging to the DHFR gene inserted itself back into the genome resulting in several intronless duplicates. This reintegration event has been found to be primate specific and the human DHFR2 retrogene arose from one of these events.

It was initially thought that the DHFR2 gene encodes a dihydrofolate reductase enzyme which is involved in de novo thymidylate synthesis in the mitochondria. However, proteomics analysis of purified human cell mitochondrial fractions using LC–MS/MS did not find any detectable DHFR2 specific peptides. We hypothesise that the overall function of the DHFR2 gene is likely to be much more complex than this. We are using a targeted proteomic approach to detect low abundance DHFR2 specific peptides from whole cell / tissue lysate from a range of cell and tissue types to understand the functionality of this novel human retrogene.

**P15. DHFR2, a long non-coding RNA candidate for regulation of one-carbon metabolism**

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Long non-coding RNAs (lncRNA) are a relatively new class of RNA that appear to play a regulatory role in gene control. While knowledge of their function is in its infancy, research so far sees lncRNA playing important roles in a number of control processes such as transcriptional and post-transcriptional regulation and chromatin remodelling. This new class of RNA is likely to have a role in most, if not all, cellular pathways and dysregulation is likely to occur in complex pathologies including neurological and cardiovascular disorders and cancer. Our research focuses on the DHFR gene family typified by the Dihydrofolate reductase enzyme that forms part of One Carbon Metabolism. This metabolic pathway is supplied with 1Cs from a number of nutrient sources such as the B-vitamin, folate, and has shown to be a central pathway during embryonic development and in cancer pathogenesis.

DHFR2 is a human retrogene and a less well studied member of the DHFR family. It expresses six different annotated transcripts, four of which harbour an Open Reading Frame that potentially encodes a second Dihydrofolate Reductase Enzyme. It is likely that DHFR2’s transcript profile is more complex than this and a family of three long non-coding RNAs are associated with this gene. We hypothesise that several of the DHFR2 RNA isoforms may have a regulatory role as cis-acting and/or trans-acting IncRNAs and we are investigating this using a variety of molecular assays in combination with genetically engineered cell lines that express varying levels of DHFR2.
P16. In silico predictive analysis and evaluation of missense variants in haem biosynthesis genes associated with the acute hepatic porphyrias

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Acute hepatic porphyrias (AHP), including acute intermittent porphyria, variegate porphyria and hereditary coproporphyria are autosomal dominant genetic disorders that can manifest with acute neurovisceral attacks causing serious morbidity. Genetic variants in HMBS, PPOX and CPOX have been identified in the vast majority of biochemically confirmed AHP kindreds, demonstrating variable clinical and biochemical penetrance and expressivity. Genetic analysis is therefore a critical component in the identification of genetically susceptible patients.

The Biochemistry Department, St James’s Hospital, Dublin, operates a national molecular diagnostic service for AHP. One of the key elements in genetic diagnostics is evaluating the pathogenicity of genetic variants and the application of ACMG guidelines has facilitated a more consistent approach in this assessment. However, while functional characterisation is classified as strong evidence of missense variant pathogenicity according to ACMG criteria, in many instances this data is not available for consideration. Consequently, there is a high degree of reliance on multiple in-silico prediction tools to provide supporting evidence in the stratification of missense changes due to single nucleotide variants (SNV). It is recommended that a concordance approach is used when applying these prediction tools.

To enhance the application of in-silico methods to the realm of AHP genetic diagnostics, several established prediction tools and meta-predictor algorithms were benchmarked against functionally validated SNVs associated with the aetiopathogenesis of AHP. This generated a consensus suite of in-silico tools that was subsequently applied to a clinically relevant dataset, while also being used to interrogate large genomic/exomic databases to assess potential AHP prevalence.

P17. Analysis of the role of maturity onset diabetes of the young (MODY) pathway transcription factors in pancreatic cancer

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With a five year survival rate of only 9%, and an average survival of seven months following diagnosis, pancreatic ductal adenocarcinoma (PDAC) has the worst prognosis of all cancers. Recent genome wide association studies (GWAS) and pathway analysis have implicated the maturity onset diabetes of the young (MODY) pathway genes in the development of pancreatic cancer.

PubMed and the NHGRI-EBI catalogue were used to search for GWAS SNPs in MODY genes associated with PDAC. SNPs were prioritized using RegulomeDB, GWAVA (Genome Wide Annotation of Variants), SNPinfo and CRAVAT (Cancer-Related Analysis of Variants Toolkit). From which, MODY pathway genes HNF1A, HNF1B, HNF4G, NR5A2 and PDX1 were found to act as transcription factors (TFs), with the latter 3 displaying differential expression between pancreatic tumour and normal tissue. The binding regions of MODY gene TFs were identified using publicly available CHiP-seq datasets. Through SNP prioritization, we identified 8 GWAS variants in MODY genes for functional validation—rs2816938 (NR5A2), rs1169288, rs2464196 (HNF1A), rs4415872, rs9581943 (PDX1), rs4794758, rs718960 (HNF1B) and rs11618581 (PLUT—PDX1 associated lncRNA). SNPs were located in intergenic, splice donor, intronic, 5′UTR, 3′UTR and missense SNP regions. Genes closest to the binding sites of the MODY pathway TFs were identified. HNF1B TF binding sites/closenest were identified to be implicated in 240 biological processes, involved in multiple pathways, including somatic stem cell population maintenance, cell proliferation and the MAPK, ERK1 and ERK2 pathway.

Prioritized SNPs are being validated using a dual luciferase assay to confirm biological function in PDAC development.

P18. Converting between genome builds: a word of caution for single nucleotide variants

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The human reference genome is a representation of each known base-pair in the human genome and provides a framework from which single nucleotide variants (SNVs) may be identified in next generation sequencing (NGS) studies. The two most recent human genome builds are referred to as GRCh38 (2013) and hg19 (2009), and both are still widely used. Given the high computational cost in aligning sequencing data, several tools have been designed to convert data from one build to another, the most frequently used is liftOver. Many publicly available annotation resources for NGS data (e.g. gnomAD, dbNSFP, CADD) rely on liftOver to allow for integration with data aligned to other builds. To examine the robustness of liftOver, we created input data for every individual base-pair position in each of the reference genome builds. For each build, we converted from the source build (e.g. GRCh38) to the target build (hg19) and back to the source build again (GRCh38) using the liftOver tool, noting sites which passed or failed at each step. We identified approx. 18 million entries on each build that pass both conversions, but which do not map back to their original position, including some which map to a different chromosome. These sites were observed to overlap known regions such as gaps in the genome build, segmental duplications, regions of low mappability, etc. Additionally, we applied the above procedure to SNVs derived from whole genome sequence data to identify similar unstable regions and examine the overlap with the full genome data.

P19. (Abstract published https://doi.org/10.3390/genes8110304).

P20. What’s next in autism genomics? Sharing research progress, potential and opportunities for public involvement

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Genomics is a key feature in the future of healthcare. Challenges to its success include public patient engagement (PPE), genomic literacy and data-complexity. To address this need, TCD’s Neurodevelopmental Disorder Research Group, with the support of PPE specialists HRB-IRC Ignite Team, ran an interactive and informative event for research participants. The event was hosted in a comfortable, accessible venue with a view of the Dublin mountains—an ideal setting to spark conversation. Those who had previously participated in our research studies, whatever their background, were invited to learn, chat and contribute in an informal
setting with genomic and autism researchers. We introduced genomics in autism, shared current research knowledge, and facilitated a conversation between two key groups – researchers and families affected by autism – through a Conversation Café. We included an open discussion on the challenges, the opportunities and the potential use of genomics to drive therapeutics. A key aspect of the event was recording the event, the creative output and media engagement that embodied the essence of the event [https://www.tcd.ie/tmi/AutismGenomics/]. The benefit for the participants was an understanding of autism genomics, a connection with researchers and a voice to shape future research. The impact on health-researchers was a subsequent interest in public involvement in research, the training of a research group that embraces engagement and the generation of knowledge to establish the meaningful ways to continue the conversation. Meaningful PPE is a key ingredient for scientists and clinicians to ensure the success of genomics to drive therapeutics.

P21. (Abstract Withdrawn).

P22. Rare genetic variation in autism; an exome sequencing study

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Background: Autism is a highly heritable complex trait. Rare genetic variants, both inherited and de novo, typically have higher effect sizes and are more penetrant than common variants in the population. Advances in next-generation sequencing technologies enable exploration of genome-wide variation in greater depth than restrictive candidate gene studies and microarray analyses. Whole exome sequencing (WES) facilitates simultaneous investigation of many classes of variation in the coding genome, across the allele frequency spectrum.

Methods: This study applies WES to a cohort of 42 individuals in families affected with autism and other neurodevelopmental disorders, with an aim to identify rare pathogenic variants. WES was carried out using the Nextera Rapid Capture Exome (v1.2) on Illumina NovaSeq6000 and data has been analysed following Genome Analysis Tool-Kit (GATK) Best Practices. Predicted pathogenic rare variants are selected through dbNSFP annotation. Putatively pathogenic variants will be filtered through known autism-associated gene sets, including SFARI and DDD gene lists.

Results: Data will be presented on high-confidence putative pathogenic genetic variants in this cohort, following stringent hard filtration.

Conclusion: Variants emerging from this analysis strategy contribute to the existing evidence supporting association of relevant genes with autism. This analysis serves as preliminary investigation of rare coding variants in this cohort, and will be followed up with wider unrestricted investigations and statistical analysis of rare variant associations.

P23. Circadian rhythms, sleep and autism – identifying the genetic overlap

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Autism Spectrum Disorder (ASD) is one of the most common neurodevelopmental disorders (disorders caused by problems with brain development at an early age). ASD is usually apparent before the age of three years old, and manifests in repetitive and restrictive behaviour and a lack of ability to communicate and interact socially. Sleep problems are the most common co-occurring condition in children with ASD. The majority of children (40–80%) with ASD have sleep problems including delayed sleep onset, poor sleep maintenance and early morning wakening. Sleep disruption contributes to the overall burden and progression of ASD by affecting memory, attention, cognitive function, language acquisition, and daytime behavioural problems. The consequences of ASD are not confined to children; it is a lifelong disorder, but also parents and other family members experience considerable loss of work (education and employment), wellbeing and sleep, thus emphasising the importance of future research that considers sleep within the family context.

The occurrence of ASD in the population is mostly due to genetic influences. The most recent genome wide association study (GWAS) meta-analysis studying 18,381 ASD cases and 27,969 controls found evidence for five common genetic risk loci and seven additional loci shared with other psychiatric disorders. In this largest study of this kind, ASD was shown to be genetically and positively correlated with the morningness chronotype among other phenotypes. The source of this genetic correlation is unknown. Here we report our research investigating the genetic overlap between chronotype, circadian rhythms, sleep timing and ASD.

P24. Assessment of meta-predictor in-silico tools and the variant functional classifier MITER in PPARG

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While NGS has greatly enhanced the capacity to provide genetic diagnostic support services one of its limitations is the degree of uncertainty relating to the functional consequences and clinical relevance of novel variants identified. Guidelines developed by ACMG have proven useful in standardising the classification of variants, with particular emphasis placed on the functional characterisation of putative genetic variants in determining pathogenicity. For many genes functional impact assessments are not readily available and alternative methods including in silico prediction tools and meta-predictors are needed to assess variant pathogenicity. However, more recent use of novel in vitro approaches has facilitated the functional assessment of multiple potential protein variants coded by specific genes.

In this study we compare the meta-predictor tools e.g. REVEL, and a functional classifier programme MITER, derived from a pooled functional assay for genetic variants of PPARG, is examined to determine the extent of concordance on clinical predication for FPLD3, a disorder recapitulating a severe metabolic phenotype with significant morbidity. Preliminary examination of the data using a combination of linear and Random Forest regression models suggests that REVEL lacks correlation with MITER experimental function score ($r^2 = 0.40$). However, further analysis using a combination of meta-predictors and in-silico tools significantly improves the association ($r^2 = 0.77$) leading to a change in PPV from 49 to 72% relative to MITER. Despite refinements leading to the development of meta-predictors using machine learning algorithms, it is likely that combinations of established in-silico tools are required to provide adequate assessment of variants of unknown significance.

P25. Clinical and functional impact of second CNV hits in autism

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Background: Autism is a common neurodevelopmental condition affecting 1 in 65 children in Irish schools. Autism is known to have a genetic basis although it is complex. Copy number variants (CNVs) are a genetic factor that has been identified in autism. A CNV is a structural change in the genome, either a deletion or a duplication. A set of CNV that are found in autism and other neurodevelopmental disorders (NDDs) are known as neurodevelopmental CNV (ND-CN). Although these are associated with autism and other NDDs, carriers may have different clinical outcomes. One possible explanation is that ND-CN carriers have additional CNV in their genome that contribute to their condition and may make the condition more severe. It is also likely that the genes affected by these additional CNV impact on brain processes important in neurodevelopment and brain cell function. Understanding this better would help provide clearer information to patients and families about the outcomes associated with ND-CN. It may also help to identify more about autism’s neurobiology.

Methods: I will study additional CNVs and other SNVs in ND-CN carriers in autism using two publicly available datasets and by hand searching supplementary materials of the published autism genomics studies. I will study if additional CNVs or SNVs impact genes that are implicated in neurodevelopmental clinical outcomes and if they alter brain development or function. The study will provide new knowledge for clinical interpretation of CNVs that may help clinical geneticists provide better care.

Results: Research is ongoing, results will be finalised before presentation.

P26. Health surveillance for children with Down Syndrome, in paediatric departments across the UK

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Down syndrome (DS) is the most prevalent chromosomal disorder worldwide, with an incidence of ~1 per 1000 live births in the UK. DS is associated with an increased risk of multiple health problems throughout the life-course. Routine health surveillance is a key component of DS healthcare and a number of UK institutions provide guidelines. However, there is no gold standard and practice tends to vary according to local practice. This may lead to inconsistent or incomplete care. We aimed to collate and compare local protocols for the routine health surveillance of children with DS, from paediatric departments across the UK. Our findings provide insight into what health surveillance is being performed on the “front line” and inform the development of future guidelines.

All paediatric departments across the UK (N = 458) were contacted via post, e-mail and through mailing lists, requesting information on their local DS health surveillance practices and a copy of their local protocol. Responses were summarised according to key aspects of DS health surveillance and awareness/use of existing national guidelines. 166 questionnaire responses and 64 protocols were received. Our findings suggest that in key areas of DS child health surveillance, UK paediatric departments demonstrate consistency and compliance with national guidelines. However, there remain other important areas of DS child health (e.g. coeliac disease, sleep disordered breathing), where practice is variable and intermittent. These areas correspond with conditions that are poorly represented in current national guidelines. These aspects of health surveillance guidelines may warrant review and revision, and/or better dissemination.

P27. Predictive testing uptake in a tertiary cardiac referral centre

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Background: Inherited cardiac conditions comprising cardiomyopathies and cardiac ion channelopathies predispose to arrhythmias, significant morbidity and sudden death. Next generation sequencing has resulted in identification of numerous causative genes. Predictive testing of unaffected first degree relatives informs management and is a cost-effective method as those that test negative can be discharged from cardiac follow up.

Aim: Investigate the uptake of predictive genetic testing in a tertiary referral centre.

Methods: Data was collected by interrogation of departmental databases and review of molecular genetics diagnostic reports at the CRY unit, Tallaght University Hospital.

Results: In 85 families where a pathogenic or likely pathogenic variant had been detected, 327 individuals came forward for predictive testing. This means that for each proband testing positive, up to four relatives attended for predictive testing. The age range for predictive testing was one month to 89 years. As expected for autosomal dominant disorders; 54% (n = 177) of patients tested positive and 46% (n = 150) tested negative. Of six families that were digenic, three patients tested positive for two pathogenic variants and one patient tested positive for two likely pathogenic variants.

Conclusion: Genetic testing is a useful tool in the management of families with inherited cardiac conditions. Uptake of testing by first degree relatives in eligible families is good. Currently this results in a significant workload for the Clinical Genetics team. By collating and analysing the results of predictive testing in a tertiary cardiac referral centre, we hope to develop a standardised care pathway for the management of these families by the cardiology teams.

P28. Bioinformatic validation of an NGS germline variant analysis pipeline

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Validation of bioinformatic pipelines is an essential part of establishing analysis procedure in the diagnostic laboratory. Here we summarise the validation of a germline variant analysis pipeline performed at the Next Generation Sequencing (NGS) Laboratory at the Mater Misericordiae University Hospital (MMUH). Targeted sequencing data was generated and aligned to GRCh37/hg19, followed by variant calling. Variants were filtered using a virtual gene panel, annotated, scored, and ranked, to identify candidates that may explain a patient’s phenotype. Variant assessment was performed according to standard ACMG guidelines.

Bioinformatic validation included assessment of accuracy, reproducibility, repeatability, comparison to standard, and analytical sensitivity. Clinical samples containing known variants, as well as Genome in a Bottle reference material (RM), were sequenced across multiple sequencing runs. Median on-target percentage was 80.36%,
while 97.79% of target bases achieved ≥20X coverage. Clinical samples showed 100% detection concordance with previously reported variants. Assay sensitivity was calculated to be 99.27%, through genotype concordance analysis (GCA) between RM variants and a high-confidence reference dataset. GCA between repeated RM samples showed a median intra-assay reproducibility of 99.31%, and inter-assay repeatability of 99.43%. To establish a lower limit of variant detection (LOD), two samples were mixed at various ratios and sequenced, and a subset of SNVs and small indels were assessed across both original and admixture libraries. LOD was found to be 10% for homozygous variants, 20% for heterozygous variants. This in-depth validation of bioinformatic analyses was an integral component of the establishing the NGS diagnostic service at MMUH.

P29. Diagnostic yield of next generation sequencing cardiac gene panel testing in families with inherited cardiac conditions

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Background: Inherited cardiac conditions (ICC) comprise cardiomyopathies and cardiac ion channelopathies. Such conditions predispose to sudden cardiac death, hence genetic diagnosis of affected individuals, followed by screening of their at-risk relatives is important to minimise the risk of premature death. Given the genetically heterogenous nature of ICC, next generation DNA sequencing panels are useful to aid genetic diagnosis.

Aim: Investigate the diagnostic yield from cardiac gene panel testing undertaken in families referred to a specialist cardiogenetic family screening clinic between 2014 and 2019.

Methods: Data was collected with respect to clinical indications for testing and genetic test result by interrogation of departmental databases, family charts, and review of molecular genetics diagnostic reports.

Results: We evaluated molecular genetic results from 255 probands. One hundred and forty-three (56%) patients were found to have at least one genetic variant; 26 probands (10%) carried more than one variant. At least one pathogenic variant was identified in 40 patients (16%); at least one likely pathogenic variant in 37 patients (14%), and at least one variant of uncertain significance in 82 patients (32%). The highest yield of actionable variants was in patients with long QT syndrome (42%), while the burden of variants of uncertain significance was in probands with mixed phenotypes (40%). Actionable variants were highest in those aged 30–59 years (31%), though this was not statistically significant compared to other age groups.

Conclusion: The diagnostic yield of pathogenic and likely pathogenic variants in this cohort was 35%, the yield of variants of uncertain significance was 33%, findings that correlate well with international studies.

P30. Molecular autopsy testing in sudden unexplained cardiac death cases from a national specialist inherited cardiac conditions clinic

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Background: Inherited cardiac conditions (ICC) comprising cardiomyopathies and cardiac ion channelopathies predispose to lethal arrhythmias and sudden death. The first indication is often the sudden death of a family member. Molecular autopsy or post-mortem genetic testing may be employed to identify carrier status of causative genes in the deceased to inform clinical management of surviving family members.

Aim: Investigate the diagnostic yield from molecular autopsy testing undertaken from 2007 to 2019 at a national specialist inherited cardiac clinic and examine the implications of such testing on surviving relatives.

Methods: Data was collected by interrogation of departmental databases, family charts, and review of molecular genetics diagnostic reports.

Results: We evaluated 29 individuals affected by sudden death who underwent molecular autopsy. Eleven individuals (38%) were found to have at least one genetic variant. From individuals with single variants (n=9; 31%), one pathogenic, one likely pathogenic and seven variants of uncertain significance (VUS) were detected. The remaining two individuals (7%) carried two VUS each. The diagnostic yield of actionable variants in this cohort was 7%, the yield of VUS was 31%. Pre-symptomatic genetic testing was offered to nine living, first-degree relatives of individuals found to have pathogenic and likely pathogenic variants. From a total of six relatives tested in two families, three were both genotype-positive and clinically affected. From eight individuals with VUS detected and clinical information available, clinical disease was found in three families.

Conclusion: Notwithstanding the low diagnostic yield compared to international studies, each sudden unexplained cardiac death referred represents an opportunity to screen families and prevent a further premature sudden death.

P31. A new way to present the recurrence risk for non-disjunction Down syndrome

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Most Down syndrome occurs due to meiotic non-disjunction, with the remainder due to a chromosome translocation or due to mosaicism. It is long established that the prevalence of Down syndrome increases with increasing maternal age, due to an increased frequency of maternal meiotic non-disjunction. A common referral to a genetic service is of parents who have had a child with meiotic non-disjunction Down syndrome, who are concerned about the risk of another child of the same condition. The data upon recurrence risk for non-disjunctional Down syndrome are derived from American and European prenatal diagnosis studies from the 1970s and 1980s, and the recurrence risk ranges from 7/1,000 pregnancies to 48/1,000 pregnancies. Two independent factors influence recurrence risk. They are the age of the mother when she had her child with Down syndrome (higher recurrence risk with a lower maternal age), and her age at the delivery of a subsequent child (higher recurrence risk with a higher maternal age).

We developed a user friendly colour table based on the data from the UK National Down Syndrome Cytogenetic Register (2005), which
presents the risk of a child with Down syndrome at a specific maternal age, given her age when her child with Down syndrome was born. The table groups the risk into low, medium, and high, as odds or percentages. The table allows clinicians to give more accurate advice to couples who already have a child with non-disjunction Down syndrome. It will be of use in genetic, maternity and GP clinics.

P32. Establishing a high throughput Next Generation Sequencing genetic testing service at the Mater Misericordiae University Hospital

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The Next Generation Sequencing (NGS) Laboratory aims to provide diagnostic germline genetic/genomic testing for Irish patients across a number of specialties including Cardiology, Ophthalmology, Gastroenterology, Haematology, Neurology, Metabolics and Endocrinology at the Mater Misericordiae University Hospital. High throughput capabilities were reached by automation of all components of the workflow, from selection of the test assay through to analysis, and incorporation of the Laboratory Information Management System (LIMS). Due to the complexity of genetic testing, patient consent is crucial and was established as standard. The laboratory workflow includes sample receipt, nucleic acid extraction, library preparation, sequencing and bioinformatic analysis. Quality metrics are recorded and taken into account at all aspects of the process. The implementation of highly sophisticated, automated instruments, such as the Roche MagNA Pure 24 for nucleic acid extraction and the Agilent Technologies Bravo liquid handling system for library preparation, is time consuming and challenging. However, it increases the throughput capabilities significantly as well as the consistency of testing. Finally, the incorporation of the LIMS and how it ensures the full traceability of the specimen from arrival in the laboratory through to release of the finalised report is described in the process.

P33. Phenotypic variability in patients with autosomal dominant Retinitis Pigmentosa due to the Asp477Gly mutation in RPE65

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Purpose: To describe the phenotypic variability seen in Irish autosomal dominant Retinitis Pigmentosa patients attending the Research Foundation at the Royal Victoria Eye and Ear Hospital in whom a heterozygous missense mutation, c.1430G>A, p.Asp477Gly, in RPE65 was identified.

Methods: Members of the families who co-operated in previous molecular genetic studies in our laboratory were clinically assessed at the Research Foundation at the Eye and Ear Hospital Dublin. More recently, patients were recruited as part of our Target 5000 initiative, a collaborative clinical characterisation and genotyping study of inherited retinal degeneration patients in Ireland involving the Research Foundation at the Royal Victoria Eye and Ear Hospital Dublin, the Mater Misericordiae Hospital Dublin, the Belfast Trust and the Ocular Genetics Unit at Trinity College Dublin. Patients were examined with particular regard to their best-corrected Snellen visual acuity, Goldmann perimetry, typically using the IV4e, 14e and O4e targets, Lanthony D15 colour vision testing, measurement of the dark-adapted threshold to an 11° white target presented at 15° above fixation (a retinal locus of relatively equal rod and cone photoreceptor density) and Ganzfeld electrotoretinography using the standards advocated by the International Society for Clinical Electrophysiology of Vision (ISCEV), including recording of pure-rod responses, mixed rod and cone responses, and cone-dominated responses to both 0.5 Hz flashes and 30 Hz flickers. Most patients had colour fundus photographs taken as well as spectral domain optical coherence tomography.

Results: To date, approximately 38 individuals have been ascertained in whom genotyping has confirmed the presence of the RPE65 Asp477Gly mutation. Wide phenotypic variability was noted, not only in age at presentation but also in the degree of compromise of visual function. The age of onset of varied widely, with some individuals being aware of difficulties in low-light environments in the second or third decades whilst others only became aware of such symptoms in the fourth or fifth decades. One individual, who was particularly mildly affected, was referred for investigation when suspicious pigmentary changes were noted by an optician whom the patient had consulted regarding the need for reading glasses due to presbyopia. The degree of visual field loss also showed wide variability. In one mildly affected individual with a paucity of retinal changes but with significantly impaired electroretinographic responses, the mid-peripheral field loss had been ascribed to low tension glaucoma, resulting in drainage surgery. The fundoscopic picture seen in affected individuals varied widely, generally correlating with the severity of symptoms. In the mildly affected individuals the retina appeared superficially normal, with a normal appearing optic disc, macula and retinal vasculature. Intra-retinal pigmentary deposits were visible in many, but not all, patients. These deposits were mainly of the bone-spicule variety, typical of Retinitis Pigmentosa, but some were more ‘clumpy’ or nummular in appearance. More severely affected individuals showed a much more dramatic fundus picture, typified by extensive diffuse chorioretinal atrophy which, in some individuals, bore a superficial resemblance to the fundus features seen in X-linked choroideraemia. Indeed, more than one affected male, where a positive family history was lacking, was referred by an experienced consultant ophthalmologist with this diagnosis.

Conclusions: Biallelic mutations in RPE65 are well known to be causative of a form of Leber Congenital Amaurosis or early onset Retinitis Pigmentosa but are extremely rare. Evidence is emerging that the autosomal dominant Asp477Gly mutation in RPE65 is more frequent, certainly in the Irish population. The phenotypic variability highlighted in our patient cohort presents challenges in clinical diagnosis and management.

P34. Challenges in applying ACMG guidelines for variant assessment in patients with cardiovascular diseases

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Background: The American College of Medical Genetics (ACMG) guidelines define a standardised approach for the classification of variants, the application of which can be difficult. Here we describe some of the challenges experienced by the Next Generation Sequencing (NGS) Laboratory at the Mater Misericordiae University Hospital (MMUH).
Methods: The MMUH NGS Laboratory uses a clinical exome and virtual targeted panels to investigate the underlying genetic causes of cardiovascular diseases. Variant assessment was carried out using Alissa Interpret analysis software. The detected variants were classified using the relevant ACMG criteria where applicable. The application of certain criteria was evaluated.

Results: Here we discuss challenges encountered when assessing variants using the ACMG criteria. The PM1 criterion refers to the location of a variant in a mutational hotspot and/or critical and well-established functional domain. We present examples of variants where a combination of literature evidence and online database resources were used for evaluation of the applicability of this criterion. Furthermore, the application of available co-segregation data (PP1) may be difficult. We provide examples of cases where the logarithm of odds (LOD) score as well as literature evidence, were considered. PP5 criterion using the evaluation of the pathogenicity evidence provided by reputable sources can be complicated. We discuss examples of variant assessment where there is conflicting evidence available.

Conclusion: We provide examples of the need for a multifaceted approach in variant assessment in the cardiovascular diseases.

P35. Establishment of a diagnostic next generation sequencing laboratory: an Irish perspective

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Genetics and Genomics and the integration into patient’s clinical record is transforming clinical practice across medical disciplines. It is increasingly becoming a key aspect of the diagnostic “work-up” and often results in change of management of patients. However, availability of diagnostic genetic testing remains very limited in the Republic of Ireland and diagnostic next generation sequencing (NGS) is unavailable resulting in the majority of genetic tests being sent abroad. The Mater Misericordiae University Hospital (MMUH) has established a purpose-built laboratory to perform diagnostic NGS germline genetic testing. Aspects of the molecular test must be considered when used in a diagnostic setting. The clinical utility of the test was established, along with the analytic performance characteristics and limitations. The test design established at the NGS Laboratory at MMUH will be presented. Key requirements to deliver a clinical genetic/genomic service were identified and explored. Many challenges were encountered while setting up a diagnostic facility including implementation of a quality management system, laboratory information management system, reporting strategy and multidisciplinary team structure. Furthermore, validation data of the test method and test limitation will also be presented. The diagnostic NGS facility established at MMUH will play a vital role in the healthcare of Irish patients and will allow for the development of precision medicine.

P36. Expanding knowledge on Claes Jensen Syndrome with first Northern Ireland family

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Claes Jensen Syndrome is an X-linked recessive intellectual disability syndrome, first reported by Claes S et al. 2000 in a family of 4 males in 2 generations who presented with severe mental retardation, slow progressive spastic paraplegia, facial hypotonia and maxillary hypoplasia. An additional 7 families were reported by Jensen LR et al. 2005 with KDM5C gene (JARID1C) variants with additional features such as aggressive behaviour and short stature. To date <50 families reported in the literature however there is an estimated frequency of 2.8–3.3% of families with X-linked mental retardation with KDM5C gene variants. We report the first family identified in Northern Ireland with 2 affected males with a maternally inherited missense KDM5C gene variant following 3 generation segregation analysis to clarify pathogenicity of variant which confirmed the maternal variant was a de novo event. The 2 affected brothers currently aged 20 and 25 years have the common features of global developmental delay, severe learning disability, moderately short stature, lower limb hypertonia, joint hypermobility and have additional phenotype of low posterior hairline, sleep disturbance, ADHD, facial dysmorphism etc. and the progression of clinical phenotype and facial features from childhood will be presented. The mother presented with mild learning difficulties, iron deficiency anaemia and subtle dysmorphism. The clinical phenotype of the unaffected brothers and maternal grandparents support genetic results confirming these individuals are not gene carriers and will be presented. This family expands the current knowledge of Claes Jensen syndrome and KDM5C gene and the phenotypic progression.

P37. Direct-to-consumer genetic testing: a bibliometric analysis

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Introduction: Direct-to-consumer (DTC) genetic testing is becoming increasingly available. The scope of this bibliometric analysis was to understand the trends in research about DTC genetic testing and to assess the characteristics of the 100 most highly cited manuscripts in this field.

Methods: Clarivate Analytics Web of Science v.5.35 database with the terms (direct-to-consumer AND (genet* OR genom*)) was used to identify indexed literature on DTC genetic testing. The 100 most commonly cited manuscripts were identified and analysed by author, year, journal, country, institution and topic.

Results: The database search yielded 1,018 manuscripts, with numbers published increasing year on year between 2001 and 2020, generating a total of 13,258 citations. The journals in which such articles most commonly appeared included Genetics in Medicine, Journal of Genetic Counseling and Personalized Medicine. The institutions in which the research was conducted were most commonly Harvard (51) and Katholieke Universiteit Leuven (51). The top 100 manuscripts in DTC genetic testing generated 6,612 citations, ranging from 36–344. The majority of the 100 most cited articles were reviews (37), followed by observational studies (30). Six of the 100 most cited articles were qualitative studies. There was only one randomized controlled trial in the 100 most cited manuscripts.

Conclusion: Managing the results of DTC testing is becoming a challenge for clinicians in primary and secondary care. The most highly-cited articles are largely retrospective reviews of practice. Although research on DTC is becoming increasingly popular, there is a scarcity of literature examining validation/veracity of DTC results.
P38. Is telephone genetic counselling as effective as in-person genetic counselling? A meta-analysis of the evidence

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Timely provision of genetic counselling is essential in cancer care, where knowledge of a patient’s underlying mutation status might help direct treatment. Considering a global shortage of trained Genetic Counsellors/Clinical Geneticists, alternatives to face-to-face consultations are considered, including telemedicine. This is particularly relevant in the context of the on-going COVID19 pandemic. Cancer-specific distress may impair the patient’s ability to retain information, impeding provision of informed consent. This systematic review and meta-analysis aimed to determine if telephone-based genetic counselling is non-inferior to in-person genetic counselling in patients undergoing testing of BRCA1 and BRCA2, considering cancer-specific distress and genetic knowledge.

Databases including Medline, Embase, PsycINFO, CINAHL, Scielo, Web of Science, CENTRAL, ProQuest Dissertation & Theses Database, Clinicaltrials.gov, and EU clinical trials register were accessed to identify relevant literature (published/unpublished), using keywords “genetic counseling” and “telephone”. Articles were manually curated and assessed for bias. Fixed and random-effects models were used for the meta-analysis.

Through database searching, 5308 studies were identified, of which four studies were included in qualitative synthesis, and three in quantitative synthesis of results. Meta-analysis showed that telephone-based genetic counselling was non-inferior compared to in-person genetic counselling for the outcomes of cancer-specific distress and genetic knowledge. Sensitivity analysis corroborated the main results. Telephone genetic counselling for BRCA1/2 testing may be an alternative model of delivering genetic services. However, the paucity of the evidence prevents from drawing strong conclusions regarding the generalizability of these results. Further research, including analysis of video-assisted telemedicine is needed to strengthen the conclusions.

P39. All may not be what it seems

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When a family member presents for predictive testing for a familial condition our job is to assess their risk. This commences with an accurate pedigree & copies of familial genetic test results to offer safe predictive testing. As such we rely on information provided by patients. We present a case of a patient requesting predictive testing for cardiomyopathy. Reports (from an accredited International laboratory) on tested relatives were received. Subsequently another first degree relative revealed that one of the siblings had given a false name (that of his brother) when having testing, to avoid negative insurance complications. This information led us to negate all previous family results and start the assessment process from the beginning. The case demonstrates the difficulties that arise when a relative reveals information that contradicts what the clinical genetics team had understood as fact. Trying to prove that the person who was tested was that actual person was not possible. When using phlebotomy, one does not check that the person who we want to get tested is the person who takes a test. Indeed, we do not check that the person who attends the consultation is the person they say they are? The case highlights the importance of clearly communicating the testing process, accuracy of family data and implications of results. Furthermore it reinforces the impact of external factors on patients pursuing genetic testing, like insurance. Additionally it demonstrates the importance of assessing genetic reports and their documented patient identifiers prior to offering cascade testing.

P40. (Abstract Withdrawn).

P41. Integration of Irish rare disease Centres of Expertise in European Reference Networks and care pathway development needs—current state of play

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Background: The development of care pathways aligned to European Reference Networks (ERNs) and accessible to primary care providers, patients, families and carers is considered a priority by national rare disease stakeholders and aligns with Slaintecare objectives. Establishment of National Centres of Expertise (COEs) is key to accurate mapping of national care pathways with local services and defining the appropriate pathways for individual patient access to ERNs and best practice.

Methods: 35 of the most prevalent/relevant rare diseases requiring multidisciplinary care across 18 ERNs were selected from the highest prevalence non-cancer rare diseases in Ireland. We reviewed their current status with regards to the existence of a national COE, availability of Clinical Practice Guidelines (CPG)/Clinical Decision Support Tools through Pubmed, Orphanet and ERN websites, and evidence for an underlying genetic etiology.

Results: The majority 32/35 have a designated national COE mapped to the Irish Orphanet website; 22/35 have an established CPG published within the last 8 years; a limited number 5/35 have a partial care pathway developed to date by the ERN; 30/35 have a significant genetic component associated with Mendelian inheritance patterns in single or multiple disease genes. This highlights the critical role of clinical genetics and genetic counselling services in care pathway provision.

Conclusion: This preliminary audit illustrates the resource planning required to improve the development of rare disease care pathways, in collaboration with primary care and patient stakeholders. This information will enhance local care coordination and provide opportunity for increased implementation of eHealth solutions and remote monitoring.

P42. Why wait to be seen? A cancer family history questionnaire pathway effectively triages cancer referrals

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Increasing demand for under-resourced genetic services, necessitates that only appropriate affected (diagnostic) and predictive high risk patients are accepted to the cancer waiting list (W/L) and offered a timely appointment.
To facilitate this process, a cancer referral can be directed to the Family History Questionnaire (FHQ) pathway instead of placing the patient directly on the W/L.

We undertook an audit of cancer genetic referrals for 22 months from November 2017–August 2019 to assess outcomes from the FHQ pathway and impact on the W/L. During this period an experienced Genetic Counsellor (0.5 WTE) exclusively managed the FHQ pathway.

1287 cancer referrals were received: 238/1287 (18.5%) were placed directly on the W/L. The remaining 1049 were sent a FHQ, of which 796 (76%) were returned. Following team assessment of the FHQ, 362 (35%) were high risk and placed on the W/L (292 diagnostic, 70 predictive).

Of 258 patients unaffected by cancer: 27 were assessed as low risk, 82 were high risk and placed on the W/L (292 diagnostic, 70 predictive).

We aimed to profile the neurobehavioural phenotypes of children/adolescents with NF1 in Ireland, and to examine the correlation between neurobehavioral functioning and severity of clinical phenotype. The patients were reviewed and investigated by Clinical/Geneticists.

### P43. Mapping the neurobehavioural phenotypes of Type 1 Neurofibromatosis (NF1)

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Type 1 Neurofibromatosis (NF1) is clinically recognisable by characteristic neurocutaneous features including café au lait spots, axillary/inguinal freckling, and development of neurofibromata. The clinical phenotype of NF1 is broad, and may include tumour predisposition (optic glioma, breast cancer, GIST, phaeochromocytoma), bony complications (scoliosis, pseudoarthrosis, bony dysplasia) and neurocognitive issues. Individuals with NF1 may demonstrate impaired cognitive functioning, behavioural difficulties, social functioning deficits, anxiety and depression. A high incidence of Autistic Spectrum Disorders (ASD) has been reported in affected individuals.

We aimed to profile the neurobehavioural phenotypes of children/adolescents with NF1 in Ireland, and to examine the correlation between neurobehavioral functioning and severity of clinical phenotype (Riccardi Scale).

Parents of affected children aged 3–18 were invited by letter to participate. 31 affected children were included in the study. Parents rated their children’s behavioural, emotional and communication deficits by completing an online survey. An objective IQ assessment was also undertaken in a subgroup (n=21).

Participants demonstrated a neurobehavioral profile more similar to children with special educational needs than typically developing children. There was a high incidence of challenging behaviour (aggression, hyperactivity) and social skills deficits. Lower average and performance IQs were noted compared to age-matched norms. Seven (23.3%) children screened positive for features of ASD. Clinical severity did not correlate with the neurocognitive variables analysed.

Awareness of neurocognitive as well as physical complications of NF1, along with investment in support services, is required for affected individuals. Further research to explore the impact of behaviour interventions in this population is required.

### P44. Genetic counselling for inherited Retinal Disease: an evolving service

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The Clinical Genetics Centre for Ophthalmology was set up to ensure that Target 5000 Inherited Retinal Dystrophy (IRD) patients receive a full, correctly interpreted explanation of their Genetic testing report through a genetic counselling appointment.

Every patient, prior to genetic counselling, has family history, clinical findings, retinal images and their genetic report reviewed at a weekly multidisciplinary meeting.

157 patients have attended for Genetic Counselling. 34 patients are currently being worked up by the Clinical Genetics team and reviewed at our weekly MDT, and 44 patients (25 families) are waiting to be seen from assessed families. 4 patients recently added to our waiting
Disease causing variants have been found in 57 genes in our cohort. 27 of these genes are unique to individual families in our dataset and for 81% of these families there is only one person affected underlying the importance of wider information sharing for any available natural history or prognostic information. The T5000 have applied to become part of ERN eye. Only likely pathogenic (class 4) or pathogenic (class 5) variants can be acted on clinically. Class 4/5 variants are important to confirm the diagnosis, to enable testing of other family members, for entry onto clinical trials and eventually for eligibility for treatment. Diagnostic reports had been issued up to 4 years before the clinical service was established. An early task of the clinical team was to re-assess the variants on the old reports before counselling. Since August 2019, we have been working from up to date diagnostic reports. A pathway has been developed for those with a class 3 variants (VOUS) so that all possible avenues are utilised to further classify the variant.

91/252 genes on the Trinity research panel are associated with different syndromes, 57 (22%) of our patients have pathogenic variants in genes associated with 7 different syndromes. Careful examination and targeted screening is important to ensure that these patients get optimal management. Since restrictions were imposed Genetic Counselling of non-syndromic cases has taken place online and initial feedback has been positive. Once restrictions are lifted, we will return to face to face meetings with online consultations for those who request it. We plan to extend our service by running much needed specialist MDT clinics for our syndromic patients.

P47. Patient involvement in development of customised care plans for genetically-confirmed Inherited Retinal Degeneration

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Inherited Retinal Dystrophies (IRD) are a leading cause of visual loss in the working-age population. This clinically and genetically heterogeneous group of disorders requires tailored management and personalized action plans at each review. There is often a lack of awareness amongst patients and professionals of all the resources, supports and therapies potentially available to them.

Sample care plans were created for Stargardt’s Disease (the most commonly detected genotypes from our IRD cohort). A template format was created which provides the phenotype (imaging and functional data with report) and genotype (distinguishing known and unknown variants) following appropriate genetic counselling. The relevant current recognised treatments of the condition and co-morbidities are highlighted. Where no active treatment is available this is indicated. Supports (co-ordinated by our Eye Clinic Liaison Officer- ECLO) are recommended. A list of the relevant pre-clinical and clinical studies (including trials) are made available. Natural history graphs were deemed inappropriate to include except by special request. This draft was subject to further review, discussion and change by focus groups comprising patients, patient relatives, advocates, geneticists, genetic counsellors, clinicians and scientists.

This format optimises communication between the ophthalmic healthcare team and the patients affected by IRDs. It should help manage patient expectations in a clear unambiguous manner while informing on the hope for upcoming therapies. The digital and accessible formats are in development.

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