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Abstracts

Abstracts for the 45th Human Genetics Society of Australasia Annual Scientific Meeting, Perth, Western Australia, 24–27 November 2022

Plenaries and Oral Presentations

PLENARY 1
Increasing Diversity in Rare Disease Research: Challenges and Opportunities

Monkol Lek

Yale University School of Medicine, New Haven, CT, USA

The current diagnosis rate in genetic diseases is approximately 40-60%. This rate is disproportionately lower in non-European populations due to the limited amount of supporting data available for variant interpretation and analysis. The resulting increased time for genetic diagnosis impacts a patient's ability to seek proactive disease management, eligibility for gene specific clinical trials and informed family planning decisions. This presentation will highlight research that addresses the challenges and opportunities regarding increasing diversity in rare disease genetics. Firstly, diverse population variant databases such as gnomAD can be used for improved variant interpretation. In addition, gnomAD can be used to estimate disease prevalence in different population groups. Second, deep mutation scanning in disease genes can provide a functional readout for each variant in a gene and is independent of population representation. Third, working in partnership with community-based organization can increase research participation for under-represented minorities. Lastly, funding initiatives such as the pediatric cell atlas that has sample diversity as explicit goals.

PLENARY 2
Genetiquette: First Nations Leadership for Equitable Access to Genetic Testing, Genomics Research and Precision Health

Gregory Pratt

QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

A descendant of the Quandamooka people of Moreton Bay, Greg grew up with the Ghughu Yalanghi people of Cape York, Queensland, Australia. In 2018, he led extensive consultations to develop guidelines for researchers 'Genomic Partnerships: Guidelines for Genomic Research with Aboriginal and Torres Strait Islander peoples of Queensland'. In 2019, Greg led a body of work with communities, partners and stakeholders to develop a suite of genomic health literacy resources. In 2020–2021 his team worked with community-controlled, primary and public hospital and health services to develop an integrated care model for precision medicine at the primary health intersect: 'Integrated Genetic Health Care: Improving Access for Aboriginal and Torres Strait Islander People to Clinical Genetics through Partnership and Primary Health Leadership'. Over the past 3 years, Greg has led more than 50 community engagements and his advice and leadership is sought on national and international committees. Through his presentation, Greg will share insights about the privilege of supporting First Nations Australians to engage in and lead conversations about genomics and precision medicine. He will reflect on the history of First Nations peoples as subjects of research and the justified decision to opt out of genetic and genomic research. He will discuss how developments and an evolution in the ethical, legal and socially responsible conduct of researchers has supported engagement, partnership and leadership by Aboriginal and Torres Strait Islander peoples. Finally, Greg will reflect on the significance and practicality of co-designing solutions that interrogate the promise, practicality and reality of precision health, genetic testing and genomics research.

PLENARY 3
Māori-Led Indigenous Healthcare Genomics in Aotearoa New Zealand

Stephen P. Robertson

Laboratory of Genomic Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand

As genomic tools become more widespread in mainstream medical practice it has become self-evident that its accuracy and precision is heavily dependent on accurate background reference data drawn from relevant populations. The inhabiting of Aotearoa New Zealand by Māori c.7 centuries ago ended one of the longest migrational journeys of any indigenous population on earth – an odyssey characterized by the crossing of latitude and longitude accompanied by strong selective sweeps, small population sizes and bottlenecks with subsequent population expansions. These forces very likely profoundly influenced and shaped the Māori genome through both genetic drift and selection. How different the Māori genome is from other Oceanian genomes is still uncertain. Māori are aware of the healthcare imperative to map and characterize this *taonga* (sacred treasure) but only under conditions that preserve its integrity. The Aotearoa Variome Project (a genome project to characterize variation across modern-day Māoridom) and the Rakeiora Project (a pilot precision medicine project) have both been established as genomic studies seated within Māori ethical frameworks that are distinct and different from much westernized practice. A challenge that lies ahead is whether westernized clinical practice, scientific endeavor

and healthcare resourcing will show themselves to be agile enough to incorporate the clearly enunciated cultural imperatives laid down by Māori communities for the implementation of genomics into healthcare.

PLENARY 4
Stem Cell Gene Therapy to Treat Childhood Dementias — A Sanfilippo Story

Brian W. Bigger

Stem Cell & Neurotherapies, Centre for Genomic Medicine, Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK

There are between 6000–9000 rare diseases described to date and ~250 new ones being discovered every year, and yet our pace of treatment development is far below that of discovery, with only around 480 approved treatments for rare diseases, some of which overlap. Almost half of these diseases are neurological and many affect children. Sanfilippo disease describes four clinically very similar lysosomal diseases (LSDs), caused by four unique genetic defects in lysosomal hydrolases that catabolise heparan sulphate. Affected children often present with developmental delay and recurrent ENT infections, typically displaying hyperactivity, behavioral and sleep issues and progressive loss of cognitive and later motor milestones with death typically in late teens in severe forms. In this talk, I will discuss the rationale for using Haematopoietic stem cell (HSC) gene therapy for lysosomal storage diseases affecting the brain and the pros and cons. The approach relies on gene modifying blood stem cells to over express enzyme, typically using lentiviral vectors. Monocytes traffic to and engraft in the brain, delivering increased doses beyond the blood brain barrier. I will describe the state of the art for HSC gene therapy including work from our own lab on HSC gene therapy for Sanfilippo (mucopolysaccharidosis types IIIA and IIIB) and MPSII Hunter disease, exploiting some of the potential avenues for HSC gene therapy treatment likely to be tested in the clinic over the next few years.

PLENARY 5
New Developments in the Identification and Interpretation of Clinically Actionable Causal and Modifier Variation

Elizabeth Worthey

The University of Alabama at Birmingham, Birmingham, AL, USA

When an individual presents with what is believed to be a genetic disorder, the patient, parents, and/or providers have many questions including: What is the definitive diagnosis? What caused this disease? Who else is at risk? What can we expect in the short and long-term? What are the existing treatment options? How safe are these options? And, when no good treatment options exist (as is often the case for rarer or complex diseases): What can we do to drive identification or development of novel or repurposed treatments? Finding the answer to these questions requires the development and/or application of molecular and computational biology tools and methods. It also requires the consideration of both causal and modifier molecular variation. Such advances are of critical importance in timely and accurate generation of knowledge aimed at delivering diagnostic, prognostic, and therapeutic information to aid in the treatment of patients with rare and not so rare diseases. This talk will provide details related to a number of personalized medicine projects ongoing within the Center for Computational Genomics and Data Sciences and collaborating groups, at both UAB and elsewhere.

PLENARY 6
Better Faster Cheaper — Choose Two? Or the Quest for the Perfect Clinical Genomics Service

Karin Kassahn

SA Pathology, Adelaide, SA, Australia

The last 10 years has seen a rapid uptake of new genomics tests in diagnostics and pathology with no sign of new test development slowing down in the near future. We provide a statewide genomics service in South Australia and over this time have seen immense changes in what tests we offer and how we deliver these services. Remember the 'perfect' test that no one ordered? Or 'just' updating the pipeline to hg38 only to find problems with the reference itself ... We have circled from many to few to many kits, all in an effort to optimise cost versus clinical utility versus lab-ease-of-use verseus ... sanity? Now, with whole genomes, are we about to break the internet? And anyway, if two labs did this test, would they get the same result? In this talk, I will reflect on our laboratory's journey, responding to changing clinical needs and how we have attempted to meet them. I will draw on examples and lessons learnt from our bioinformatics and service development team. And because we can, why not be bold and share our vision for the next ten years. I am sure reality will be nothing like it!

PLENARY 7
The Complicated and Little-Explored World of Histone Genetics

Louise Bicknell

Department of Biochemistry, University of Otago, Dunedin, New Zealand

Chromatin is essentially an array of nucleosomes, each of which consists of the DNA double-stranded fiber wrapped around a histone octamer. This organization supports cellular processes such as DNA replication, DNA transcription, and DNA repair in all eukaryotes. Chromatin has become a major focus in developmental disorders and cancer, with chromatin remodellers, writers and erasers modifying histones to control gene expression and cell fate during development and cell functioning. However, histones themselves have not been so heavily focused on. Human histone H4 is encoded by 14 canonical histone H4 genes, all differing at the nucleotide level but encoding an invariant protein. We have recently identified a large cohort of individuals with de novo missense variants in six of fourteen H4 genes, which have a variable neurodevelopmental condition. Our findings establish a broader involvement of H4 variants in developmental syndromes and suggest variants in such genes could play a role in more genetically complex conditions of brain development.

PLENARY 8
The Genetic Basis of Severe Childhood Speech Disorder

Angela Morgan

Murdoch Children's Research Institute, Melbourne, VIC, Australia, University of Melbourne, Melbourne, VIC, Australia, Royal Children's Hospital, Melbourne, VIC, Australia

Childhood apraxia of speech (CAS), the prototypic severe childhood speech disorder, is characterized by motor programming and

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planning deficits. Children with CAS have difficulty producing speech sounds accurately, in the right sequence, and with correct prosody. Knowledge of the etiology of CAS was limited for decades, and largely since the condition was first recognized 70 years ago. The first gene associated with CAS, in the absence of intellectual disability, was FOXP2, identified in 2001. With advances in genetic sequencing and analysis, there has been an exponential leap in our understanding of the genetic bases of CAS in recent years. It is now established that CAS has a strong genetic basis, with a monogenic pathogenic variant identified in a third of cases, with 34 single genes implicated to date. A critical role for chromatin organization and DNA binding has been identified in typical child speech development. Further, CAS-susceptibility genes are shown to be co-expressed during brain development, suggesting they are part of specific biological pathways. The increasing overlap between genes conferring risk for a range of neurodevelopmental disorders, including CAS, epilepsy, autism spectrum disorder and intellectual disability, has also been confirmed. Notably, however, patients may also have CAS in isolation without comorbid conditions. Understanding the etiological basis of CAS is a critical starting point for unravelling the biological basis of communication, a unique human skill. From a clinical perspective, new knowledge is important to end the diagnostic odyssey, identify comorbidities and ensure patients are poised for precision medicine trials.

PLENARY 9
Ten Years of Disease Gene Discovery and Diagnostics in Neurogenetic Diseases

Gianina Ravenscroft

Harry Perkins Institute of Medical Research, Perth, WA, Australia, and Centre for Medical Research, University of Western Australia, Perth, WA, Australia

More than 500 genes listed in the Neuromuscular Disorders Gene Table have now been associated with neuromuscular diseases. Nevertheless, comprehensive gene panel or clinical exome testing fails to identify a precise molecular diagnosis in >50% of probands. Both the Perth Neurogenetics Research Group and the diagnostic Neurogenetics Unit at PathWest were early adopters of short-read next generation sequencing. This led in the last decade or so, to identification and characterisation of >15 novel human disease genes and extended the phenotype associated with multiple known disease genes. The success of this research has relied heavily on the close collaboration between the Neurogenetic Unit, (a national referral centre for neuromuscular disease molecular diagnosis), the Perth research groups, the Royal Perth Hospital Neurogenetic Clinic, other WA clinicians, and national and international networks. This collaboration has a long history of researching early, including in-utero onset muscle diseases. More recently it has expanded to include long-read, and targeted long-read, sequencing researching late-onset neurodegenerative disorders. Notably, two novel pathogenic repeat alleles in RFC1 causing CANVAS and prevalent in our Asian and Oceanian geographic region have been identified. This presentation will cover key findings and learnings over the past decade. The critical roles of regular multidisciplinary team meetings bringing together the lexicons of the clinic, genetics and pathology and accurate phenotyping and functional genomics in these discoveries and their accelerating pace. This internationally interconnected research has led to diagnostic improvements and an accurate genetic diagnosis for many patients and families across Australia and around the world.

PLENARY 10
Rapid Rare Disease Diagnosis on a National Scale: An Integrated Multi-Omic Approach

Sebastian Lunke[1,2,3], Sophie E. Bouffler[3], Chirag V. Patel[4], Sarah Sandaradura[5,6], Meredith Wilson[5,6], Jason Pinner[7,8], Matthew F. Hunter[9,10], Christopher P Barnett[11,12,13], Mathew Wallis[14,15], Benjamin Kamien[16], Tiong Y Tan[1,2], Mary-Louise Freckmann[17], David Francis[1], Belinda Chong[1], Dean Phelan[1], Karin S Kassahn[12,13], Thuong Ha[12], Song Gao[12], Stefanie Eggers[1], Simon Sadedin[1,2,18], Kirsten Boggs[5,7], Ana Rakonjac[5,7], Gemma R Brett[1,2], Michelle G. de Silva[1,2,18], Amanda Springer[9,10], Michelle Ward[14], Kirsty Stallard[11], Cas Simons[18], Thomas Conway[18], Katrina M. Bell[1], Andreas Halman[18], Alison Compton[2,18], David Thorburn[2,18], John Christodoulou[2,3,18] and Zornitza Stark[1,2,3]

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Background: Whole genome sequencing (WGS) is increasingly deliverable at scale and speed across healthcare systems. However, the improved analytical performance and ever earlier test initiation exacerbate interpretive challenges. Extended bioinformatic analysis and integration of multi-omic approaches hold the promise to optimise diagnostic performance. *Methods:* Trio ultra-rapid WGS was performed in a national cohort of 290 critically ill pediatric patients with rare disease, ascertained prospectively between January 2020 and January 2022. Undiagnosed patients underwent research-based RNA sequencing and extended bioinformatic and research analyses. Functional assays and targeted orthogonal tests were employed in selected cases. *Results:* Ultra-rapid WGS resulted in a diagnosis in 135 patients (47%), with an average time to clinical report of 2.96 days. Of the 155 patients remaining undiagnosed, 21 (14%) were subsequently diagnosed. RNA sequencing identified three diagnoses related to non-coding variants and contributed to classification of five variants. Functional assays, including clinical and bespoke assays, secured ten further diagnoses, and evolution of the clinical phenotype resulted in three more. Extended bioinformatic analyses identified one triplet expansion disorder and a transposon. Four diagnoses were made using orthogonal tests, highlighting limitations of current WGS pipelines in identifying uniparental disomy, variants in regions with poor mappability, and mosaic variants. Further studies are underway in four novel gene candidates. *Conclusion:* We demonstrate the integration of multi-omic approaches in a broad clinical

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cohort of rare disease patients to rapidly optimise WGS diagnostic yield, arguing for increased integration of these approaches into mainstream diagnostic practice.

PLENARY 13
Beyond Clinical Utility: Assessing Patient-Reported Benefits from Genomic Results

Erin Turbitt[1], Jennefer N. Kohler[2], Frank Angelo[3], Ilana M. Miller[4], Katie L. Lewis[5], Katrina A.B. Goddard[6], Benjamin S. Wilfond[7], Michael C. Leo[6] and Barbara B. Biesecker[8]

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Background: People report benefits of receiving genomic information, even in the absence of medically actionable options. It is critical to understand, define and measure such benefits to enable the equitable application of genomics in medicine. There is a need for improved clarity on how to define and measure such personal utility in genomic medicine. *Aim:* We aimed to construct and psychometrically evaluate a scale to measure the personal utility of genomic results – the PrU. *Methods:* We used an operational definition of personal utility that we produced from our systematic literature review and using data from our Delphi survey. This definition formed the basis from which we developed the PrU that was piloted with 24 adults enrolled in a genome sequencing research study. We administered the PrU to adults enrolled in one of two Clinical Sequencing Evidence-Generating Research (CSER) studies after receiving genomic results ($n = 841$). CSER studies prioritized the engagement of populations that are traditionally underrepresented in genomics research. *Results:* Respondents identified as White (37.7%), Black (28.5%), and/or Hispanic/Latino (21%) and most were female (77.2%). A principal-axis factor analysis suggested a three-factor solution. We labelled the three factors 'self-knowledge and control' ($\alpha = .94$), 'reproductive planning' (($\alpha = .89$), and 'practical benefits' ($\alpha = .87$). *Conclusion:* We have demonstrated the reliability and validity of three subscales of personal utility from genomic test results that converge on the broader concept. The ability to measure the dimensions of personal utility in genomic medicine contributes to understanding patient experiences and guiding the implementation of genomics in clinical care.

PLENARY 15
Relationship and Reproductive Experiences and Outcomes for Young People with an Inherited Cancer Syndrome

Laura Forrest,[1,2], Rowan Forbes Shepherd[1], Louise Keogh[3], Allison Werner-Lin[4], Martin Delatycki[5,6,7], Cass Hoskins[1], Erin Tutty[1], Rebecca Purvis[1], Mary Shanahan[1], Alex Boussioutas[1], Mandy Lobley[6], Sunni Kasprowicz[6], David Amor[6], Alisha Harpur[1], Mary-Anne Young[8], Lucinda Salmon[9], Linda Warwick[10], Jo Burke[11,12], Rachel Williams[13,14,15], Catherine Beard[1], Rebecca D'Souza[16] and Paul James[1,2]

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Background: Young people with an inherited cancer syndrome (ICS) traverse their formative developmental years negotiating complex and significant decisions about genetic testing, cancer risk management, and reproduction. *Aim:* To investigate the impact of having an ICS on young people's reproduction and partnering. *Methods:* An exploratory sequential mixed methods study was undertaken between 2014 and 2022. Qualitative data were collected using semi-structured interviews with young people with and at risk of an ICS. Informed by interpretive description, team-based, reflexive thematic analysis was undertaken. Quantitative data were collected using an online survey with a case-control design from June 2019 to May 2021. Eligible participants were young women who had predictive BRCA1/2 testing. Outcomes included childbearing, relationship status, and intimacy. Descriptive and inferential statistics were used; p values $< .05$ were considered statistically significant. *Results:* Eighty-three young people participated in interviews exploring lived experiences of ICS and 21 described their experiences of using preimplantation genetic testing (PGT) for an ICS. Participants' sense of genetic responsibility influenced uptake of risk reducing surgeries and tempered their family formation, including reproductive decision-making. 579 women participated in the survey (62.0% BRCA1/2 positive; 38.0% BRCA1/2 negative). More women who were BRCA1/2 positive had children compared to those who tested negative ($p = .045$), with these women more likely to have children after genetic testing ($p = .03$) and have more children after genetic testing ($p = .01$). *Conclusion:* Living with an ICS modifies normative experiences and outcomes for young adults. These findings contribute to the evidence-base to inform long-term follow-up for young people with ICS.

PLENARY 16
The Genetic Basis of Severe Childhood Speech Disorder

Angela Morgan

Murdoch Children's Research Institute, Melbourne, VIC, Australia, University of Melbourne, Melbourne, VIC, Australia, Royal Children's Hospital, Melbourne, VIC, Australia

Childhood apraxia of speech (CAS), the prototypic severe childhood speech disorder, is characterized by motor programming and planning deficits. Children with CAS have difficulty producing speech sounds accurately, in the right sequence, and with correct prosody.

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Knowledge of the etiology of CAS was limited for decades, and largely since the condition was first recognized 70 years ago. The first gene associated with CAS, in the absence of intellectual disability, was FOXP2, identified in 2001. With advances in genetic sequencing and analysis, there has been an exponential leap in our understanding of the genetic bases of CAS in recent years. It is now established that CAS has a strong genetic basis, with a monogenic pathogenic variant identified in a third of cases, with 34 single genes implicated to date. A critical role for chromatin organization and DNA binding has been identified in typical child speech development. Further, CAS-susceptibility genes are shown to be co-expressed during brain development, suggesting they are part of specific biological pathways. The increasing overlap between genes conferring risk for a range of neurodevelopmental disorders including CAS, epilepsy, autism spectrum disorder and intellectual disability, has also been confirmed. Notably, however, patients may also have CAS in isolation without comorbid conditions. Understanding the etiological basis of CAS is a critical starting point for unravelling the biological basis of communication, a unique human skill. From a clinical perspective, new knowledge is important to end the diagnostic odyssey, identify comorbidities and ensure patients are poised for precision medicine trials.

PLENARY 17
Clinical Benefit for Genome Profiling Prostate Cancer Health Disparities

Vanessa M. Hayes

Ancestry & Health Genomics Laboratory, Charles Perkins Centre, University of Sydney, Sydney, Australia

Prostate cancer presents clinically with significant geo-ancestral disparity. Within the USA, African American men are at 2.7 to 5-fold greater risk of a prostate cancer associated mortality than Americans of European or Asian ancestry, respectively. Geographically, mortality rates in Sub-Sharan Africa are 2.5-fold greater than global averages, 2.7-fold greater than Australia/New Zealand. The link between lethal prostate cancer and African ancestry or being from Africa, suggests genetic or non-genetic factors, or a combination. The Ancestry & Health Genomics Laboratory at the University of Sydney, is using the power of genomics to unravel both genetic and non-genetic drivers, generating tumor and blood matched data for men from Africa and directly comparing technically and computationally matched profiles with non-African Australians. Our hypothesis, while germline data determines ancestral risk, it is the tumour genome data that holds to the key to identifying non-genetic contributing exposures. In a first-of-its-kind study for Africa, the team identified, along with South African colleagues, a novel spectrum and broader range (including structural variation) of African-specific oncogenic drivers and potential therapeutic targets, describes a new ancestral-specific all mutational prostate cancer taxonomy capable of predicting clinical outcome, identifies mutational signatures of potential nongenetic contributions to aggressive disease in African men, while addressing significant differences in germline risk profiling. Through a new consortium dedicated to African inclusion, the team is hoping to lead change in prostate cancer genetic research, through a focus on health disparity and the value of genomic advances not only adding genetic value, but also nongenetic value through the identification of exposure driven patterns of somatic variation.

ORAL 1
Insights Into the Genetics and Pathomechanisms of Cortical Dysplasia by Analysis of Patient-Derived Brain Tissue

Matthew Coleman[1,2], Katherine B. Howell[1,2,3], Colleen D'Arcy[3], A. Simon Harvey[3], Wirginia Maixner[3], Sarah E.M. Stephenson[1,2], Wei Shern Lee[1,2], Richard J. Leventer[1,2,3], Christopher A. Reid[4] and Paul J. Lockhart[1,2]

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Background: The link between focal cortical malformations and epilepsy is well established, especially among individuals with focal cortical dysplasia type II (FCDII) due to somatic mutations in mTOR pathway genes. Although the mechanisms underlying seizures remain unclear, we and others have demonstrated abnormal cells are abundant at the center of the dysplasia. Moreover, a recent study showed ectopic expression of nucleotide-gated potassium channel isoform 4 (HCN4) in abnormal cells mediated seizure generation in a mouse model of tuberous sclerosis. *Aim:* To investigate the genetic and molecular characteristics of abnormal cell types in FCDII and relationship to seizure generation. *Methods:* Targeted panel deep sequencing was performed on brain-derived genomic DNA from 23 individuals with drug-resistant focal epilepsy and FCDII. Histopathology was performed and single cell laser capture was utilized to isolate abnormal cell types. *Results:* Pathogenic variants were identified in eleven individuals in genes associated with the mTOR pathway (*MTOR*, *DEPDC5*, *NPRL3* and *RHEB*). Somatic variant load directly correlated with the size of the dysplasia, and laser capture microdissection showed enrichment of pathogenic variants in abnormal cell types. Histopathologic analysis of brain tissue from nine individuals with pathogenic variants in six different mTOR pathway genes demonstrated elevated HCN4 in abnormal cell types. *Conclusion:* Our results suggest that the abnormal cell types that characterize mTORopathies are enriched for somatic variants and display dysregulated and overactive HCN4-mediated channel activity. Therefore, HCN4 may be a potential therapeutic target for seizure control in patients that are not candidates for surgical resection of dysmorphic tissue.

ORAL 2
Germline Variants in Tumour Suppressor Fbxw7 Lead to Impaired Ubiquitination and a Novel Neurodevelopmental Syndrome

Sarah E.M. Stephenson[1,2], Gregory Costain[3,4,5], Laura E.R. Blok[6], Michael A. Silk[7,8], Thanh Binh Nguyen[7,8], Xiaomin Dong[1], Dana E. Alhuzaimi[1], James J. Dowling[9,10], Susan Walker[10,11], Kimberly Amburgey[5,9], Robin Z. Hayeems[12,13], Lance H. Rodan[14,15], Marc A. Schwartz[16,17,18,19], Jonathan Picker[14,20], Sally A. Lynch[21], Aditi Gupta[22,23], Kristen J. Rasmussen[24], Lisa A. Schimmenti[25,26,27], Eric W. Klee[22,23,24,25], Zhiyv Niu[24,25], Katherine E. Agre[25], Ilana Chilton[28], Wendy K. Chung[28,29], Anya Revah-Politi[30], P.Y. Billie Au[31], Christopher Griffith[32], Melissa Racobaldo[32], Annick Raas-Rothschild[33,34], Bruria Ben Zeev[33,35], Ortal Barel[36,37], Sebastien Moutton[38,39,40], Fanny Morice-Picard[41], Virginie Carmignac[40], Jenny Cornaton[39], Nathalie Marle[42], Orrin Devinsky[43], Chandler Stimach[44], Stephanie Burns Wechsler[45], Bryan E. Hainline[46], Katie Sapp[46], Marjolaine Willems[47], Ange-line Bruel[48], Kerith-Rae Dias[49,50], Carey-Anne Evans[49,50], Tony Roscioli[49,50,51], Rani Sachdev[51,52], Suzanna E.L. Temple[49,50,51], Ying Zhu[49,53], Joshua J. Baker[54], Ingrid E. Scheffer[1,2,55], Fiona J. Gardiner[55], Amy L. Schneider[55], Alison M. Muir[56], Heather C. Mefford[56], Amy Crunk[57], Elizabeth M. Heise,[57], Francisca Millan[57],

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Background: Neurodevelopmental disorders are highly heterogenous conditions resulting from abnormalities of brain architecture and/or

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function. *FBXW7* (F-box and WD repeat domain containing 7), a recognized developmental gene and tumour suppressor, has been shown to regulate cell cycle progression, cell growth and survival by targeting substrates including CYCLIN E1/2 and NOTCH for degradation via the ubiquitin proteasome system. *Methods:* We used a genotype-first approach, global data sharing platforms and clinical deep phenotyping to identify individuals with *FBXW7* variants. We undertook *in silico* protein modelling, expression of recombinant *FBXW7* missense variants in cultured HEK293T cells, and pan-neuronal knockdown of the *Drosophila* ortholog, *ago*, to understand their functional impact. *Results:* We identified 35 individuals harbouring germline *FBXW7 de novo* and inherited monoallelic chromosomal deletions, nonsense, frameshift, splice site and missense variants associated with a neurodevelopmental syndrome. The *FBXW7* neurodevelopmental syndrome is distinguished by global developmental delay, borderline to severe intellectual disability, hypotonia and gastrointestinal issues. Brain imaging detailed variable structural abnormalities affecting the cerebellum, corpus callosum and white matter. A crystal structure model of FBXW7 predicted missense variants clustered at the substrate-binding surface of the WD40 domain and may reduce FBXW7 substrate binding affinity. Expression of recombinant *FBXW7* missense variants in cultured cells demonstrated impaired CYCLIN E1 and CYCLIN E2 turnover. Pan-neuronal knockdown of the *Drosophila* ortholog, *ago*, impaired learning and neuronal function. *Conclusion:* Collectively, we present evidence of another F-Box protein-related phenotypically variable neurodevelopmental disorder associated with monoallelic variants in *FBXW7*, expanding the genetic landscape of intellectual disability.

ORAL 3
Defining the Phenotype of White-Kernohan Syndrome

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Background: The DNA damage binding protein 1 (DDB1) is part of the CUL4–DDB1 ubiquitin E3 ligase complex (CRL4), which is essential for DNA repair, chromatin remodelling, DNA replication, and signal transduction. In 2021, we reported eight unrelated individuals, identified through Matchmaker Exchange, with *de novo* monoallelic variants in the MMS1 domain of *DDB1*, including one recurrent variant in four individuals, and showed that cells derived from affected individuals had altered DDB1 function resulting in abnormal DNA damage signatures and histone methylation following UV-induced DNA damage. *Aims and Methods:* We now present detailed clinical findings in twelve affected individuals and delineate the evolution of the phenotype over time using detailed clinical data, serial growth measurements and photographs. *Results:* The key features are hypotonia, mild to moderate intellectual disability, and similar facies including horizontal or slightly bowed eyebrows, deep-set eyes, full cheeks, a short nose, and large, fleshy, and forward-facing earlobes, demonstrated in the composite face generated from the cohort. Digital anomalies including brachydactyly and syndactyly were common. While weight was typically in the low normal range in early childhood, all individuals in the cohort over the age of ten years had obesity. Loss-of-function variants in genes encoding the CRL4 complex components CUL4 and PHIP have been reported to cause syndromic intellectual disability with hypotonia and obesity and we contrast the features in these three emerging neurodevelopmental-obesity phenotypes mediated by disruption of the CRL4 ubiquitin ligase pathway. *Conclusion:* White-Kernohan syndrome is a distinctive neurodevelopmental phenotype within the CRL4 complex disorders, notable for its dysmorphic features and the development of obesity in adolescence.

ORAL 4
RFC1 in an Australasian Neurological Disease Cohort: Extending the Genetic Heterogeneity and Implications for Diagnostics

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Background: Cerebellar ataxia, neuropathy and vestibular areflexia syndrome (CANVAS) is a progressive late-onset, neurological disease associated with biallelic pentanucleotide expansions in intron 2 of the *RFC1* gene. *Aim:* The aims of this study were to determine the contribution of pathogenic *RFC1* expansions to neurological disease within an Australasian cohort, further investigate the heterogeneity exhibited by the locus and to provide a workflow for

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comprehensive *RFC1* testing in diagnostic laboratories. *Methods*: A combination of flanking and repeat-primed PCR (RP-PCR) was used to screen a cohort of 243 Australasian neurological disease patients. Patients whose data indicated gaps within expanded alleles following RP-PCR underwent targeted long-read sequencing to identify novel repeat motifs at the locus. To increase diagnostic yield, additional probes at the *RFC1* repeat region were incorporated into the PathWest targeted neurological disease gene panel to enable first pass screening of the locus. *Results:* Within the Australasian cohort we detected known pathogenic biallelic expansions in 15.6% ($n = 38$) of cases. We also identified five novel repeat motifs in expanded alleles using targeted long-read sequencing. We showed that short read sequencing can be used to reliably screen for the presence or absence of biallelic *RFC1* expansions. *Conclusion:* Our results show that *RFC1* pathogenic expansions make a substantial contribution to neurological disease in the Australasian population and further extend the heterogeneity of the locus. To accommodate the increased complexity, we have devised a multi-step workflow utilising both targeted short and long-read sequencing to achieve a definitive genotype and provide accurate diagnoses for patients.

ORAL 5
An Interactive, Online Education Program to Prepare the Australian Workforce to Incorporate Rapid Genomics in Pediatric Critical Care

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Background: Rapid genomic testing is increasingly becoming standard-of-care for critically ill pediatric patients with rare disease. *Aim:* This study aimed to develop, deliver, and evaluate an interactive online genomics education program for non-genetic specialists working in neonatal and pediatric critical care, which would increase competence (knowledge, skills, and attitudes) and confidence in genomic medicine. *Methods:* The education program was co-designed with experts in clinical genetics, critical care, genetic counseling, genomics education and evaluation. Program implementation and outcomes were evaluated quantitatively using surveys at baseline, post-workshop and three-month follow-up, online module learner analytics and quizzes, and workshop polls. *Results:* The program comprised of four online modules and a virtual, case-based workshop. 270 people registered – intensivists (45%), pediatricians (33%), clinical geneticists (5%), genetic counselors (6%), nurses (9%), and allied health professionals (2%) – from over 20 sites around Australia. 8% of registrants were from overseas. 175 accessed online materials and 160 attended one of five workshops held in 2021. Gains in knowledge and skills were seen for all professions, for all genomic test result types. Confidence to practise genomics increased (average 50% to 82%). At follow-up, 71% reported performing more genomics-related activities. *Conclusion:* An interactive, wholly online education program can positively impact genomic competence, confidence, and practice, and support equitable access to education for geographically dispersed healthcare workforces. Our sustainable approach addresses current unmet needs for genomics education and the modular design can translate to other national and international settings as use of genomic testing increases.

ORAL 6
The National Genomic Autopsy Study: A Summary of Results, Outcomes and Instructive Families from 254 TRIOS/QUADS.

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Background: The cause of pregnancy loss and perinatal death remains unexplained in at least 25% of cases, despite a high perinatal autopsy rate in Australia. The genomic autopsy study is a national collaborative study aimed at determining the cause. *Aim:* To use WES and WGS to identify genetic causes of fetal/newborn abnormalities that result in termination of pregnancy, death in utero or in the newborn period, in view to providing families with answers regarding cause and likelihood of recurrence. *Methods:* WES and/or WGS was performed, after non-diagnostic microarray. Prospective cases are families referred to the Genetics unit (parent-fetus trios/quads). High priority cases are consanguineous families, fetuses with multiple malformations, and unexplained fetal/newborn death. Statistical, bioinformatic and experimental laboratory techniques are used to confirm causality of variants. *Results:* 254 prospective trios (228) or quads (26) have been recruited and sequenced from around Australia. 121/254 (47.6%) are either solved or have a strong candidate gene identified. Of the 121 solved families, 60 (50%) have been clearly solved by identification of a pathogenic mutation in a known gene. An additional 37/121 (30%) have a novel VUS in a known disease gene. Numerous instructive cases involving numerous genes (e.g., KIF14, SIK3, LAMC3, ARSL) will be presented. *Discussion:*

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Extensive genomic investigation of pregnancy loss and perinatal death should be offered as standard care, particularly when congenital abnormalities are present. Many families have benefitted from a clear diagnosis which could not be made on clinical grounds. Fetal genetic causes of late stillbirth are rare.

ORAL 7
Evaluation of the NSW Newborn Screening Pathway for SMA

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Background: Spinal Muscular Atrophy (SMA) is a progressive neuromuscular disease causing muscle weakness, paralysis and respiratory insufficiency. New therapies have emerged with best outcomes if delivered prior to symptom onset. Newborn screening can detect homozygous loss of exon 7 in the survival of motor neuron 1 (*SMN1*) gene. As *SMN2* gene copy number is a significant predictor of the clinical phenotype, which also influences therapeutic decision-making, *SMN2* gene copy number determination is also part of the screening protocol. *Aim:* To evaluate and report the performance of NSW's newborn screening pathway for SMA, with reference to specificity, precision and turnaround time. *Methods:* NSW/ACT's SMA newborn screening protocol involves a first tier four-plex real-time quantitative PCR assay for *SMN1* exon 7 homozygous loss and a second tier screening assay, which utilises droplet digital PCR (ddPCR) to determine *SMN2* copy number. Screen positive cases (SMN1 exon 7 homozygous deletion) are rapidly referred for pediatric neurological assessment and management. *Results:* To date 364,883 babies have been screened (Aug 2018–Feb 2022) and 28 screen positive cases detected. *SMN2* copy number findings to date are 2 copies (15 cases), 12 with 3 copies (12 cases) 4 copies (1 case). Among those with 2 copies, 10 infants remained free of symptoms; however, 5 infants had already developed clinical signs, the youngest was <2 weeks. *Conclusion:* The SMA newborn screening pathway is robust for newborn screening purposes. The very early emergence of symptoms among those with 0SMN1 and 2SMN2 genotypes, who are at risk of the SMA type 1, emphasises the urgency. The inclusion of *SMN2* copy number determination into the NBS pathway has greatly facilitated the rapid turnaround time and early clinical referral, crucial in this setting where the pre-symptomatic time interval is narrow.

ORAL 8
The New Language of Methylation Episignatures in the Old Talk Addressing Developmental Delays

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Background: Investigations for developmental delays (DD) attract multiple approaches to address the vast heterogeneity of underlying genetic factors entwined in a complex interaction with the environment. The importance of genetic testing is supported by national/international guidelines and Federal funding; however, over 50% of patients with DD lack a formal diagnosis and the sequence of testing is very much open to interpretation. *Aim:* To validate and assess the utility of methylation episignatures in the landscape of genomic testing for DD. *Methods:* We employed EpiSign, a clinical grade epigenomic assay for over 120 disorders associating with DD. The validation study included a range of clinical scenarios involving DD, including fragile X syndrome, imprinting and rare monogenic disorders associated with epigenetic differences. The novel testing modality was also applied as a screening tool after standard of care testing and as a functional assay for variants of uncertain clinical significance (VOUS). *Results:* EpiSign showed 100% accuracy for the range of clinical scenarios assessed at PathWest, Western Australia, the first site to trial the test in Australia. The study has demonstrated over 8% new diagnoses after standard testing and re-classification of 1/3 of VOUS, ending many diagnostic odysseys. It has also advanced the current knowledge by adding a new biomarker for the rare monogenic Diets-Jongmans syndrome (article in press). *Conclusion:* EpiSign is a powerful new language that is evolving and having the potential to become the first line in the diagnostic 'wongi' for DD.

ORAL 9
Australian Genomics State and Territory Health Systems Consistency Project Identifies 21 Gaps and/or Inconsistencies in Genomics Health Plans

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Background: Currently, each jurisdiction aligns to their respective legislation, frameworks, policies, funding, and geographical constraints when implementing genomic health care. The State and Territory Health Systems Consistency project is a national collaborative effort enabled through Australian Genomics that brings together clinical, diagnostic and policy representatives, aimed at establishing consistent health practices to facilitate equitable access to appropriate clinical and diagnostic genomic services for all Australians. *Aim:* To develop and promote a nationwide minimum set of guidelines to inform policy development to facilitate equitable and quality standard of care for clinical and diagnostic genomic health care. *Method:* Existing national and jurisdictional genomic strategies and implementation plans were reviewed, and high-level details summarized under: Services, Digital/IT, Education of genomics workforce, Aboriginal and Torres Strait Islander peoples-specific priorities/Regional, Funding models, and Integration of research into standard practice. *Results*: Despite a high level of concordance, 21 gaps (not addressed by any plan) and/or inconsistencies (addressed by some, or to varying extent) were identified; 13 of these were mapped against existing projects (e.g. Australian Genomics or GHFM). One gap (standards for bioinformaticians) and two inconsistencies (standard genetic referral processes; testing/referral processes for non-genetic specialists) were selected for a detailed review and consultation process

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towards development of national guidelines. *Conclusion:* Mapping national genomic healthcare practices highlights the disparity of service delivery and workforce composition in each jurisdiction, warranting systematic service and professional guideline development, and introduction of decision support tools, where relevant. Re-review of local progress against documented jurisdictional priorities remains indispensable for evaluating translation.

ORAL 10
New Conversations With Health Care Practitioners – Offering Reproductive Genetic Carrier Screening: Mackenzie's Mission, Australia

Stephanie Best[1,2,3,4,5], Janet C. Long[1], Zoe Fehlberg[1,2], Alison D. Archibald[5,6,7], Anaita Kanga Parabia[5,6,7], Madeline Harris[6,7], Camron Ebzery[8], Tenielle Clinch[8], Kris Barlow Stewart[9], Kirsten Boggs[2,10], Jillian Kennedy[11], Samantha Edwards[12], Sarah Righetti[10,13], Lara Fitzgerald[14], Lucinda Freeman[15] and Jeffrey Braithwaite[1]

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Background: Reproductive genetic carrier screening (RGCS) provides prospective parents the opportunity of identifying their chance of passing on selected genetic conditions. Mackenzie's Mission, a national research project, has investigated the provision of free RGCS to couples in early or pre-pregnancy. *Aim:* To examine influences on health care practitioners (HCPs) offering RGCS and identify implementation strategies to support them. *Methods*: We used a mixed methods study design. Prior to enrolment in Mackenzie's Mission, and education, participating HCPs completed Survey 1 about their experience and views towards offering RGCS. After eight weeks, HCPs were invited to interview to investigate their experiences. Data from Survey 1 and interviews were collated to generate Survey 2, asking HCPs to identify optimal interventions to support offering RGCS. Quantitative data were analyzed through descriptive statistics and qualitative using deductive content analysis, informed by the Theoretical Domains Framework (TDF). *Results:* Upon analysis of survey 1 ($n = 599$) and interviews ($n = 31$) we distilled factors influencing HCPs offering RGCS into three target behaviors: 1. Engaging with RGCS, 2. Identifying eligible patients, and 3. Offering RGCS. Barriers were predominantly categorized as 'Environmental Context and Resources' e.g., time constraints, followed by 'Knowledge' e.g., awareness of the process and 'Beliefs about Capabilities' e.g., concern about giving increased-risk results to patients. Top ranked supports from Survey 2 ($n = 390$, GP = 61%) theoretically aligned with barriers and identified the key role of genetic counselors (GCs) for supporting couples with complex results. *Conclusion:* Findings demonstrated the need to prioritise a comprehensive model of care to support HCPs when offering RGCS including GC support.

ORAL 11
The Reclassification Odyssey: From Genes and Variants of Uncertain Significance, in the Perinatal Setting, to Clinical Utility for Recurrence Risk.

Thuong T. Ha[1,2], Peer Arts[1], Marlie Frank[1], Alicia B. Bryne[1,3], Jinghua Feng[1,2], David M. Lawrence[1,2], John Toubia[1,2], Paul Wang[1,2], Milena Babic[1], Lynn Pais[3], Luis Arriola[1,2], Alison Gardner[1,6]Genomic Autopsy Study Research Network, Sarah L. King Smith[1], Matilda R. Jackson[1,4], Andreas W. Schreiber[2,5], Anne O'Donnell-Luria[3], Christopher P. Barnett[6,7] and Hamish S. Scott[1,2,4,6,#]

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Background: Our Genomic Autopsy Study has revealed that genetic candidates can be detected in 129/270 clinically unresolved cases, albeit only half can be used prenatally to assess recurrence risk, despite compelling evidence from animal models, gene constraints and expression data. The current ACMG guidelines have limited capacity to interpret findings from prenatal cases with novel *in utero* phenotypes, or severe and/or lethal forms of existing genomic disorders. *Aims*: Reclassify variants and/or genes of uncertain significance based on additional genetic or experimental evidence. Method: Genes with novel phenotypes or disease associations were shared with genematching platforms or expert disease curators. Variants predicted to cause aberrant splicing and/or epi-signatures were assessed using RNA and methylation studies, while a subset had gene-specific assays, or characterisation using mouse models. *Results*: Seven genetic candidates have been reclassified using RNA-based evidence ($n = 5$) and/or phenotypically-matched patients ($n = 2$). Another 10 candidates had one or more phenotype matches, including four involved in larger genotype-to-phenotype cohort studies. *Conclusion*: From the reclassification, there were five recessively inherited and two *de novo* variants, which relays a 25% and 1% chance of recurrence, respectively. Where gene novelty exists, additional patients from genematching platforms, direct correspondence or new publications, enabled reclassification the fastest (1-2 years turnaround). Experimental evidence, particularly those involving animal models, were unsurprisingly laborious (5-6 years turnaround), but imperative for highly intolerant or pleiotropic genes. Our study highlights the translational benefits of systematic follow-up of candidate disease genes, further extending patient care beyond gene discovery.

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ORAL 12
GENEEQUAL: Listening and responding to the information and support needs of people with intellectual disability in genomic healthcare

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Background: A key gap in the delivery of accessible and equitable genomic healthcare is knowledge of the preferences of people with intellectual disability. *Aims*: This inclusive research study explored knowledge, perspectives, and experiences of people with intellectual disability of genomic healthcare, and how they would like genomic information presented. *Methods*: In phase 1, an inclusive qualitative research approach involved semi-structured interviews with 17 people with intellectual disability and their support people. Inductive content analysis was used, with four main themes emerging. Triangulation was performed with a self-advocacy focus group, and multi-stakeholder advisory workshops. Phase 2 involves co-production and evaluation of genomic healthcare information and clinician education resources. *Results*: Phase 1 identified four main themes related to the genomic health care experiences of people with intellectual disability: (1) access to genomic testing and health services is inequitable, and barriers common in the informed consent process; (2) many people with intellectual disability experience frustration, exclusion and fear when accessing genomic healthcare; (3) genomic counseling and diagnoses can have major impacts, yet many people experienced barriers to translating genomic diagnosis into tailored healthcare, appropriate support, peer connections and reproductive planning; and (4) people with intellectual disability have a high incidence of previous trauma and can find genomic healthcare emotionally triggering. Conclusion: Co-designed accessible, point-of-care educational and consent resources accompanied by tailored professional education for healthcare providers are needed to improve equity and appropriateness of genomic healthcare for people with intellectual disability. These are being developed in the next phase of this project.

ASDG ORAL 1
Improving Fragile X Syndrome Carrier Screening with the Inclusion of Agg Interruption Analysis

Michelle Challis[1], Isabelle Danos[1], Melissa Chow[1], Justine Marum[1], Clare Hunt[1], Katrina Scarff[1], Lauren Thomas[1], Gladys Ho[2,3], Katrina Fisk[2], Bruce Bennetts[2,3], Nicola Flowers[1], Mark D. Pertile[1,4], Martin B. Delatycki[1], Melanie Smith[1] and Alison D. Archibald[1,4]

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Background: Females with an *FMR1* premutation are at risk of having offspring with fragile X syndrome (FXS), with the risk of expansion to a full mutation increasing with maternal CGG repeat size. The presence of AGG interruptions within the CGG repeat increases allele stability and may assist in delineating small, stable premutation alleles from those at risk of expansion to full mutation. *Aim:* To demonstrate the impact of including AGG interruption analysis as part of *FMR1* carrier screening. *Methods:* Females identified with small premutations (55-69 CGG repeats) through reproductive genetic carrier screening (RGCS) performed at VCGS underwent reflex AGG interruption analysis at the Molecular Genetics Laboratory at Children's Hospital Westmead. *Results:* RGCS for FXS identified 49 females with premutations from early 2020 - July 2022. Of these 34/49 (69.4%) were small premutations. 28/34 (82.4%) were reported as low risk for FXS after AGG analysis; 55-64 CGG repeats with one or two AGG interrupts, or 65-69 CGG repeats with two AGG interrupts. The remaining 6/34 (17.6%) were reported as increased risk for FXS after AGG analysis; 55-64 repeats with zero AGG interrupts or 65-69 with zero or one AGG interrupt. AGG interruption analysis has reduced the number of clinically actionable results by 57.1%. Prenatal outcomes and clinical case examples will be presented. *Conclusion:* AGG interruption analysis for females with small premutations has improved the clinical utility of *FMR1* carrier screening. This has reduced requests for prenatal diagnosis and/or PGT-M for FXS and enabled genetic counseling resources to be focused on supporting carriers of potentially unstable premutations.

ASDG ORAL 2
Detection of SMA Risk Alleles in Diagnostics, Carrier Screening and Newborn Screening

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Background: Deletion of exon 7, exons 7 and 8, or the entire SMN1 gene causes spinal muscular atrophy. Accurate detection of *SMN1* copy number can be used diagnostically, as well as in newborn screening and reproductive carrier screening. However, the presence of a near-identical pseudogene, *SMN2*, has prevented integration into modern next-generation sequencing or other multi-plex assays, leading to the need to retain slower and less cost-effective assays in diagnostic laboratories worldwide. *Aim:* To compare the different methods available for SMN1 deletion genotyping in a diagnostic laboratory and determine if NGS-based assays can be implemented. *Methods:* We compared the use of MLPA and qPCR for the detection of *SMN1* exon 7 deletions. Next, we developed a novel in-house NGS-based assay, based on CNV analysis, and used this to compare >3000 samples genotyped using MLPA and qPCR. We also compared the performance of these assays on DNA extracted from blood and buccal swabs/saliva. *Results:* MLPA is a well-established technique whose characteristics are well known. We showed that qPCR is able to detect and quantify *SMN1* copy number accurately and reliably. We also showed that our novel NGS-based assay is highly accurate, reproducible and able to quantify *SMN1* and *SMN2* copy number from DNA from both blood and buccal cells. The challenges around SMN1 genotyping in a carrier screening context, including the '2+0' haplotype problem, will be discussed. *Conclusion: SMN1* genotyping has advanced rapidly and is now able to be integrated into routine NGS-based testing regimes.

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ASDG ORAL 3
Results from an Australian Prenatal Exome Sequencing Cohort and Hypercomplex Cases Requiring Multidisciplinary Team Reporting

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Background: Prenatal exome sequencing (pES) is increasingly utilized to diagnose fetuses with anomalies. *Aim:* To determine the diagnostic yield and proportion of cases requiring complex genomic reporting with multidisciplinary team (MDT) discussion. *Methods:* A retrospective review was undertaken of 65 families with fetal anomalies referred for pES. Thirty PreGen families nationwide were part of a mixed-methods psychosocial study, including three within this cohort. *Results:* 38.5% (25/65) of referrals had multisystem anomalies and 61.5% (40/65) single system. Eighty percent (52/65) of families had trio pES. Diagnostic yield was 36.9% (24/65, likely pathogenic/pathogenic), with trio versus singleton analysis 44.2% and 7.7%, respectively. Trio analysis aided result interpretation: 6.2% (4/65) would have been variants of uncertain significance (VUS) in singleton analyses. High-complexity reporting was required in 12.9% of variants (4/31 including VUS) with VUS relevant to the prenatal phenotype, reported after MDT. These included compound heterozygous hypomorphic *PKD1* variants (echogenic kidneys), parentally inherited *LZTR1* (cystic hygroma), reclassification of a heterozygous *IFITM5* VUS to likely pathogenic following parental segregation (skeletal dysplasia) and a homozygous *CDAN1* VUS (hydrops) with a confirmed clinical diagnosis based on postmortem investigations. All PreGen families (100%, 30/30) reported satisfaction with their decision to undertake genomic testing. *Conclusion:* The results of this first Australian cohort highlight the role and value of trio pES for the prenatal diagnosis of fetuses with anomalies. Sequencing should be undertaken in accredited laboratories with clinical MDT support for the resolution and reporting of complex cases. Further analysis of the economic and psychosocial impact of testing in PreGen families is underway.

ASDG ORAL 4
A False Positive False Negative! Noninvasive Prenatal Testing Results and Lessons in Placental Biology

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Background: Placental derived cell-free DNA is used a proxy for the fetus in screening for fetal aneuploidy by non-invasive prenatal testing (NIPT). Confined placental mosaicism is where the placenta and the fetus do not have the same chromosome complement and therefore NIPT results may be false positives or false negatives. *Aim:* We present a case series where the NIPT result is both a false positive and a false negative for the fetal karyotype. Through these cases we explore the mechanisms of mosaicism in the early embryo. *Methods:* Genome-wide NIPT (gw-NIPT) was performed on cfDNA extracted from maternal plasma using a combination of VeriSeq NIPT16 (Illumina Inc., San Diego, CA, USA), VeriSeq NIPT solution v2 (Illumina Inc.), and WISECONDOR algorithms (Straver et al., 2014). Prenatal diagnosis was recommended to confirm high and increased risk results. Samples for prenatal diagnosis include chorionic villus and amniotic fluid. Cytogenetic analysis was performed using single nucleotide polymorphism (SNP) microarray analysis (Infinium Global Screening Array-24 v2.0, Illumina Inc, San Diego, CA, USA) and conventional G banded karyotyping. *Results:* Four cases are presented where the gw-NIPT result was a false positive result for either monosomy X, a segmental aneuploidy, or a rare autosomal aneuploidy. Prenatal diagnosis detected a different, but apparently related and clinically distinct abnormality to that detected by gw-NIPT. *Conclusion:* This case series of discordant NIPT results offer insights into early embryology. These biological discordances highlight the limitations of NIPT as a screening test and could be considered in the genetic counseling of these patients.

ASDG ORAL 5
Accurate Screening of Pregnancies From Known Carriers of Balanced Reciprocal Translocations Using Genomewide NIPT

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Background: Balanced reciprocal translocations are carried by approximately 1 in 500 people. Carriers are at increased risk for a

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range of adverse pregnancy outcomes including recurrent pregnancy loss, fetal abnormalities and birth defects associated with an unbalanced form of the translocation. *Aim:* Genome-wide NIPT enables screening of segmental chromosome abnormalities from 5-7Mb in size. We report our experience screening pregnancies from known reciprocal translocation carriers from August 2015-December 2021. We also reviewed the frequency of unbalanced translocations identified in pregnancies without a prior history from March 2019-December 2021. *Methods:* Translocations were assessed for eligibility using parental G-banded karyotypes or microarray data from unbalanced karyotypes. To ensure high screening accuracy, all unbalanced forms of the translocation required at least one segmental imbalance of ≥15Mb in size, which was used to track unbalanced forms of the translocation. Minimum fetal fraction and sequence read counts were required. WISECONDOR algorithm was used to detect segmental abnormalities of the autosomes. From March 2019, a double analysis method using Illumina VeriSeq NIPT Solution v2 and WISECONDOR algorithm was employed. *Results:* 375 of 382 (98.2%) eligible pregnancies were successfully screened. 29 of 375 (7.7%) cases were assessed as high risk for an unbalanced translocation, while the remaining 346 cases were low risk. No known false-positive or false-negative results were reported. Six pregnancies without a family history were also identified and confirmed with an unbalanced reciprocal translocation (1/12,000 pregnancies screened). *Conclusion:* Employed conservatively, genome-wide NIPT enables accurate assessment of unbalanced reciprocal translocations in pregnancies from known carriers.

ASDG ORAL 6
Introduction of Noninvasive Fetal Rhesus D Genotyping in Western Australia.

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Background: Severe haemolytic disease of the fetus and newborn, due to alloimmunisation of a RhD negative mother to RhD positive fetus, is prevented by RhD immunoglobulin (RhD Ig) prophylaxis. Routine RhD Ig prophylaxis is provided to all RhD negative women, however approximately 40% of these women will have an RhD negative fetus. The use of non-invasive prenatal screening (NIPS) for fetal *RHD* is used internationally to provide targeted RhD Ig prophylaxis. *Aim:* To develop a high-throughput NIPS assay to determine fetal RhD status. The assay should accommodate for the unique geographical and logistical issues posed in Western Australia, and interstate, whilst providing highly accurate and reliable results. *Method:* Circulating cell-free DNA (ccfDNA) from RhD negative women attending King Edward Memorial Hospital clinics at 20-28 weeks gestation was subjected to sequential quantitative- real-time PCR (q-rtPCR) assays. The primary q-rtPCR targets were specific for *RHD* sequences (exon 5 and 7). All samples with absence of signal for *RHD* were assessed by a secondary q-rtPCR to determine the fetal fraction (hypermethylated *RASSF1* gene). Results were compared with neonatal cord blood serology. *Results:* A cut-off of 2% fetal fraction in the cffDNA was used to report conclusive results. From 553 patient results, 100% sensitivity and 98.91% specificity with a 6.5% inconclusive rate was achieved. *Conclusion:* Implementation of this assay appears to offer a 0% false negative rate and would reduce unnecessary RhD Ig prophylaxis by 30%, which would have a significant impact on the use of the specific human-derived product vulnerable to supply pressures.

ASDG ORAL 7
Escaping Early: Frequency, Impact, and Interpretation of Start-Proximal Termination Variants

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Background: Premature termination codons (PTCs) downstream of the final 54bp of a transcript's penultimate exon treated with caution due in variant classification guidelines dut to the possibility of Nonsense-mediated mRNA decay (NMD) escape. Emergent evidence shows that start-proximal PTCs within the first ~100bp of the coding sequence may also escape NMD. *Aim:* Analyze the frequency and impact of start-proximal PTCs in matched genome and transcriptome data to inform clinical variant curation guidelines. *Methods:* We analyzed 80 trios with matched genome and transcriptome data to identify differences in allele specific expression (ASE) between start-proximal PTCs and controls. In addition, we performed an audit of all previously curated PTC variants in our laboratory variant database ($n = 1484$) to determine if the original variant classification remains appropriate. *Results:* We identified 217 (10 unique) early PTC variants with informative ASE data. There were high levels of variation in ASE signal, however eight of the unique variants had good evidence for NMD escape, while two showed a strong NMD signal. Control data showed a distinctly stronger signal of NMD for PTCs in the middle of the gene. Of the PTC variants previously reported by our laboratory, 41 (2.8%) had PTCs occurring within the first ~100bp of the coding region, 6 of which were reclassified to VUS following review. *Conclusion:* NMD escape for PTCs in the first 100bp is sufficiently common to allow distinction from other PTC variants. This needs to be considered during variant interpretation and should be incorporated into clinical variant curation guidelines.

ASDG ORAL 8
National Engagement of Australian Clinical Genetic Testing Laboratories via the Shariant Platform Identifies Mechanisms to Prioritise Variant Evaluation

Emma Tudini[1,2], James Andrews[1,3], David Lawrence[3], Marie-Jo Brion[1,2], Hamish S. Scott[1,3,4], Amanda B. Spurdle[2] and on behalf of Australian Genomics and the Shariant User Group

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Background: Sharing genomic variant interpretations across laboratories promotes consistency in assertions. Shariant is a controlled access platform for interlaboratory automated sharing of structured evidence for clinically curated variants. *Methods:* To assess Shariant usage and outcomes, evidence-sharing statistics were monitored. In October 2020, a User Group was established to facilitate Shariant

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development according to the needs of participating laboratories. *Results:* Since 2021, Shariant entries increased from ~7000 to >18,000 variant interpretations, from 11 clinical genetic testing laboratories across four states. Between-laboratory discrepancies have been identified for ~7% of variants submitted by multiple laboratories. Shariant-supported submissions to ClinVar has commenced for five laboratories. User Group ranked development priorities were: (1) Identification and notification of differences to a ClinGen expert panel variant classification; (2) Support for Copy Number Variants; (3) Resolving Variants of Uncertain Significance (VUS). Analysis of current Shariant data identified 968 variants (~6.7% of total unique variants) as classified by a ClinGen expert panel; 30 (3.1%) were discrepant with a laboratory-submitted classification. Seventy-three variants were classified as VUS by multiple laboratories. For ~40% of the variants interpreted using ACMG/AMP guideline codes, Likely Pathogenic classification would be reached by addition of one point of evidence (9 supporting, 8 moderate, 13 strong), providing impetus for priority review to compare and consolidate curated evidence across laboratories. *Conclusion:* These findings demonstrate successful national engagement to implement and improve the Shariant platform, including mechanisms to prioritise variants for re-evaluation. Overall, results demonstrate the value of Shariant in promoting variant classification standardisation across Australia, and potentially globally.

ASDG ORAL 9
Reanalysis of Genomic Data in Rare Disease: Current Practice and Attitudes Among Australian Clinical and Laboratory Genetics Services

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Background: Reanalysing stored genomic data over time is highly effective in increasing diagnostic yield in rare disease. Automating the process holds the promise of delivering the benefits of reanalysis at scale. *Objectives:* To understand current reanalysis practices among Australian clinical and laboratory genetics health professionals and explore attitudes towards large-scale automation. *Methods:* Audit data regarding testing and reanalysis volumes as well as policies and procedures were collected from all Australian diagnostic laboratories accredited to provide genomic testing in rare disease. A genetic health professionals' survey explored current practices, barriers to reanalysis, preferences and attitudes towards large-scale automation. *Results:* Between 2018−2021, Australian diagnostic laboratories performed over 25,000 new genomic tests and 950 reanalyses of existing data, predominantly in response to clinician requests. Laboratory and clinical genetic health professionals ($N = 134$) identified workforce capacity, funding and process issues as the principal barriers to reanalysis. No specific laboratory or clinical guidelines or policies were identified nationally, and 44% of clinical respondents were not aware of Medicare funding for reanalysis. Preferences for ideal frequency of reanalysis varied, with 38% favouring a 2−3 year interval and 18% a continuous reanalysis model. Perceptions of acceptability and feasibility of an automated reanalysis model were positive, with professionals emphasising patient and workflow benefits, while raising concerns about consent and result return. *Conclusion:* There is a large and rapidly growing unmet need for reanalysis of existing genomic data. Beyond developing scalable automated reanalysis pipelines, leadership and policy are urgently needed to successfully transform service delivery models and maximize patient benefit.

ASDG ORAL 10
Whole Genome Sequencing Partnership Program: A Risk-Sharing Agreement to Implement WGS as a First Line Test in Pediatric Monogenic Disease.

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The Whole Genome Sequencing Partnership Program is a risk-sharing agreement established in 2020 between Illumina, Metro North Hospital and Health Service and Pathology Queensland (PQ) to implement whole genome sequencing (WGS) as a first-line test for pediatric patients suspected of having a monogenic disorder. Patients are recruited through Genetic Health Queensland with a minimum annual target of 300 over three years. PQ was clinically accredited for WGS in 2020 and an integrated workflow has been developed with multiple engagements between the clinical and scientific teams throughout the process. This includes variant prioritisation meetings (VPM), variant review meetings, and multidisciplinary team meetings. To date 380 patients have been recruited with 241 reported. 83 patients received diagnostic results (34.4%) and 29 received a result of uncertain significance with potential for future upgrade to likely pathogenic (12%). The most common indications were intellectual disability, deafness, and epilepsy. Analysis is performed on singletons only with follow-up parental testing performed after initial reporting where required. Average time spent per case was 11.42 hrs with 63% of time attributed to analysts, 27.5% to senior analysts and 9.5% to genetic pathologists. 52.4% of cases were reviewed at MDT prior to reporting taking an average of 8.25min per case. A health technology assessment aiming at evaluating the clinical and economic impact of WGS as a first-line test is scheduled to be commenced in 2024 following full recruitment. This presentation will focus on the implementation of WGS in PQ and the initial outcomes of the service including exemplar cases.

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ASDG ORAL 11
Recognising Variable Phenotypic Expressivity in Genomic Analysis of Severe Monogenic Disorders

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Background: Congenital genetic disorders at the severe end of the spectrum are generally assumed to be monogenic and follow Mendelian inheritance patterns. However, in an increasing number of cases, we detect (likely) causative variants that are autosomal dominantly (AD) inherited from a mildly or unaffected parent. *Aims:* Assess the frequency of AD inherited variants causing severe Mendelian disorders and elucidate the mechanism driving phenotypic variability. *Method:* As part of research and routine diagnostic testing, over 700 exome trios were analyzed and classified following ACMG guidelines. Prioritized AD inherited variants were reviewed for phenotypic overlap with previously described cases in databases or the literature, and a subset selected for experimental follow-up. *Results:* In this cohort, 14 patients with AD inherited variants showed significant phenotypic overlap, 8 variants were classified as (likely) pathogenic and 6 as VUS. For one of the cases with a pathogenic variant, experimental follow-up of the mother in a family with a *FOXF1* frameshift variant showed that a protective regulatory SNV in the *FOXF1* promotor increased expression from the WT allele to compensate for the loss-of-function allele. *Conclusion*: In contrast to de novo variants, the contribution of AD inherited variants to severe genomic disorders is likely underestimated, as these are either dismissed in analysis or challenging to interpret without patient-specific follow up. In addition to (revertant) mosaicism resulting in a milder phenotype, other factors (including the genomic context, regulatory variants, epigenetic changes, and allelic expression) should be considered in the gene dosage model for rescued disease phenotypes.

ASDG ORAL 12
How Do We Do It Now? Reanalysis of Genomic Data – Looking Towards Automation

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Background: Although use of genomic testing is growing in routine clinical practice, not every patient receives a diagnosis. Sequenced data remains available for reanalysis however the process and drivers required to achieve this are unclear. *Aim:* To articulate the current steps in reanalysis of genomic data and identify perceived challenges to automating the process. *Methods:* We used a qualitative study design informed by implementation science theory (Theoretical Domains Framework) and undertook interviews ($n = 13$) with genetic professionals and laboratory scientists across Australia who are involved with the process of reanalysing genomic data. We shared an outline of the key steps for reanalysis and talked through the current process at their laboratory/department. Triggers, barriers, and enablers to automating reanalysis were discussed. Interview data and process maps were analyzed using content analysis. *Results:* We generated 13 process maps and six key steps/decision points for reanalysis of genomic data including when to consent patients and returning results. Current triggers for reanalysis included change in phenotype and time since primary test. Participants discussed benefits of automating reanalysis e.g., equity of access and diagnostic yield and raised several barriers e.g., trust in the process, return of results and workforce implications. 23% thought reanalysis should be triggered by new knowledge, 61% preferred a time dependent approach, and 15% saw a combination. Several participants noted specific triggers such as starting school or reproductive planning. *Conclusion:* This study process mapped the current approach to reanalysis of genomic data. Understanding what happens now is essential if future attempts to automate the process are to be successful in each local context.

AACG ORAL 1
A Randomized Controlled Trial of Vosoritide in Infants and Toddlers with Achondroplasia

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Background: Vosoritide increases annualized growth velocity (AGV) in children with achondroplasia aged 5 to 18 years. This global, phase 2, randomized, double-blind, placebo-controlled study evaluated the safety and efficacy of vosoritide on growth in children with

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achondroplasia aged 3 months to 60 months. *Methods:* This study compared once-daily subcutaneous administration of vosoritide, at doses of 15 or 30 g/kg of body weight, with placebo. Eligible patients had participated, for up to 6 months, in an observational growth study to calculate baseline AGV. The primary objective was to evaluate the safety and tolerability of vosoritide in children with achondroplasia. The primary efficacy evaluation was the change from baseline in height Z-score versus placebo at week 52. *Results:* A total of 75 patients were enrolled, with 11 sentinel subjects who received vosoritide to establish PK and safety. A further 32 were randomized to receive vosoritide and 32 to receive placebo. A total of 73 patients completed the 52-week trial. Four serious adverse events occurred with vosoritide and 8 with placebo, none were treatment related. Two participants discontinued, one on vosoritide who had a fatal respiratory arrest and one on placebo who withdrew consent. In the full analysis population, vosoritide ($n = 43$) compared to placebo ($n = 32$), increased height Z-score by 0.30 SD (95% CI 0.07, 0.54); increased AGV by 0.92cm/year (95% CI 0.24, 1.59); and did not worsen upper-to-lower body segment ratio. *Conclusions:* Daily, subcutaneous administration of vosoritide to young children with achondroplasia was safe and resulted in increases in height Z-score and AGV.
(Funded by BioMarin; ClinicalTrials.gov NCT03583697).

AACG ORAL 2
Audit of a Multidisciplinary Hearing Impairment Clinic

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Background: Pediatric-onset hearing impairment occurs in 3.2 per 1000 children in Australia and may present as an isolated feature or as part of a genetic syndrome. The majority of patients in this group do not receive a molecular diagnosis due to high heterogeneity and poor access to funding for genomic testing. A multidisciplinary pediatric genetic hearing loss clinic has been running since 2015 at Monash Health to facilitate evaluation and genomic testing where appropriate. *Methods:* An audit was conducted for patients seen in our clinic between 2015 and 2021, with an emphasis on the 2020 and 2021 patient cohorts. Demographic data, referral source, phenotypic information, inheritance pattern, family history, genetic testing methodology and molecular diagnosis information were extracted and analyzed. *Results:* More than 200 patients attended our clinic in the 7-year period. The majority were referred from the local pediatrician-led hearing loss investigation clinic where patients were prescreened for *GJB2*, copy number changes on microarray, structural anomalies on neuroimaging, congenital cytomegalovirus infection, thyroid dysfunction, and haematuria/proteinuria, prior to genetics referral. Funded genomic testing was offered based on clinical utility, such as management or pregnancy implications, or where there was a family history. *Discussion:* Through this retrospective review, we describe the diagnostic rates achieved using our local algorithm. We propose a standardized approach to the investigation and the provision of funded genomic testing for patients with pediatric-onset hearing impairment.

AACG ORAL 3
Mechanisms of Incomplete Penetrance-Pathogenic Variants Can Be Passed from an Unaffected Parent to an Affected Child Via Two Dozen Mechanisms.

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Background: Incomplete penetrance and variable expressivity can result in challenges with variant curation. Pathogenic variants in healthy population databases can further confound analysis. Benign variants can be erroneously classified as pathogenic in the literature and incorrectly interpreted as evidence for incomplete penetrance. Recognition of genes and mechanisms in which a pathogenic variant can be inherited from an unaffected or mildly-affected parent can be helpful in both laboratory and clinical settings. *Method:* A literature review was conducted of 4722 genes. Search terms in Pubmed and OMIM included 'penetr*', 'parent', 'norm*', 'unaffect*', 'digenic', 'triallelic' and 'oligogenic', along with an OMIM search for imprinting disorders and articles matching search terms for transient neonatal, infantile seizures, benign neonatal and 15 other similar terms. Only genes with a non-cancer phenotype were included. *Results:* 527 genes were identified in this study, the majority of which followed autosomal dominant inheritance with incomplete penetrance or variable expressivity. Other mechanisms included digenic inheritance ($n = 60$), transient infantile or neonatal disorders ($n = 33$), imprinting ($n = 12$), gonadal mosaicism and skewed x-inactivation. At least twenty other mechanisms were documented. *Conclusion:* This study categorises common and rare ways in which an unaffected parent can pass a pathogenic variant to their affected child. The 2-3 dozen mechanisms by which this can occur is clinically intriguing. As genomic trio analyses are increasingly ordered by pediatricians and by geneticists after a telehealth appointment, inherited pathogenic variants from a mildly-affected parent may become more common. This presents an urgent need for a list of genes relevant to this phenomenon.

AACG ORAL 4
Muscle RNA Sequencing: An Increasingly Important Neuromuscular Diagnostic and Gene Discovery Tool

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Background: Short-read RNA-sequencing (RNA-seq) is now being routinely used as a diagnostic and gene discovery tool in the rare disease setting. This technology also shows great promise as a means of furthering our understanding of disease mechanism in scenarios where the genetic basis of disease has already been established. *Aims and methods:* (1) To review existing literature regarding how short read muscle RNA-seq is currently being used to further our

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understanding of genetic neuromuscular disorders. (2) To incorporate these approaches into our in-house bioinformatic workflows. *Results:* Short read RNA-seq is currently being used to (1) facilitate the identification of candidate disease genes via the detection of aberrant transcript expression patterns in patient tissue, (2) functionally confirm the transcript-level impacts of canonical and putative non-canonical splice-altering variants (3) explore whether known disease-causing variants have additional previously unrecognized splice impacts. Key elements of all effective workflows include effective patient tissue processing, and robust analytical techniques including differential gene expression analyses and splicing outlier detection. Access to large high-quality age-matched healthy muscle (control) RNA-seq reference datasets is also essential. Our in-house muscle RNA-seq workflows are now being successfully deployed to explore diagnosis and mechanism of disease in multiple Australian families. *Conclusion:* Muscle short-read RNA-seq is now routinely being used by to facilitate disease gene discovery, to functionally validate splice variants, and to explore other aspects of disease mechanism(s). The integration of this technology into existing diagnostic and research pipelines is highly feasible and has already resulted in a range of important new discoveries.

AACG ORAL 5
Multispecialty Collaboration Solves a NGLY1 Second-Hit Mystery: The Answer Lies in the RNA

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We describe the multispecialty genetic diagnostic pathway of a fifteen-month-old boy who presented to clinical genetics with a distinctive clinical phenotype, characterized by hyperkinetic involuntary movements, dysmorphism, deranged LFTs, intermittent anisocoria, hypolacrima, seizures, hearing impairment, esotropia, and severe global developmental delay. Neurotransmitter assessment found borderline low HIAA. A clinical diagnosis of NGLY1 deficiency was made; a recessive, congenital disorder of deglycosylation. Trio whole exome sequencing identified a heterozygous, maternal, previously described, pathogenic variant in *NGLY1* – but no second variant. A targeted SNP array was uninformative. Biochemical testing confirmed an increase in urinary aspartylglucosamine and related oligosaccharides, relative to age-matched controls, supporting the clinical diagnosis. Postulating that the proband had an undetected intronic or regulatory variant affecting *NGLY1*, RNA diagnostic studies were coordinated. Reverse transcription PCR and RNA-sequencing collectively identified pathogenic mis-splicing due to a previously undetected paternal deletion of exon 4 and mapped to the intron 3/intron 4 breakpoint. Exon 4 deletion is associated with two mis-splicing events absent from controls: (1) Exon 4 skipping that results in a frameshift and encoded premature termination codon (NM_018297.4;p.Ala166Serfs*3) predicted to comply with nonsense-mediated decay, and (2) Exon 4-5-6-7 skipping causing in-frame deletion of 219 amino acids from the encoded NGLY1 protein (NM_018297.4;p.Ala166_Val384del). Long-range PCR established the proband did not produce any canonically spliced *NGLY1* mRNA encoding a full length NGLY1 protein. Multidisciplinary collaboration lent clinical, biochemical, DNA and RNA pieces of evidence to this diagnostic puzzle to identify compound heterozygous pathogenic *NGLY1* variants in the affected proband, efforts appreciated by the family.

AACG ORAL 6
Expanding the Speech and Language Phenotype in Koolen-De Vries Syndrome: Late Onset and Periodic Stuttering a Novel Feature

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Background: Koolen-de Vries syndrome (KdVS) is a chromatin-related disorder caused by a *KANSL1* variant or 17q21.31 deletion encompassing *KANSL1*. Speech and language impairment is core in KdVS, yet only one study has examined this empirically. *Aim:* To define speech, language, and functional/adaptive behavior in KdVS; while deeply characterising the medical/neurodevelopmental phenotype in the largest cohort to date. *Methods:* Speech, language, literacy, and social skills were assessed using standardized measures, alongside an in-depth health and medical questionnaire. *Results:* 81 individuals with KdVS were recruited (35 female, mean age 9y 10mo). 56 harboured the typical 500-650kb 17q21.31 deletion. The core medical phenotype was intellectual disability (largely moderate), eye anomalies/vision disturbances, dental problems, sleep disturbance, musculo-skeletal abnormalities, and cardiac defects. Most were verbal (62/81, 76.5%), while minimally-verbal communicators used alternative and augmentative communication (AAC) in spite of speech production delays. Speech was characterized by apraxia (39/61, 63.9%) and dysarthria (28/61, 45.9%) in verbal participants. Stuttering was described in 36/47 (76.6%) verbal participants and followed a unique trajectory of late onset and fluctuating presence. Receptive and expressive language abilities were commensurate, but literacy skills remained a relative weakness. Social competence, successful behavioral/emotional control, and coping skills were relative strengths, while communication difficulties impacted daily living skills as an area of comparative difficulty. *Conclusion:* Individuals with KdVS make communication gains beyond childhood and should continue to access targeted therapies, including early AAC implementation, motor speech therapy, language/literacy intervention, as well as strategies implemented to successfully navigate activities of daily living that rely on effective communication.

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AACG ORAL 7
Integration of Episign, Machine Learning Facial Phenotyping and Lirical in the Classification of an Arid1b Missense Variant

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Background: Heterozygous *ARID1B* variants result in Coffin-Siris Syndrome or *ARID1B*-Related Disorder. Clinical manifestations may include intellectual disability, microcephaly, epilepsy, autism, corpus callosal anomalies, hypertrichosis, hypoplastic fifth fingernails, feeding difficulties, and short stature. Most reported cases are due to loss of function variants in *ARID1B,* with only rare missense variants attributed causative. *Aim:* We report on a one-year-old male with moderate global developmental delay, feeding difficulties, aspiration, chronic lung disease, slow growth and hypotonia where the pathogenicity of an *ARID1B* missense variant was refined through combined methodologies including Machine Learning (ML) facial phenotyping, EpiSign and LIRICAL. *Methods:* Diagnostic trio exome sequencing and EpiSign genome-wide methylation signature analysis were performed at Randwick Genomics. ML facial phenotyping utilises artificial intelligence to compare facial images and clinically documented features. LIRICAL performs phenotype-driven prioritisation of candidate diseases and genes in the setting of genomic diagnostics described with the Human Phenotype Ontology (HPO). *Results:* Trio exome sequencing identified a *de novo* heterozygous missense variant in *ARID1B* (NM_001374828.1):c.3682T>C | p.(Tyr1228His) reported as a variant of uncertain significance with a posterior probability of pathogenicity of 80-90%.[9] The ACMG classification of the variant was refined by a supportive EpiSign methylation signature, artificial intelligence facial recognition assessment and the positive correlation of *ARID1B* utilising HPO through LIRICAL. *Conclusions:* The genotype-phenotype correlation in *ARID1B*-related neurodevelopmental disorders has been expanded through an extended analysis of missense variation. The adjunct platforms EpiSign, ML-facial phenotyping and LIRICAL demonstrate the utility of genome-wide methylation signatures, Machine Learning and likelihood-ratio test phenotyping for the interpretation and reclassification of genomic data.

AACG ORAL 8
Single-Centre Experience with Real-Time Prenatal Genomic Testing for Counseling and Pregnancy Management

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Background: From 2020 onwards, our centre has utilized rapid turn-around prenatal trio exome as part of core clinical diagnostics, pregnancy management and counseling. *Aim:* To review the clinical outcomes of pregnancies that were tested within the first 18 months of testing availability. *Methods:* An audit of the referrals, diagnostic outcomes and clinical outcomes of pregnancies managed by our centre in this time was performed. *Results:* A total of 42 prenatal trio exomes were reported, with an average turn-around-time of 12 days from receipt of sample to reporting of results. Reported variants were limited to likely pathogenic and pathogenic, with exceptions including compound heterozygous variants of uncertain significance in *EXOSC3* following consultation with the referring clinician. Noteworthy diagnoses included nemaline myopathy (*NEB*), Skraban-Deardorff syndrome (*WDR26*) Smith-Lemli-Optiz Syndrome *(DHCR7)*, thanatophoric dysplasia (*FGFR3*), Sotos syndrome (*NSD1*) and primary ciliary dyskinesia (*DNAL1).* Noonan syndrome was diagnosed in multiple cases, including two *de novo PTPN11* variants, and one maternally inherited *PTPN11* variant. We profile the impact of a rapid turn-around prenatal trio exome result upon clinical management, pregnancy counseling and decision-making regarding perinatal care and future pregnancies. *Conclusion:* Our centre has expanded prenatal genomic care to include rapid-turn around trio exome results with an average time to result of 12 days from receipt of request. This was performed within the pre-existing diagnostic framework, without the need for on-demand sequencing. We report on the impact of this service upon clinical decision-making and perinatal care, highlighting the potential for broader implementation, including tertiary care hospitals and laboratories.

AACG ORAL 9
Bionano Optical Genomic Mapping for FSHD1 Molecular Diagnosis

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Background: Facioscapulohumeral muscular dystrophy (FSHD) is a common neuromuscular disease mainly affecting the face, shoulder girdle and upper arms. FSHD typically presents in adolescence and is predominantly caused by contraction of the D4Z4 repeat on the 4qA haplotype of Chr4 (FSHD1). Southern blot has been the gold standard diagnostic test for FSHD1 and sizes the contraction, but the technical requirements and labour-intensive nature of this method mean that molecular diagnosis for FSHD is not readily available in Australia. *Aim:* We aimed to explore Bionano optical genomic mapping (OGM) for the diagnosis of FSHD and to implement this

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into diagnostic testing for FSHD for Australia. *Methods:* We obtained blood samples from FSHD individuals with known D4Z4 contractions and extracted ultra-high molecular weight DNA using the Bionano DNA extraction kit. DNA was fluorescently labelled, counterstained to label the DNA backbone, loaded onto a nanochannelchip and imaged on the Bionano Saphyr instrument. Data were analyzed using the automated Bionano EnFocus FSHD analysis pipeline. *Results:* Bionano OGM provided a timely and accurate molecular diagnosis in FSHD patients with known D4Z4 contractions previously detected by Southern blotting. The workflow is less labour-intensive than Southern blotting, is able to provide more accurate D4Z4 repeat sizing, and simplifies identification of the 4q haplotypes. *Conclusion:* Bionano OGM appears to be a reliable technique that has the potential to streamline FSHD1 diagnostics nationwide. Once validated, PathWest Diagnostic Genomics will be the first diagnostic laboratory in Australia to implement this technology.

AACG ORAL 10
Findings of the Agha Neuromuscular Disorders Flagship

Jevin Parmar[1], Chiara Folland[1], Georgie Hollingsworth[1], Denise Howting[1], Samantha Edwards[1], Martin Delatycki[2,3], Tyson Ware[4], Anita Cairns[5], Phillipa Lamont[6], Mark Davis[7], Gianina Ravenscroft[1] and Nigel Laing[1]

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Background: Genetic neuromuscular disorders are highly heterogeneous. Next-generation sequencing (NGS) technologies have increased the identification of disease genes and variants causing these disorders. Nevertheless, 30−50% of neuromuscular disorder patients evade genetic diagnosis. *Aim:* Research the genetic cause in a cohort of 61 undiagnosed neuromuscular disease patients. *Methods:* Neuromuscular disease patients without a molecular diagnosis following sequencing on PathWest neurogenetic disease gene panel/s were triaged into the Australian Genomic Health Alliance (AGHA) Neuromuscular Disorders Flagship to test the efficacy of whole-genome sequencing (WGS), including trios, to provide further diagnoses. Candidate disease-causing variants were confirmed using Sanger sequencing, with co-segregation and functional studies performed where necessary. Some cohort patients have previously been published in novel disease gene discovery or gene-specific cohort studies. *Results:* A conclusive genetic diagnosis was achieved for 10 patients. Variants were found in six known neurogenetic disease genes (*CHRNA1*, *MME*, *MYBPC1*, *SBF1*, *SMPX*, *SPTAN1*). This included de novo variants or bi-allelic variants in known disease genes that did not reach thresholds for classification as Class 4 or 5 using ACMG guidelines when analysis was restricted to the proband. Phenotypic expansions were demonstrated for one gene (*SPRED2*). The study identified two new neurogenetic disease genes (*NEMF*, *NRG1*). *Conclusion:* WGS provided genetic diagnoses in 16.4% of patients. Trio analysis was crucial in some diagnoses. Data sharing and international collaboration were critical. The study highlights the utility of research WGS where targeted gene panels are negative. Analysis is ongoing, including structural variant and short tandem repeat calling.

AACG ORAL 11
Is Genomic Analysis of Products of Conception Worthwhile? A Population-Based Study of Postnatal Chromsome Testing From 2020−21

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Background: Women who experience a miscarriage or antepartum stillbirth may choose to have postnatal diagnostic testing of products of conception (POC). The uptake of diagnostic testing of POC samples has been facilitated by chromosome microarray (CMA) which has a lower failure rate than G-banded karyotyping. *Aim:* To analyze clinical indications for, and diagnostic yield of, chromosomal analysis performed on POC. *Methods:* Retrospective population-based study of diagnostic tests performed on POC in Victoria from 2020-21. Infant samples were excluded. We defined a major chromosomal condition as any of: polyploidy, aneuploidy, pathogenic copy number variants, unbalanced rearrangements, and gestational trophoblast disease. *Results:* 2524 POC underwent diagnostic testing in the 24-month study period; 94.5% were evaluated by CMA. Gestational age was available for 717 (53.0%); 21.9% were performed at <14 weeks, 22.3% at 14-23 weeks, and 6.6% at ≥24 weeks. Clinical indications included pregnancy loss at an unspecified gestation (22.6%), miscarriage at <20 weeks (21.1%), and a fetal abnormality on ultrasound (18.8%). A major chromosome condition was found in 46.5%. The most common group were the rare autosomal aneuploidies (17.4%), followed by common autosomal trisomies (9.2%) and sex chromosomal aneuploidies (4.8%). The diagnostic yield was highest for women with increased chance prenatal screening results: cell-free DNA-based screening (76.5%), and first trimester combined or second trimester serum screening (72.4%). A previous or 'recurrent' miscarriage also had a high yield (68.0%). *Discussion/Conclusion:* Postnatal microarray analysis of POC is common in local clinical practice. These results may inform genetic counseling for women following a pregnancy loss.

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AACG ORAL 12
Two Patients With Rnu4atac Related Disease: Clinical Presentation and Genotypic Findings.

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Background: RNU4ATAC is a non-coding RNA gene forming part of the minor spliceosome. Biallelic mutations result in one of three similar but distinct phenotypes - Microcephalic Osteodysplastic Primordial Dwarfism type 1 (MOPD1), Roifman syndrome (RS) and Lowry-Wood syndrome (LWS). Each features pre- and postnatal growth failure with variable additional complications. Prognosis differs from significantly life limiting (MOPD1) to normal life expectancy. Here we report two patients with compound heterozygous *RNU4ATAC* variants, and the association of their clinical picture with reported phenotype-genotype correlations. *Case 1:* An infant Indigenous Australian male was investigated for prenatal onset growth restriction, strabismus, sparse fine hair, developmental delay and dysmorphic features. There were no skeletal, cardiac or renal anomalies. He suddenly developed seizures, and passed away at 14 months and the exact cause of death is unknown. Genetic testing found compound heterozygous *RNU4ATAC* variants. One variant, n.51G>A was reported to cause MOPD1 in the majority, but also RS and LWS in compound heterozygotes. The other variant, n.55G>A was associated with MOPD1. Our clinical findings support the previously reported genotype-phenpotype correlation of MOPD1 with these variants. *Case 2:* A newborn Caucasian male was referred due to significant prenatal growth restriction, retinal dystrophy, syrinx, dysplastic corpus callosum, short long bones and spondyloepiphyseal dysplasia. He underwent genetic testing through the Acute Care Genomics research project, which detected compound heterozygous *RNU4ATAC* variants. The novel n.18G>A mutation neighboured a previously reported RS associated variant. The n.50G>A variant was described in a MOPD1 patient. Prognostication was complicated by conflicting phenotype-genotype associations.

ASGC ORAL 1
Models of Communication for Polygenic Scores and Associated Psychosocial and Behavioral Impacts on Recipients: A Systematic Review

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Background: Polygenic scores (PGS) have potential to benefit clinical care. However, there are no guidelines for communicating PGS, and little is known about associated psycho-behavioral outcomes. *Aims:* Systematically review current models for communicating PGS and associated psycho-behavioral outcomes. *Methods:* Articles included were original research which communicated PGS and reported on psycho-behavioral outcomes. Search terms were applied to five databases and limited by date (2009-2021). Three researchers conducted a narrative synthesis and discordances were discussed and consolidated. *Results:* Twenty-eight articles, representing 16 unique studies were identified. Studies provided PGS in several disease settings. There was limited consistency in communication, evaluation, and reporting of outcomes. Most studies ($n = 13$) presented risk numerically, verbally and/or visually. Only three studies provided personalized lifestyle advice and additional resources. Of fourteen studies evaluating psychosocial outcomes, eight found no long-term negative psychosocial impacts, up to 12 months post-result. Of 13 studies reporting on behavior, 9 found at least one preventative behavior change following receipt of PGS, including screening ($n = 2$), lifestyle ($n = 8$), and medication changes ($n = 2$), especially in high-risk PGS. Low-risk PGS was not associated with uptake of harmful behaviors ($n = 3$). Only 1/13 studies reported using behavior change theory to inform PGS delivery. When mapped to the COM-B model of behavior change, most interventions (10/13) only facilitated psychological capability. *Conclusion:* PGS has potential to benefit health behavior. High variability among studies emphasizes need for developing standardized guidelines for communicating PGS and evaluating psycho-behavioral outcomes. We call for development of best communication practices and high-quality interventions informed by behavior theories.

ASGC ORAL 2
Evaluation of an Online Training Program on Healthcare Providers' Knowledge and Confidence Towards Personalized Cancer Risk

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Introduction: Integration of polygenic risk (PGS) into hereditary breast and ovarian cancer (HBOC) risk prediction tools (i.e., CanRisk) has potential to provide more accurate risk assessments and support risk management decision-making. Genetic healthcare providers report a lack of knowledge and confidence in understanding PGS, posing a significant barrier to clinical translation. *Aims:* To develop and evaluate an online education module for genetic healthcare providers to improve their confidence and knowledge of PGS for HBOC. Methods: This study was conducted alongside the PRiMo trial, a randomized clinical trial that aims to evaluate the impact of providing PGS for HBOC. The training is comprised of two stages: an online self-guided module covering theoretical aspects of PGS for HBOC, and a virtual workshop comprised of role plays and case discussions. All participants were invited to complete two online anonymous surveys: pre-and post-training. *Results*: The training has been delivered to 100 clinicians from across Australia. 51 pre-and 36 post-training surveys were completed. Pre-training, the most frequently

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identified benefit of PGS was improved access to tailored screening ($n = 92\%$ as beneficial/very), and the most frequently identified concern was the accuracy of PGS due to undiscovered SNPs ($n = 86\%$ as concerned/very concerned). Completion of the training did not change attitudes toward the use of PGS clinically. However, there were significant improvements in preparedness for, confidence with, and knowledge of PGS ($p < .001$). *Conclusion:* Completion of our training program was associated with improved knowledge and confidence in PGS. Our findings provide a framework for workforce education of this new technology.

ASGC ORAL 3
Co-Design, Implementation, and Evaluation of Plain Language Genomic Test Reports

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Background: Understanding and communicating genomic results can be challenging for families and health professionals without genetic specialty training. Unlike modifying existing laboratory reports, plain language genomic test reports provide opportunity for patient/family-centred approaches. However, emerging examples have lacked co-design and/or evaluation in real-world settings. *Aim:* This study aimed to co-design, implement, and evaluate real-world use of plain language genomic test reports in a national acute pediatric setting. We hypothesized these reports would facilitate patient/family and caregiver understanding and communication of genomic test purpose, outcome, and potential clinical implications. *Methods:* Through co-design involving patient groups, plain language experts, educators, and genetic health professionals, plain language genomic test report templates were produced for common test outcomes in rare disease. These reports were implemented as part of a national pediatric ultra-rapid genomic testing program. Family and genetic health professional experiences with report layout, content, and use were explored using surveys. *Results:* Eight plain language genomic test report templates were developed. Of 154 families and 107 genetic health professionals issued with reports, 51 families and 57 clinicians completed surveys (RR = 33% and 53%, respectively). Most families (82%) found their report helpful in understanding the result. Reports were shared by 63% of families, predominantly with family members (72%), or health professionals (68%). Clinicians (15%) adapted the reports for other settings. *Conclusion:* Through co-design, plain language genomic test reports implemented in a real-world setting can facilitate patient/family and caregiver understanding and communication of genomic test purpose, outcome, and potential clinical implications.

ASGC ORAL 4
Laboratory Genetic Counselors in a Stewardship Program Supported Behavior Change Among Nongenetic Clinicians

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Background: Metro North LINK funding supported a demonstrator Genetic Testing Stewardship (GeTS) program with the goal of supporting effective genetic testing processes by non-genetic clinicians. The GeTS team comprised a Senior Scientist, two Senior Genetic Counselors (GCs), a Genetic Pathologist and a Clinical Geneticist. The GCs had primary responsibility for the clinical review of the test requests and interaction with the requesting clinicians. *Aim:* Review genetic test requests submitted by non-genetic clinicians to ascertain if testing processes improved after interaction with the GeTS GCs. *Methods:* The Metro North clinical department with the highest volume of genetic testing was identified and a GeTS GC delivered a one-hour education seminar prior to 'Go Live'. From 1 January 2022 until 30 June 2022, a total of 52 genetic test requests were reviewed from 11 consultants from this department. A GeTS GC assessed each request for documentation of patient consent, test selection, sufficient clinical details, test duplication, and inappropriate predictive testing. *Results:* For the first test reviewed from each of the 11 consultants, only 2/11 (18%) had consent documented. An education email was sent to each clinician, and some engaged further with the GeTS GCs. Of the subsequent reviews, improvement was noted with 30/41 (73%) tests having consent documented. The next most common issue was test selection. Of test requests reviewed Jan −Feb, 5/15 (33%) required GeTS input while only 6 (16%) of the 37 subsequently reviewed required similar input. *Conclusion:* Interaction with the GeTS GCs supported improvement of test request processes by non-genetic clinicians.

ASGC ORAL 5
Psychiatric Genetic Counseling: A Survey of Australasian Genetic Counselors' Practice and Attitudes

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Background: Genetic counseling plays a critical role in supporting individuals and their families' adaption to psychiatric disorders, addressing the multifactorial nature of these conditions in a personally meaningful and empowering way. However data related to the practice and attitudes of Australasian genetic counselors about psychiatric genetic counseling (PGC) is limited. *Purpose:* This survey investigated the practice of Australasian genetic counselors, and their attitudes towards PGC. *Methods:* Genetic counselors ($n = 393$) were invited to participate in an anonymous online survey between March and May 2022. The survey consisted of 20 Likert scale questions. *Results:* Forty-four genetic counselors (response rate = 11%) from Australia and New Zealand responded. No respondents practice in psychiatry genetics as their speciality area; most respondents do not see *any* patients where the primary indication is a personal and/or family history of psychiatric disorders (91%). Greater than

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half of respondents (56%) believed there was sufficient evidence to support PGC, and 64% enquire about personal and/or family history of psychiatric disorders, but only 25% provide counseling on this topic. Most respondents do not feel confident providing risk assessments for psychiatric disorders (72%), while the majority expressed interest in attending specialist training (96%), and in incorporating PGC into future practice (77%). *Conclusion:* Genetic counselors would benefit from psychiatric genetic education and training, and establishment of specialized PGC services would address this gap in patient care, while providing opportunities for genetic counselors to gain skills and experience in PGC.

ASGC ORAL 6
Using Virtual Clinical Placement to Enhance Student Learning and Readiness for Practice

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Background: Standardized clients (actors trained to simulate the psychological, emotional, historical and physical manifestations of a client) are used to effectively prepare medical, nursing and allied health students for practice. The global pandemic required genetic counseling education to move online and limited opportunities for students to attend clinical placements. In response, we developed simulated week-long virtual clinical placements (VCP) that mimic practice and align with the HGSA Competency Standards for Genetic Counselors. Working in teams alongside a clinical supervisor, students participate in virtual activities designed to simulate clinical placement. We aimed to evaluate student satisfaction with VCPs to inform our program. *Methods:* We distributed an anonymous online survey using a modified validated satisfaction with simulation scale to first- and second-year students participating in VCPs during 2020. Data were analyzed using descriptive statistics and content analysis. *Results:* 37 students completed the survey (19 first years and 18 second years). Overall mean satisfaction with the VCP was 93.05%. 100% of participants reported that the VCP enabled development and demonstration of their clinical communication skills. Of the 27 participants who had previously attended clinical placements, 57% ($n = 21$) found the VCP provided more opportunities for hands-on practical experience and gave them greater autonomy. *Conclusion:* VCPs are well received by students, enhancing development of clinical communication skills and enabling them to demonstrate readiness for practice. VCPs are now embedded in our curriculum. Students are required to pass the final VCP before graduating. Our presentation will discuss the implications of VCP for genetic counselor education.

ASGC ORAL 7
Decision-Making About Reproductive Genetic Carrier Screening in Mackenzie's Mission

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Background: Through Mackenzie's Mission, Australian couples were offered free reproductive genetic carrier screening (RGCS) by healthcare providers. The online enrolment process was designed to support decision-making, and comprised RGCS education, a knowledge quiz, an optional decision aid (DA) and surveys. Couples could choose not to proceed with RGCS at any point in the process. *Aim:* To examine factors influencing decision-making about RGCS through Mackenzie's Mission. *Methods:* Scores of knowledge ($\geq 7/10$ = good), DA ($\geq 46/75$ = leaning toward RGCS), decisional conflict scale ($<25/100$ = low conflict) were summarized with descriptive statistics. Logistic regression analyses examined factors associated with proceeding/not proceeding with RGCS. Interviews were conducted with participants who did ($n = 29$) or did not proceed with RGCS ($n = 25$) and analyzed using inductive content analysis. *Results:* 10,038 couples initiated enrolment: 9107 completed RGCS, 931 did not proceed with RGCS. Participants who had RGCS had good knowledge (95.7%), high DA scores (mean = 65), low decisional conflict (mean = 10.5) and positive attitudes toward RGCS – considering RGCS an important part of reproductive planning. Interview participants expected to feel reassured by results. Couples living in lower socioeconomic areas were more likely not to proceed than those in higher socioeconomic areas ($OR = 2.4$, 95% CI [1.9, 3.0], $p < .001$). Reasons for not proceeding included: worry about possible results, feeling results would not change reproductive plans, and concerns about genomic data usage/storage. *Conclusion:* The delivery of online education and a DA effectively supports decision-making and facilitates engagement in RGCS. This can be further adapted to address perceived barriers to RGCS, which will be important as RGCS becomes more widely accessible.

ASGC ORAL 8
Reproductive Outcomes Matched to Disease Severity for Couples at Increased Chance on Expanded Carrier Screening

Lucinda Freeman[1,2], Annabelle Kerr[3], Erin Macauley[3], Ellie Greenberg[3], Grace Morrison[3], Stephanie Groube[3], Zoë Milgrom[3], David Amor[4,5], Julia Wilkinson[6], Nathan Slotnick[6], Swaroop Aradhya[6], Nicole Faulkner[6], Edwin P. Kirk[7,8] and Martin B. Delatycki[4,9]

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Background: Reproductive genetic carrier screening (RGCS) is widely available through commercial providers and is soon to be supported by government funding in Australia. There is limited data on the reproductive choices made by increased chance couples and the

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severity of the condition. *Aim:* This study reports on reproductive decisions made by increased chance couples and aims to describe decisions alongside severity of conditions. *Methods:* An online survey was circulated to increased chance couples who had RGCS through commercial provider, Invitae. 122 patients completed the survey providing details of reproductive decisions. Clinical providers at Eugene Labs, a private genetic counseling company, also completed the survey on 332 of increased chance couples. Data was combined with pathogenic variant details from Invitae. Results: Couples reported altering their reproductive decisions following their increased chance RGCS and these included deciding to have prenatal diagnosis or seeking IVF with PGT-M. Some couples received their results before becoming pregnant whilst others were screened during pregnancy. Couples reported some reasons for declining prenatal diagnosis including fear of miscarriage risk or that they did not consider the condition to be severe enough to warrant intervention. *Conclusion:* Most increased chance couples altered reproductive planning following their result, demonstrating the clinical utility of RGCS. Severity of condition appeared to be linked to reproductive decision making.

ASGC ORAL 9
Referral Indications for Prenatal Genetic Services Over 15 Years: Trends and Practice Implications for Genetic Counseling

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Background: Prenatal screening and testing options have dramatically increased in the last decade. Our initial study analyzed the indications for referral for genetic counseling in our tertiary maternity center over a 10 year period 2006–2016, reflecting increased screening and ultrasound sensitivity. The study was extended to 15 years to capture changes in service implemented during the last 5 years. *Aim:* To extend audit to 15-year time period analyzing indications for referral for genetic counseling and implications. *Methods:* Indications and referral numbers were retrieved from databases, medical records and genetic files. Four time frames over 15 years from 2006–2021 were audited. Referrals were categorized into a single major indication for referral. Case complexity was measured as the number of hours required for case management from category 1 (approximately 1 hour) category 4 (6–8 hours). *Results:* Significant changes were noted over the study period 2006-2021. Referrals for fetal anomaly increased from 17% (83/486) to 52% (461/886) ($p < .05$). Diagnostic yield following prenatal diagnosis increased from 4% (13/294) to 31% (69/220) ($p < .05$). Accordingly, category 4 cases compromised 19% (92/486) of referrals in 2006 compared to 31% (272/886) in 2021 ($p < .05$). *Conclusion:* Our audit provides insight into the evolving role of genetic counseling in a tertiary maternity hospital. It is reflective of worldwide trends in prenatal ultrasound and screening sensitivity, and introduction of genomic testing options, resulting in a more complex patient population. Our service has responded to these demands with increased staff, greater opportunities for education and continued attention to self-care practices to ensure optimal patient care.

ASGC ORAL 10
Mainstreaming Genomic Testing for Pediatric Inborn Errors of Immunity: An Evaluation of a Novel Model of Care for Genetic Counselors

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Background: Genetic diagnosis of pediatric of inborn errors of immunity (IEI) influences management decisions and can alter clinical outcomes through guiding targeted or curative therapy. With increasing demand for genetic services, new models of care are needed to ensure families have coordinated, appropriately targeted and timely access to genomic testing. *Aims:* To i) evaluate the feasibility of a mainstreaming model of care in identifying positive cases of IEI, ii) impact of genomic testing on treatment outcomes, and iii) patient reported outcomes of parents of children who had genomic testing. Methods: This state-wide program included a genetic counselor embedded within the pediatric immunology service, fortnightly multidisciplinary team meetings (MDT) to guide patient and test selection, interpretation of whole exome sequencing results, and variant prioritisation meetings. Parents completed pre-and post-testing survey assessing understanding of, and impact of genomic testing. Recruitment occurred between November 2020 and September 2021. *Results:* Of the 43 children recruited, nine (21%) received a genetic diagnosis, of which four progressed to curative therapy. Additional investigations were arranged for children with a suspicious VUS ($n = 2$) and negative result ($n = 2$). On average, 14 healthcare providers attended the state-wide MDT, including pediatric and adult immunologists, genomic pathologists, genetic counselor, and other non-genetic-healthcare providers. Mean time of referral to consent was 34 days. Parents demonstrated understanding of the implications of testing and reported minimal decisional regret. *Conclusion:* Genomic testing can be mainstreamed for pediatric IEI. Our program improved access to genomic testing, facilitated treatment decision-making, and was acceptable to parents and clinicians alike.

ASGC ORAL 11
Young People's Experience of Predictive Genetic Testing for Inherited Cardiac Conditions: A Qualitative Study

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Background: Inherited cardiac conditions (ICC), like inherited cardiomyopathies (ICMs) and long QT syndrome (LQTS), are serious conditions that carry a risk of sudden death. Predictive testing (PT) is routinely available, however, the impact of this testing during

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the adolescent period is understudied. *Aim:* To understand the experience of young people who have undergone PT for ICC, from the perspective of the young person and their parent(s). *Methods:* Semi-structured, in-depth interviews were conducted with a purposive sample of young people aged 10-17 years who underwent PT for an ICC between January 2009 and July 2020. Their parents were also invited to participate. Thematic analysis was utilized to elicit a deep understanding of the experiences and needs of this cohort. *Results:* Nineteen predictively tested young people were interviewed (8 ICM, 11 LQTS; of these, 11 were gene-positive) as well as 15 parents. Three intersecting themes were identified: 'It's a family affair', highlighting the impact of family relationships and experience of the condition; 'Recognising day-to-day implications', including integrating gene status into self-perception and daily living; and 'Needing developmentally-appropriate intervention and support', recognising the evolving needs of the young person as an individual and within their family unit. *Conclusion:* Through exploration of young people's experiences and views, it was found that, regardless of their gene status, young people require individualized support and follow-up from both their genetic and cardiology specialists. Family structure and experience influences perception and understanding of the PT process, highlighting the need to appropriately involve, support and educate all family members.

ASGC ORAL 12
Integrating Genetic Testing and Counseling Into Ophthalmic Care: A Review of Genetic Testing Outcomes in Clinical Practice

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A retrospective audit of the families seen in the multidisciplinary Ocular Genetics Clinic (OGC) between December 2018 and May 2022 was conducted by reviewing the medical records, with a focus on genetic testing and outcomes. In this period, 430 patients have been seen by the geneticist/genetic counselor with a total of 393 genetic tests ordered. Of these, 186 diagnostic results have been received and disclosed to patients. The diagnostic rate was 67% (125/186). Of those with a pathogenic or likely pathogenic variant, the genetic diagnosis led to a change in clinical diagnosis in 12 patients (9.6%). Eighteen patients had variants of uncertain significance identified (10%) and a molecular diagnosis could not be reached in 43 patients (23%). Condition-specific detection rates were calculated to provide tailored genetic counseling. Macular/Cone-rod dystrophy ($n = 44/186$) and isolated rod-cone dystrophy ($n = 61/186$) were the largest groups, with detection rates of 72% and 70%, respectively. Statistical analysis was undertaken to review the effect of age at diagnosis, family history and sex assigned at birth, in obtaining a molecular diagnosis. This demonstrated that a pathogenic variant was more likely to be detected with a younger age at diagnosis (<20 years, $p = .018$). In contrast, no significant difference was identified in regards to family history ($p = .36$) and sex assigned at birth ($p = .37$). The implementation of the OGC is achieving its aims of providing expert care to families through increased access to genetic testing and identifying accurate diagnoses.

ASIEM ORAL 1
The Changing Face of Newborn Bloodspot Screening – A Rare Disease Sector Forum': Reframing Policy Conversations Through Collaborative, Multistakeholder, Informed Discussion

Louise Healy[1] and Nicole Millis[1]

[1]Rare Voices Australia

Background: The Australian Government's commitment to invest in the Newborn Bloodspot Screening (NBS) Program provides an opportunity to invest in and improve an important, successful rare disease program. The Government's commitment responded to, and was influenced by different stakeholders with a highly varied understanding of Australian NBS practice and policy. This resulted in different advocacy styles/strategies, including some misinterpretation of key measures. Rare Voices Australia facilitated a novel collaborative multistakeholder forum to facilitate rare disease sector education; consider complexities; and facilitate effective key stakeholder engagement; for effective and informed policy reform. *Aim:* Educate the rare disease sector to consider and respond to NBS complexities and encourage ongoing consultation with informed key stakeholders; to progress NBS policy reform that is appropriately informed by multistakeholder, specialist NBS expertise. This is aligned with the principles and priorities of the National Strategic Action Plan for Rare Diseases. *Methods*: Reviews of advocacy and political messaging related to NBS, consultations/discussions with key NBS stakeholders; including political leaders, Commonwealth and state and territory Departments of Health, NBS program managers, HGSA and rare disease patient group leaders. All of this informed speaker selection and key topics of the forum. *Results:* 142 people 'attended' the forum. The multi-stakeholder delegation included advocates; NBS specialists, state NBS Program managers/staff; Commonwealth and state departments of screening; the Commonwealth Department of Health Technology Assessment (HTA); Human Genetics Society of Australasia (HGSA); key political leaders; and industry. The forum engaged multiple stakeholders and brought people together as a rare disease sector to share expertise and problem-solve together.

ASIEM ORAL 2
Newborn Genomic Sequencing: Therapy Ready and Information for Life

Bruce Bennetts[1,2] and Gladys Ho[1,2] and on behalf of the Newborn Gen Seq Trail Consortium

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Newborn screening (NBS) is one of the most successful population health programmes, enabling the early diagnosis of a serious health condition, early management and better health outcomes. New genomic technologies and treatments are effecting opportunities to increase the number of conditions and benefits offered by NBS programs, guided by fundamental principles taking account of the condition, the screening test and intervention, and the impact on the whole program. The MRFF funded Newborn Gen Seq Trail (Newborn Genomic Sequencing: Therapy Ready And Information

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for Life) study will accelerate capabilities for using whole genome sequencing (WGS) technologies by assessing: feasibility, scalability (automation and bioinformatics), effectiveness and acceptability. In addition, the quality, safety, secure storage and oversight of genomic sequencing data generated will be evaluated. This will open up opportunities for future analysis of whole genome data, enabling rapid and efficient genetic diagnosis beyond the newborn period - potentially for life. The project will use a large cohort of de-identified NBS cards as well as cohorts: traditionally identified by NBS; babies with high creatine kinase; babies undergoing acute care trio WGS and finally a consented group of newborns with no apparent phenotype.
The team will collaborate with a national consortium (GENSCAN) co-ordinated by Australian Genomics to share learnings and to ensure all Australians benefit. Newborn Gen Seq Trail will provide high quality evidence to inform the integration of new models of genomic sequencing in newborn screening programs to be ready for new treatments and better health.

ASIEM ORAL 3
Introducing the Genomic Screening Consortium for Australian Newborns (GenSCAN)

Michael T. Gabbett[1], Sebastian Lunke[2], Gladys Ho[3], Bruce Bennetts[3] and on behalf of GenSCAN

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In 2022, the Genomics Health Futures Mission (GHFM), awarded $12 million to support research that will 'enable effective diagnosis in newborns of diseases caused by genetic mutations to support development of earlier and more effective interventions and treatments'. Genomic newborn screening stands to become the largest paradigm shift to one of society's most successful public healthcare initiatives. Already, large projects in the USA (The BabySeq Project) and the UK (Genomics England's Newborn Genomics Programme) are well underway, examining how best to implement this major evolution in the way in which newborns are screened for inherited diseases. In Australia, newborn screening programs are managed and delivered along jurisdictional lines by State Health Departments. This results in different screening practices across the country. In 2021, an Australian Parliamentary inquiry released its report (The Zimmerman Report) recommending that the disparate programs are harmonized into a National newborn screening program. GenSCAN is a consortium established in the wake of the GHFM genomic newborn screening grants. Its primary aim is to facilitate cross-fertilisation of ideas and lessons from the discrete research projects being established across Australia. Its secondary aims are to learn from the experience of traditional newborn screeners, policy makers, health economists and ethicists; and to look towards harmonisation of a genomic newborn screening program, as recommended in the Zimmerman report. This paper will introduce how GenSCAN was established, demonstrate its composition and governance, and inform how it plans to become to peak reference body for genomic newborn screening in Australia.

ASIEM ORAL 4
Rare Metabolic Disease Workforce White Paper: Advocating For National Reform

Falak Helwani[1], Nicole Millis[1], Angela Jackson[2] and Lauren Geatches[2]

[1]Rare Voices Australia, Australia and [2]Equity Economics and Development Partners

Background: Rare metabolic diseases are a heterogenous group of complex conditions causing overwhelming burden on families and the healthcare system. Despite growing demand due to improvements in diagnosis and survival, the Australian rare metabolic diseases workforce remains under resourced, impacting patients. In a novel collaboration involving clinicians, researchers, patients, carers, advocates and industry, and with the support of an expert steering committee and representatives from ASIEM, Rare Voices Australia led research to develop the 'Rare Metabolic Disease Workforce White Paper: Toward a Strengthened Rare Disease Workforce for Australia' (White Paper). *Aim:* To progress implementation of foundation principles and priorities in the National Strategic Action Plan for Rare Diseases, the White Paper explored the current composition, distribution, capacity and resourcing of the rare metabolic workforce to provide high-quality care to Australians living with a rare metabolic condition. The White Paper informs ongoing workforce advocacy and reform. Methods: Questionnaires, surveys and focus groups brought together hundreds of stakeholders. Since the launch of the White Paper, consultations with state departments of health, governments, HGSA and ASIEM have informed goals, recommendations and priority actions for rare metabolic disease workforce reform. *Results:* The White Paper's key findings highlighted the current state of rare metabolic care in Australia and challenges, strengths and variation in care across all jurisdictions. These findings informed development of baseline criteria for rare metabolic disease care and further consultations have led to a national strategy for a recognized, connected, coordinated, sustainable and innovative rare metabolic disease workforce.

ASIEM ORAL 5
Childhood Dementia: The Facts, Symptoms and Lived Experience

Gail Hilton

Childhood Dementia Initiative, Sydney, NSW, Australia

Background: Childhood dementia is an umbrella term encompassing 70+ rare genetic conditions that impact 700,000 children and young people globally. In Australia, childhood dementia causes more than 90 premature deaths per year; for comparison, there are 92 deaths per year in Australia from cancer in children aged 0–14 (Australian Institute of Health and Welfare, 2020). Collectively addressing childhood dementia provides the opportunity for greater scale, impact and improvement of both services and therapy development. *Aims:* The audience will: Understand childhood dementia causes and symptoms; Understand that when considered together, the disorders that cause childhood dementia cause a relatively high proportion of pediatric deaths; Gain further insight into the wide reaching impacts of dementia on children and their families; Consider how services can more appropriately meet needs. *Methodology:* This

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presentation will explore what childhood dementia is, the symptoms children and young people experience and statistics associated with it. Through a series of videos, families share their experience and talk about what they need from the health system. The materials presented in this presentation have been developed with funding from the Australian Federal Government and are informed by a burden study prepared by THEMA Consulting: Childhood Dementia in Australia. *Discussion:* This new approach within rare disease is driving *new conversations* that have the potential to change systems and practice across many disciplines resulting in accelerated therapeutic development and improved care and quality of life.

ASIEM ORAL 6
The Importance of a Genetic Diagnosis for Adult-Onset Mitochondrial Disorders: Motivations for Genetic and Genomic Testing

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Background: Mitochondrial disorders (MD) are rare, debilitating genetic conditions that are often difficult to diagnose due to the heterogeneity of presentations. The onset of symptoms can appear in childhood or later in life. Many individuals with MD experience a prolonged diagnostic journey to secure a molecular diagnosis. Advances in genetic and genomics and variant/gene-disease correlations for MD have improved diagnostic rates, however patients' lived experiences and motivations for seeking a genetic diagnosis remain unexplored. *Aim:* To understand the motivations of individuals and their families for seeking genetic or genomic testing for MD, and to understand the importance of a genetic diagnosis. *Methods:* A sequential exploratory study was employed, utilizing quantitative surveys to inform more in-depth semistructured interviews exploring the motivations and perspectives of patients with MD. Quantitative data were analyzed using STATA and qualitative interviews underwent thematic analysis for identification of emerging themes. *Results:* The Mito Foundation and other rare disease patient support and advocacy groups were fundamental in recruitment of participants with a genetic diagnosis of adult-onset MD. The following themes have emerged from preliminary data: finding an answer, validation of a real condition, uncertainty about the future and management and treatment implications. More in-depth analysis will be presented. *Conclusion:* Results of this project may provide insight to healthcare practice to better support patients with MD in their diagnostic journey, as motivations for, and the importance of a diagnosis are understood. MD support and advocacy groups can utilise results to further understand the needs of the MD community.

ASIEM ORAL 7
Incidental Diagnosis of Metabolic Conditions on Carrier Screening – Experience of Changes in Treatment in an Adult Metabolic Centre

Sarah Donoghue[1,2], Julie Panetta[1], Tim Fazio[1,3], Martin Delatycki[4,6], David Amor[4,6], Kate Lefebure[1], Claire Rutledge[1], Kaye Quick[1], Christine Fischer[1], Anne-Marie Desai[1] and Gerard de Jong[1,3]

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The improved access to preconception testing has resulted in the identification of pathogenic variants associated with clinically relevant inborn errors of metabolism. We report on 3 years of experience regarding the new diagnosis of metabolic conditions in individuals undergoing carrier screening and the resulting changes in their medical management. From July 2019 – July 2022 there were 8 referrals to the statewide metabolic service following the incidental diagnoses of metabolic conditions in prospective parents. This testing resulted in the identification of 1 patient with Glycogen Storage Disease type V, 1 patient with hyperphenylalaninaemia, 2 patients with MCAD deficiency, and 4 patients with OTC deficiency. 5 of the 6 women diagnosed required provision of delivery plans to ensure metabolic stability. 62.5% of the 8 patients had experienced symptoms of their metabolic condition, with the preconception screening providing closure of previously unexplained symptoms. Following diagnosis, 3 out of the 4 patients with OTC deficiency opted for PGT or prenatal diagnosis during pregnancy. The pattern of referral illustrates that carrier testing has led to the identification of conditions in patients who did not receive the benefit of newborn screening, as well as the recognition of conditions beyond the scope of newborn screening. The disclosure of the diagnoses had implications for the management of the pregnancies and foetal development. This highlights the merit of the screening program in conjunction with timely follow up of newly diagnosed patients in the statewide centre for management of adult patients with inborn errors of metabolism.

Special Interest Group Meetings

Australasian Society of Diagnostic Genomics

Identifying Chromosome Haplotype Blocks Using SNP Chromosome Microarray Genotyping – A Proof of Concept

Con Ngo[1,4], Bruce Bennetts[3,4], Elizabeth Farnsworth[3], Bernadette Hanna[2], Gladys Ho[3,4], Tiffany Lai[3] and Dale Wright[1,4]

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Background: Segregation of a variant of uncertain significance (VUS) to strengthen pathogenicity evidence can be challenging when only a single parent is available. While SNP microarray is widely used for detecting copy number changes and regions of homozygosity, SNP genotyping can identify haplotypes that may aid segregation studies. We present a proof-of-concept using SNP genotyping for haplotype analysis and apply to a heterozygous GABRA1 (c.440G>A) VUS with unknown inheritance. Neither mother nor unaffected sibling were carriers and the father was unavailable. *Aim:* Identify haplotype blocks to segregate a variant with incomplete family pedigree. *Methods:* SNP genotyping using Illumina CytoSNP-12 Beadchip was performed by Duo analysis of siblings to identify haplotype blocks of shared alleles

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[0, 1 and 2]. Trio analysis was then performed between one parent and siblings to track inherited parental alleles. We first did this in a healthy family then applied the same approach to our family with the GABRA1 variant. *Results:* Duo genotyping of the healthy family showed multiple haplotype blocks of shared alleles between siblings. Trio genotyping showed haplotypes where i) both siblings received the same parental allele, or ii) each sibling received a different parental allele. The GABRA1 gene was found within a haplotype block, where both siblings received the same parental alleles. *Conclusion:* This 'proof-of-concept' study with Duo/Trio genotyping of shared haplotypes between siblings and single parent can identify haplotype blocks that can assist with variant segregation. For the GABRA1 variant, the shared haplotype blocks between siblings infers a likely de novo origin.

Saliva Sampling Shows Increased Technical and Clinical Utility over Blood Sampling in Genetic Investigation of Syndromic Intellectual Disability

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SNP-microarray analysis is considered the first-tier test for neurodevelopmental disorders. Traditionally, testing has required blood sampling, which is invasive and may be stressful for the patient. Recently, genomic DNA from saliva has become an important source for genetic testing. We investigated the suitability of DNA extracted from saliva versus blood for SNP-microarray. Secondly, we investigated whether SNP-microarray genomic testing of saliva has a different diagnostic yield than blood for pathogenic copy number variants (CNVs). For quality and logistics, we compared DNA and SNP microarray quality metrics for >20,000 saliva and blood collections. 5000 saliva samples were also investigated for quality metrics of in home versus clinic collections. To assess clinical utility we, analysed outcomes from 366 patients who underwent microarray testing on both blood and saliva. The quality and quantity of DNA was comparable between blood and saliva with no difference in CNV detection sensitivity. Home saliva sampling gave better DNA yields and quality metrics over clinic sampling. Of the clinical utility cohort, 16/366 (4.4%) had mosaic pathogenic CNVs or aneuploidy detected in saliva that was not detected in blood. All 16 individuals had syndromic intellectual disability (ID), accounting for 7.2% of the cohort who had syndromic ID (220/366). By contrast, nonmosaic pathogenic CNVs were 100% concordant between blood and saliva. Given that microarray testing on DNA derived from saliva has equivalent quality, logistical advantages and has a superior diagnostic yield to blood in individuals with syndromic ID, it should be the preferred sample type in this population.

Germline Sequencing of DNA-Damage-Repair Genes in Two Hereditary Prostate Cancer Cohorts Reveals Rare Risk-Associated Variants

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Background: Rare, inherited variants in DNA damage repair (DDR) genes play an important role in prostate cancer (PrCa) susceptibility. *Aim:* To interrogate two independent high-risk familial PrCa datasets to identify novel, rare DDR variants that contribute to PrCa risk. *Methods:* Massively parallel sequencing data from Australian and North American familial PrCa datasets were examined for rare, likely deleterious variants in 35 DDR genes. Putative high-risk variants were prioritised based on frequency (minor allele frequency <1%), mutation type (nonsense, missense, or splice), segregation with disease, and in silico predicted deleteriousness. Six prioritised variants were genotyped in a total of 1,963 individuals (700 familial and 459 sporadic PrCa cases, 482 unaffected relatives, and 322 screened controls) and M_{QLS} association analysis performed. *Results:* Statistically significant associations between PrCa risk and rare variants in ERCC3 (rs145201970, $p = 2.57\text{x}10^{-4}$) and BRIP1 (rs4988345, $p = .025$) were identified in the combined Australian and North American datasets. A variant in PARP2 (rs200603922, $p = .028$) was significantly associated with risk in the Australian dataset alone, while a variant in MUTYH (rs36053993, $p = .031$) was significantly associated with risk in the North American dataset. *Conclusion:* Our study implicates several rare germline DDR variants in familial PrCa risk. Further, we provide evidence that a proportion of rare DDR variants will elude screening where it is confined to early-onset or high-grade familial disease, with implications for the selection of gene-based therapies targeting DDR pathways in PrCa patients.

Prostate Tumors from HOXB13 G84E Rare Variant Carriers Have Distinct Proteome and Transcriptome Signatures Compared To Noncarriers

Kelsie Raspin[1], Zainab Noor[2], Adel Aref[2], Chol-hee Jung[3], Shaun Donovan[4], Steve Williams[2], Peter Hains[2], Qing Zhong[2], Jodee A. Gould[5], Rosemary Balleine[2], Phillip J. Robinson[2], Roger R. Reddel[2], Liesel M. FitzGerald[1] and Joanne L. Dickinson[1]

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Background: Prostate cancer (PrCa) has the highest heritability of any common cancer, and the most well-known rare PrCa risk variant is G84E in HOXB13 (rs138213197). This variant alone has been associated with a 3-16-fold increase in PrCa risk across multiple studies, including our Tasmanian PrCa Genetic Study resource ($OR = 6.59$; $p = 4.2\text{x}10^{-5}$). Although there have been numerous studies attempting to elucidate how this variant drives prostate tumor development, the exact mechanism remains unknown. *Aim:* There is growing evidence that germline genetic variants, including rare variants, drive transcriptome and proteome signatures in tumors. Our aim was to determine whether prostate tumors from HOXB13 G84E rare variant carriers have distinct proteome and transcriptome signatures compared to non-carriers. *Methods/Results:* We have identified 210 proteins that are differentially expressed in prostate tumors from HOXB13 G84E carriers ($n = 6$) compared to noncarriers ($n = 18$) using Data-Independent Acquisition Mass Spectrometry. The pathways of the proteins significantly expressed in G84E variant carrier tumors included mitochondrial translation and organisation, cytokinesis, post-translational modification, and mRNA destabilisation. We have also employed the Human Ampliseq Transcriptome GE panel to generate transcriptome signatures of these tumors ($n = 6$ carriers and 14 noncarriers). Preliminary analysis indicates that 22 of the 210 differentially expressed proteins also overlap the

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significantly differentially expressed genes from the transcriptome analysis. *Conclusion:* Tumor proteome and transcriptome data identify complementary information regarding HOXB13 G84E prostate tumors, which may be used to understand the biology of these cancers and possibly identify treatment targets.

Germline Copy Number Variants and Endometrial Cancer Risk

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Endometrial cancer is the most common gynecological cancer in New Zealand, with Māori and Pasifika women under the age of 50 experiencing increased prevalence and mortality over the past 20 years. Women with first- and/or second-degree family history of endometrial cancer have two-to-three-fold increased risk of developing the disease. Inherited genetic variants associated with endometrial cancer provide evidence of genes or functional domains that lead to disease predisposition. While single nucleotide polymorphisms have been shown to alter the risk of endometrial cancer, the impact of copy number variants (CNVs) has been underexplored. Through international collaboration, we have performed a genome-wide association study (GWAS) using data on rare CNVs from 4115 endometrial cancer cases and 17,818 controls. CNV burden analysis demonstrated that women who developed endometrial cancer exhibited a significantly greater number of CNVs throughout their genome (1.2-fold, $p = 3.79^{-93}$), with the largest cohort burden differences occurring when CNVs encompass functionally important regions, including genes (1.3-fold, $p < 3x10^{-70}$) and exonic regions (1.3-fold, $p < 1x10^{-49}$). Furthermore, proportion tests between cohorts have shown an increased deletion load within established cancer risk genes such as mismatch repair genes ($p < 3x10^{-6}$), BARD1 and AKT1 ($p < .05$). ACMG-CNV classification guidelines are being applied to these variants to further refine potential clinical relevance. Our CNV-GWAS identified multiple novel candidate risk genes for disease, including NPL ($OR = 1.7$, $p = .002$). Pathway analysis identified 16p11.2 proximal deletion syndrome ($p < 1 \times 10^{-21}$) which is associated with severe obesity, a known risk factor for endometrial cancer. Results from this study provide further insight into the etiology of endometrial cancer.

Somatic Mutational Landscape of Hereditary Hematopoietic Malignancies caused by Germline Variants in RUNX1, GATA2, and DDX41

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Predisposition to hereditary hematopoietic malignancies (HHMs), caused by germline RUNX1, GATA2, or DDX41 variants, have a highly variable risk for leukemogenesis. Gaps in understanding pre-malignant states in HHM syndromes have hampered efforts to design effective clinical surveillance regimes, provide personalised preemptive treatments, and appropriate counseling to patients. We have addressed some of these knowledge gaps using the largest known international cohort of germline RUNX1, GATA2, or DDX41 variant carriers, including both without 'unaffected-carriers' and with malignancy 'affected-carriers'. We utilized a uniform bioinformatics approach, to identify somatic variants which

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develop in HHM-carriers before and after malignancy diagnosis, identifying distinct and unique leukemogenic mechanisms for each syndrome. We identified striking heterogeneity in rates of clonal hematopoiesis (CH) with a high prevalence in RUNX1 and GATA2 unaffected-carriers (including early-onset) and a paucity of CH in DDX41 unaffected-carriers. In RUNX1-driven CH we detected 'high-risk' variants in TET2, PHF6 and most frequently in BCOR, all of which were recurrently mutated in RUNX1-driven malignancies, suggesting CH is a direct precursor to malignancy. Leukemogenesis in both RUNX1 and DDX41 carriers was often driven by second-hit variants in RUNX1 and DDX41 respectively, with somatic RUNX1 variants likely representing a 'late' leukemogenic event. This study lays the foundation for developing novel-preventative therapies and the implementation of gene-specific clinical monitoring requirements. Individuals with RUNX1 variants will require regular monitoring for somatic variants in several genes throughout their lifetime, while DDX41 carriers are likely to benefit from monitoring throughout adulthood for driver DDX41 variants using sensitive technology to detect low-frequency initiating events.

Oxford Nanopore Sequencing for the Resolution of De Novo Copy Number Variants (CNVS) in Patients Undergoing Preimplantation Genetic Testing (PGT-M)

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De novo variants historically excluded patients from accessing Preimplantation Genetic Testing (PGT-M) as testing relies on linkage. Whole genome amplification has allowed patients with de novo variants detectable by Sanger sequencing or microarray, to increasingly utilise PGT-M. However, de novo 'intermediate' sized CNVs, single exon to ~10Mb in size, are not easily resolved. Patients with these variants have to date only had the option to undertake prenatal testing of naturally occurring pregnancies. We hypothesised decoding the breakpoints of de novo 'intermediate' variants by long-read sequencing could allow these patients access to PGT-M. We undertook long-read sequencing of two patients with de novo intermediate CNVs using Oxford Nanopore GridION sequencing, confirming the breakpoints by Sanger sequencing, and performing PGT-M using single tandem repeat (STR) linkage. Patient 1 has a deletion of exons 4-5 of RUNX2 estimated to be 6.1-68.9Kb in size. Nanopore sequencing yielded a single read spanning 10.9Kb and Sanger sequencing confirmed a heterozygous NM_001024630.3(RUNX2):c.424-414_685+4321del variant. PGT-M showed the breakpoint-specific sequence segregated with a single allele in 7/9 embryos. Patient 2 has a deletion of exons 16-20 of PHEX estimated to be 14.7-54.8Kb in size. Long-read sequencing identified five reads spanning 31Kb and Sanger sequencing confirmed a heterozygous NM_000444.6(PHEX):c.1646-1275_2071-2725del variant. PGT-M for this patient is ongoing at time of writing. As increased sequencing yields more de novo CNVs, the importance of resolving 'intermediate' variants will also increase. Nanopore sequencing is an efficient and increasingly cost-effective method to undertake long-read sequencing and facilitate PGT-M for these patients.

Use of Karyomapping for Preimplantation Genetic Testing for a Monogenic Condition (PGT-M) in Consanguineous Couples

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Background: Preimplantation genetic testing for a monogenic condition (PGT-M) is a reproductive option for couples at risk of passing a monogenic condition on to their child. Testing is often performed using Karyomapping, a linkage-based technique in which PGT-M diagnosis is based on an assessment of Single Nucleotide Polymorphism (SNP) markers surrounding the gene of interest. While Karyomapping has been widely adopted worldwide, only a few studies have reported the application of this technique in consanguineous couples with shared SNP haplotypes. *Aim:* This study aimed to assess whether Karyomapping could provide a reliable and accurate method of PGT-M for four consanguineous couples presenting for treatment at Monash IVF. *Methods:* Karyomapping was validated for each consanguineous couple prior to IVF/PGT-M. Validation was performed using a DNA sample from each partner and a reference (close relative of known genetic status). Karyomapping was performed using Illumina's HumanKaryomap-12 BeadChip coupled with BlueFuse Multi software (Illumina). The SNP profile of each partner was compared with the SNP profile of the reference to identify a unique SNP fingerprint (haplotype) for the affected and unaffected gene copies. These SNP profiles were compared against those of the embryo/s to facilitate PGT-M diagnosis. *Results:* PGT-M was feasible for all four consanguineous couples, despite shared SNP haplotypes due to known consanguinity. In addition to PGT-M, analysis of key and non-key SNPs during feasibility testing enabled the parental origin of a familial variant to be determined in a heterozygous reference. *Conclusion:* PGT-M using Karyomapping is a viable option for consanguineous patients.

Re-Defining Polycystic Kidney Disease: How Atypical Presentations of Early-Onset PKD are Shining New Light on Genotype-Phenotype Correlations of the DISORDER

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Background: Polycystic kidney disease (PKD) is an inherited condition that causes cysts to form in the kidneys and liver, eventually leading to organ failure. Typically, autosomal dominant inheritance

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results in late-onset PKD, while autosomal recessive inheritance causes aggressive early-onset phenotypes. Here, we outline atypical fetal presentations of PKD that demonstrate the genotype-phenotype correlation of PKD is not as clearly defined as first thought. *Aim:* To determine the genetic cause of congenital onset PKD in cases referred to the Genomic Autopsy Study. *Methods:* Familial trio exome sequencing was utilized as part of the national genomic autopsy study to identify potentially causative variants in fetal cases identified with PKD on post-mortem examination. *Results:* One proband with a family history of ADPKD presented with polycystic kidneys, however post-mortem examination suggested this case was atypical for the late-onset disorder. Compound heterozygous variants in an ADPKD gene, PKD1, were identified suggesting a severe early-onset case of PKD. A subsequent proband was identified with ARPKD with compound heterozygous variants in an ADPKD gene, DNAJB11. Two probands with atypical presentations of PKD were found to have compound heterozygous or homozygous variants in the autosomal recessive PKD gene PKHD1, indicating that ARPKD phenotypes are likely to be highly heterogeneous. *Conclusion:* These results suggest that biallelic ADPKD should be considered in atypical fetal polycystic kidney disease and there is more heterogeneity in ARPKD than previously thought. This expansion of knowledge ensures appropriate clinical testing is requested to better inform clinical counseling and reproductive care for families with both AR and AD presentations of PKD.

Defining The Role of a Novel Gene 'MyoD Family Inhibitor Domain Containing (MDFIC)' Important in Cardiovascular Development

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Background: Central conducting lymphatic anomaly (CCLA), characterised by dysfunction of core collecting lymphatic vessels including the thoracic duct and cisterna chyli, often manifests in utero as non-immune hydrops fetalis (NIHF). CCLA is a severe disease for which few effective treatments are available. The genetic etiology of CCLA remains uncharacterised in most cases. *Methods/Results:* By exploring the genetics underlying lymphatic vascular disorders, we identified seven affected individuals in six independent families with CCLA in whom biallelic variants in MDFIC were identified. Generation of a mouse model of a recurrent human MDFIC truncating variant (Met131Asnfs*3) revealed that $Mdfic^{M131fs*/M131fs*}$ homozygous mutant mice died perinatally exhibiting chylothorax with accumulation of lipid rich chyle in the thoracic cavity. The lymphatic vasculature of these mice was profoundly mispatterned, particularly in the diaphragm and thoracic wall, and exhibited defects in lymphatic vessel valve development. This work is the first to identify pathogenic MDFIC variants underlying human lymphatic vascular disease and reveals that MDFIC plays a pivotal role in the development of lymphatic vessel valves. *Conclusion:* We demonstrate that the cysteine-rich C-terminus of MDFIC, which is absent in the MDFIC p.Met131fs* truncated protein, is essential for interaction with GATA2. Alteration in GATA2 subcellular localisation and transcriptional activity within cells in a setting of MDFIC deficiency was detected. Our preliminary data also suggest that biallelic truncating MDFIC variants in patients exhibiting CCLA increases MAPK/ERK signalling activity, raising the question as to whether dampening activity of this pathway might provide a therapeutic opportunity for the treatment of CCLA caused by MDFIC variants.

A Two-Step Approach for Detecting and Phasing Variant Associated MIS-Splicing

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Background: Short-read RNA sequencing (srRNA-seq) struggles to align aberrant transcripts resulting in loss of diagnostically important information. We present a two-step approach using RT-PCR to validate splice aberrations identified by srRNA-seq and phase canonically spliced transcripts for accurate variant interpretation. *Methods:* Blood RNA from an individual with Aicardi-Goutières syndrome and compound heterozygous variants in RNASEH2B NM_024570.3:c.[321+287C>G];[529G>A]) was prepared using

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rRNA depletion to yield ~216M 150 bp paired-end reads. Reads were aligned to GRCh38 using STAR aligner. Gel-extracted RT-PCR amplicons were analysed by Sanger sequencing. *Results:* srRNA-seq identified exon 4 skipping and cryptic acceptor activation within intron 4 of RNASEH2B associated with paternal variant c.321 +287C>G. Manual inspection of reads revealed ectopic inclusion of a pseudoexon (PE) within intron 4. STAR aligner could not align split reads splicing from the PE donor and were instead soft-clipped or misaligned as exon 4 skipping. Custom alignment allowed split reads to align to the PE donor. RT-PCR confirmed PE inclusion and exon 4 skipping was not detected. Sanger sequencing of an amplicon encompassing the c.529G>A variant in trans showed canonically spliced transcripts were detected exclusively from the maternal allele. *Discussion:* Misaligned and/or soft-clipped reads remain a significant caveat of srRNA-seq. Apparently low levels of detected PE inclusion could be due to partial mis-splicing or transcripts degraded by nonsense mediated decay. Use of a coding SNV to phase transcripts by RT-PCR confirmed complete mis-splicing from the paternal allele. We recommend custom alignment of srRNA-seq data followed by RT-PCR validation for increased diagnostic confidence.

Improving Clinical Translation of High-Throughput Functional Assay Data with MAVEDB

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Background: Understanding the effects of genetic variants is essential for using a patient's sequence to guide diagnosis and treatment. However, our ability to acquire sequence data vastly outstrips our ability to interpret it, leading to the rapid accumulation of Variants of Uncertain Significance (VUS) in diagnostic datasets. High-quality functional assay data is important evidence for interpreting VUS, but traditional functional assays only evaluate a handful of variants at a time. By contrast, Multiplexed Assays of Variant Effect (MAVEs) deliver accurate, ancestry-agnostic functional data for thousands of variants in a gene simultaneously, making them a powerful tool for variant reclassification, and data generation continues to accelerate. *Aim:* Our goal is to make MAVE data easier for clinical curators to use for variant interpretation by addressing challenges in discoverability and interpretability. *Methods:* We have developed MaveDB, the database of record for MAVE datasets, and have defined purpose-built data models and standards to enable clinical translation and integration into clinical workflows. *Results:* MaveDB already contains more than 250 datasets and 3 million variant effect measurements across diverse targets, including clinically actionable genes such as BRCA1, MSH2, PTEN, SCN5A and TP53. Recent international studies have shown that 50-93% of VUS can be reclassified using MAVE data. Analysis of Australian diagnostic laboratory data (Shariant, December 2021) showed that only 10% of variant classifications used functional data, demonstrating opportunity for broader adoption of MAVEs nationally. *Conclusion:* Wider adoption of MAVE data within Australia enabled by MaveDB will help reduce the number of VUS returned clinically.

Australasian Society of Genetic Counsellors

Evaluation of the Parkville Familial Cancer Centre Breast Cancer Mainstream Genetic Testing Program

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Introduction: Increasing demand for genetic testing as a standard test for many breast cancer patients has necessitated new models of care for clinical genetics services. To improve accessibility the Parkville Familial Cancer Centre (PFCC) established a program of mainstream breast cancer genetic testing in surgical and oncology clinics. A comprehensive program evaluation was undertaken after two years to examine the impact and outcomes of this model. *Aim:* Evaluate patient experiences and outcomes, clinician impact, and the health service implications of mainstreaming breast cancer genetic testing. *Methods:* Data were collected via a clinical audit, patient survey and semistructured interviews, and breast specialist survey. Descriptive analysis was undertaken for quantitative measures and content analysis for qualitative data. *Results:* Between 2017 and 2019, 72 breast specialists from nine hospitals facilitated genetic testing for 230 patients, resulting in changes to treatment for most patients (87%). Sixty-eight patients (30%) completed the survey with most satisfied with the information provided by their breast specialist before testing (94%) and after results (86%). Twenty patients were interviewed and most preferred testing via mainstreaming rather than an FCC due to the existing relationship with their trusted breast specialist and feeling overwhelmed by many treatment-related appointments. Forty-five breast specialists responded (63%), and most had discussed (87%) and consented (80%) patients for mainstream genetic testing. The majority (89%) believed mainstream genetic testing should be part of their role and felt well supported by the PFCC (90%). *Conclusion:* This mainstreaming model implemented by the PFCC has successfully met patient and clinician needs.

Genetics Follow Up After Rapid Genomic Sequencing in Intensive Care: Current Practices and Recommendations for Service Delivery

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Background: The clinical utility of rapid genomic sequencing (rGS) for critically unwell infants and children has been extensively

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demonstrated. However, the delivery of rGS occurs at a time of immense pressure and stress for parents. While previous research has highlighted the value of pre- and post-test genetic counseling as an integral part of delivering rGS in a way that supports the information and psychological needs of families, contact with families after rGS result disclosure presents an opportunity to meet these needs as they evolve. However, limited research has explored such follow-up practices. *Aim:* To explore the practice, preferences and perspectives of health professionals and parents of genetics follow-up after rGS. *Methods:* Semi-structured interviews were conducted with 30 parents, seven genetic counselors (GCs) and four intensive care physicians with experience in rGS. Transcripts were analysed using reflexive thematic analysis. *Results:* Current practices surrounding genetics follow up after rGS were highly variable, resulting in some families not receiving the ongoing care they needed. Reasons identified by families for wanting follow-up care represented only a subset of those identified by health professionals. While GCs routinely provided their details to allow parents to initiate further contact, this was not always sufficient for follow-up care. Health professionals identified both organisational and psychosocial barriers to conducting follow up. *Conclusion:* As rGS transforms the diagnostic pathway in rare disease, there is a need for a co-designed, standardised but flexible model for follow-up care with genetics professionals so that families' evolving needs are met.

ASGC Interesting Case Report: Polycystic Kidney Disease and the Hunt for the Elusive Causative Variant

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Referral: A 65 year old woman with polycystic kidney disease (PKD). She remained well 15 years post kidney transplant. *Family history:* Mother (died age 61 on dialysis), two maternal aunts diagnosed PKD, both siblings diagnosed PKD, one had a kidney transplant, She had two sons diagnosed with PKD and two unaffected sons. *Indication for genetic testing:* The patient's two affected sons were in the early stages of kidney transplant planning. Both of her unaffected sons had come forward as potential living kidney donors. In order to offer predictive genetic testing to clarify their risk of PKD prior to kidney donation, familial pathogenic variant needed to be identified. *Outcome:* The genetic testing odyssey involved three genetic services, two research studies, genetic testing of four family members using five different platforms, and spanned seven years. Eventually, a PKD1 likely pathogenic variant was identified. This case highlights the importance of choosing the right test and the impact it can have on generations of a family.

A Complex Prenatal Case Involving Long Continuous Stretches of Homozygosity (LCSH), Telehealth, Interpreters, Uncertain Results and Laboratory Complications

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A consanguineous couple have a daughter with homozygous SDBS gene mutations and RD3 gene deletions. She is blind (caused by the RD3 deletions) with intellectual disability (ID) and autism (ASD), presumably but not certainly caused by the SDBS mutations. Another daughter has homozygous SDBS mutations with no health concerns. We saw them in their third pregnancy to arrange prenatal diagnosis. They were very concerned about having another child with ID, autism and blindness. Laboratory complications delayed the prenatal results, which confirmed the baby had extensive LCSH and carried homozygous RD3 deletions but not the SDBS mutations. After careful deliberation, the couple requested a termination of pregnancy (TOP). We discuss complex counseling issues, including genetic counseling regarding uncertainty, using interpreters via telehealth, obtaining informed consent, and facilitating informed decision-making regarding TOP in complex prenatal cases. Additional challenges here include navigating laboratory delays due to technical limitations and accessing TOP options.

Ethical Complexity of Counseling Monozygotic Twins With Differing Views on Predictive Testing for Early Onset Alzheimer's Disease

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Fifty-five year old, female, asymptomatic monozygotic twins were referred for genetic counseling to discuss predictive testing for a PSEN1 familial mutation known to be associated with Early Onset Alzheimer's disease in their family. The twins were seen separately over multiple appointments by the same counselor. Genetic counseling revealed the twins held discordant attitudes towards predictive testing for PSEN1. This case study examines the unique counseling issues that emerged, and reflects on the complex ethical issues the genetic counselor navigated while exploring each patients' views around genetic testing while supporting autonomous decision making. Other issues raised by this case include grief and loss, transference and countertransference. Finally, this case explores the genetic counselor's reflections on the therapeutic relationship, especially when working with twins and the value of supervision.

Removing Choice? An Experience of Returning a Pathogenic Variant Detected Through Population Genomic Screening.

Yasmin Bylstra

SingHealth Duke-NUS Institute of Precision Medicine, Singapore

Through a population genomic screening initiative in Singapore, a 35-year-old female was identified with a pathogenic MSH2 variant. Reporting a significant family history of ovarian and colorectal cancer, the possibility of Lynch syndrome did not appear to be unexpected. During the genetic counseling consultation she shared her father carried a MSH2 pathogenic variant and she had decided not to proceed with predictive testing. Her response was unexpected as she had consented to receive genomic findings and agreed to attend an appointment. With her genetic report in hand, this situation posed great discomfort as I deliberated whether to disclose the finding she had chosen not to receive. This case will review the inherent challenges of disclosing genomic test results in absence of traditional genetic counseling models which are tailored towards addressing client expectations and decision making, considerations relevant to implementing population screening programs.

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Would You Like More Results With That?

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Summary: In this case, carrier testing initiated well in advance of pregnancy for familial genetic conditions revealed a potential diagnosis and resulted in rapid prenatal diagnostic testing for an unrelated condition. This demonstrates some of the issues that may arise with reanalysis and the receipt of new information mid trimester of pregnancy, and the impact on patients. *Case:* A women initially presented with a family history of Lesch-Nyhan syndrome and subsequently with a family history of cystic fibrosis (CF). She had *HPRT*1 gene analysis and expanded carrier screening for reproductive planning purposes and was found to be a carrier for a number of conditions and potentially affected by a CFTR-related disorder. Further testing performed for her mother and partner indicated they are both also carriers for a CFTR-related disorder. The couple presented again in pregnancy to consider prenatal diagnosis for CF. The prenatal diagnostic testing result indicates their baby is a compound heterozygote for two variants in the CFTR gene rarely associated with CFTR-related disorders and they proceeded with the pregnancy. However, months later an amended report was received indicating a 1 in 4 (25%) chance of Wilson disease in the pregnancy. Rapid trio exome sequencing with targeted analysis for familial variants in the ATP7B gene indicates both *ATP7B* gene variants are present in the pregnancy.

Approaching Discussions About Genetics With People Who Have Palliative Care Needs: A Qualitative Exploration With Genetic Health Professionals

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Background: Genetic information can provide clinical benefits to families of palliative patients. However, efforts to mainstream genetics and genomics have not focused on palliative populations, leaving an evidence gap about the barriers and facilitators affecting the integration of genetics into palliative care. *Aim:* To explore the views and experiences of genetic clinicians in approaching genetic discussions with palliative patients and their families, and generate possible solutions to support clinicians to integrate genetics into palliative care. *Methods:* We conducted an interpretive descriptive qualitative study with genetic counselors and clinical geneticists using semistructured interviews and focus groups. Findings were generated using reflexive thematic analysis. *Results:* Twenty-six genetic clinicians participated across two focus groups and 13 individual interviews. Three themes were identified: (1) Focusing on the benefit to the family, (2) The discomfort of addressing genetics near end-of-life, and (3) 'It's always on the back-burner': challenges to getting genetics on the palliative care agenda. The benefits of discussing genetics were tempered by concerns of 'intruding' upon palliative patients and their families at end-of-life. Participants perceived genetics as low priority and value to palliative care clinicians. Possible solutions to enhance palliative-genetic awareness, integration and access included technology use (e.g., telehealth consultations and improved electronic medical record systems) and having a specialised palliative care genetic counselor. *Conclusion:* Genetic clinicians want improved service leadership and awareness of the benefits of palliative-genetic testing. Health services must support clinicians to address reported barriers for the benefits of genetic information to be realised by palliative patients and their families.

Attitudes of Filipino Parents of Children With Down Syndrome on Noninvasive Prenatal Testing

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Background: Globally, there has been an increasing uptake of Non-Invasive Prenatal Testing (NIPT). In the Philippines, the test is currently available through private laboratories and can be availed by the families who can afford the out-of-pocket cost. In a country where elective termination of pregnancy is not an option, the question arises as to the relevance of this testing, even among health professionals. *Aim:* This study aimed to explore the attitudes of Filipino parents of children with Down Syndrome (DS) toward non-invasive prenatal testing (NIPT), in order to better understand the benefits and drawbacks of NIPT within the Filipino sociocultural, legal, and healthcare contexts. *Methods:* This study used an exploratory qualitative study design drawing from phenomenology and symbolic interactionism frameworks, using thematic analysis of in-depth interviews. *Results:* Five major themes were generated from the study: (1) experience at diagnosis and journey to acceptance, (2) NIPT is available, simple and safe, but not affordable, (3) NIPT will allow you to prepare, (4) NIPT may cause anxiety and abortions obtained illegally or abroad, and (5) long-term consequences include better prenatal care and 'opening Pandora's Box'. *Conclusions:* Study participants acknowledged the value of NIPT in providing early diagnosis and subsequently emotional, mental, spiritual, and financial preparation. This said, they also emphasized that such early detection may cause anxiety and even thoughts of termination for some despite abortion being against the law and predominant religious beliefs. For those undergoing NIPT and receiving positive results, study participants highlighted the need to receive proper and non-biased counseling from both health professionals and parents who have children with DS.

Our Voice: Mito Community Priorities for the Australian Mitochondrial Donation Pilot Program

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Background: The Mitochondrial Donation Law Reform (Maeve's Law) Bill, passed in March 2022, allows for a pilot study of this specialised IVF technique. Mitochondrial donation will enable women

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with known pathogenic mtDNA changes to have genetically related children without transmitting severe mitochondrial disease. *Aim:* Mito Foundation aimed to understand mito community members' (those living with, or supporting loved ones with mito) priorities for a successful pilot program implementing mitochondrial donation in Australia. *Methods:* We conducted semi-structured interviews with 16 individuals purposively sampled from the mito community. Interviews explored expectations, hopes, concerns and information needs. Transcripts were analysed using thematic analysis. *Results:* We identified four themes. The mito community: (1) needs clarity on trial timeframes, (2) has questions about eligibility, (3) sees both outcomes and support through the process as important, and (4) wants clear information about the pilot for themselves and the wider community. Interviewees raised concerns about the possible exclusion of specific types of mito from the pilot program, travel burden, psychological support and the integration of health services with the research team. We developed six recommendations in response and shared the project report with researchers preparing applications to run the pilot program, the Australian Department of Health, and other stakeholders. *Conclusion:* The project demonstrates an approach to rapid consumer engagement to support policy making and research planning. Ongoing engagement with the mito community is important for a successful mitochondrial donation pilot program. These findings will inform the pilot design to achieve the best outcome for the mito community.

Race, Ethnicity and Ancestry Reporting in Genetic Counseling Research: A Modified Scoping Review

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Background: Studies on the use of Race, Ethnicity and Ancestry (REA) concepts and terms in genetic research are limited. *Aim:* To offer a snapshot of how REA data are collected, reported, and used in genetic counseling research. *Methods:* We undertook a modified scoping review of the Journal of Genetic Counseling 2021 publications. Data extraction was performed systematically using a tool based on the Race, Ethnicity, And Culture in Health checklist. *Results:* 132 articles met our inclusion criteria of reporting primary data about participants. The sample REA characteristics were described in 80 (61%) articles. 6% and 23% of these 80 articles provided a definition or conceptualization of the REA term/s used and a rationale for their study in terms of REA factors, respectively. Most studies (79%) ascertained REA characteristics by participants' self-report. Population descriptors were predominantly reported using category groupings, such as 'race', 'ethnicity', 'race/ethnicity', and 'ancestry'. However, several population descriptors were used under different categories. For instance, the term 'White' was used under all categories. 20% of studies referred moderately or a great deal to REA factors in the results interpretation, 46% acknowledged the REA factors in the study limitations, and 15% discussed the implications of REA reporting for genetic counseling practice. *Conclusion:* This review documents extensive variation in how genetic counseling research studies describe their sample REA characteristics. These findings provide a baseline against which to evaluate the effects of future guidelines and recommendations for the collection, responsible use, and report of participants' REA information in genetic counseling research.

Prognostic Testing in Children with Genetic Neurodevelopmental Conditions to Predict Cognitive and Behavioral Outcomes

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Background: Prognostic tests can provide more precise information on future functioning and projected outcomes for children with genetic neurodevelopmental conditions. Consumer engagement in the application of new medical tests is critical and could provide important insight into the use of prognostic testing. *Aim:* We aimed to investigate parents' attitudes, opinions, and emotions about testing their child's genes using new technology that may provide more precise prognostic information such as expected intellectual functioning and autism features. *Methods:* We used a cross-sectional, qualitative study design. We collected data through semi-structured interviews with parents, which were analysed using reflexive thematic analysis. *Results:* We interviewed 32 parents from across Australia. Parents had a child with a genetic neurodevelopmental condition, such as Fragile X syndrome (28%), 22q11.2 deletion syndrome (16%) or Angelman syndrome (16%). We found that parents of children who were more mildly impacted or those with older children were tolerant to prognostic uncertainty. Parents found conversations about their child's prognosis stressful and emotional, with a preference to discuss their child's potential strengths as well as challenges. While most were enthusiastic about new prognostic tests and described many motivations for testing, the potential for prognostic information to contribute to a loss of hope was also discussed. *Conclusion:* Our data provide evidence of the dual nature of uncertainty in the context of prognostic information for pediatric neurodevelopmental conditions. Genetic counselors could consider strengths-based framing of prognostic information gained from current and emerging technologies when returning results to families.

Australasian Society for Inborn Errors of Metabolism

Invited Speaker Presentation: Chasing the Holy Grail – How Does Pathology Lead to Cognitive Loss in Certain Lysosomal Diseases?

Brian Bigger,, Helen Parker and Oriana Mandolfo

Stem Cell and Neurotherapies, University of Manchester, Manchester UK

Mucopolysaccharidosis IIIA or Sanfilippo disease is a lysosomal storage disease resulting from the lack of a lysosomal hydrolase catabolizing the glycosaminoglycan (GAG) heparan sulphate (HS). The resulting build-up of undegraded HS primary substrate and the knock-on effect on lysosomal processes such as defective autophagy, the buildup of secondary storage materials and chronic inflammation are typically global outcomes across the lysosomal storage diseases. In the case of MPSIIIA, the primary organ affected is the brain, with patients manifesting from an early age with progressive cognitive and later motor decline, hyperactivity, with death typically in late teens. Teasing apart the role that pathological processes might have

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on behavior and cognition is critical to developing better treatments for patients excluded from gene and cell therapies. Here we discuss how pathological HS from MPSIIIA interacts with secondary storage substrates seen in MPSIIIA, such as cholesterol, Abeta, and even potassium flux to activate the inflammasome and mediate neuronal cell death via pyroptosis. We present new data showing that chronic viral infection exacerbates disease, worsening hyperactivity and cognitive working memory defects in mouse models of MPSIIIA via inflammasome activation and neuronal loss. Finally, we discuss how IL1beta, the primary driver of inflammasome mediated pyroptosis can be modulated to correct behavior and cognitive working memory in MPSIIIA mice, independently of lysosomal storage. Inflammasome activation is increasingly recognized as a causative factor in phenotypic outcomes across multiple lysosomal storage diseases, Alzheimer and delirium. As such targeting IL1beta may prove effective at reducing symptomology across multiple lysosomal diseases

Standard Biomarkers Do Not Correlate With Disease Progression in Childhood-Onset Cobalamin C Disease

Arthavan Selvanathan[1], Ashley Hertzog[2], Carolyn Ellaway[1], Katherine Lewis[1], Kate Lichkus[1], Louisa Adams[1], Kaustuv Bhattacharya[1] and Adviye Ayper Tolun[2]

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Background: Cobalamin C (CblC) defect is an inborn error of cobalamin activation, resulting in combined methylmalonic acidemia and hyperhomocysteinemia. Despite current treatment strategies, which help suppress methylmalonate and total homocysteine levels in plasma, many patients have both neurocognitive and ophthalmological decline. This suggests that the above biomarkers are unreliable for predicting disease severity and progression, and new biomarkers are needed. *Aim:* To evaluate the standard biomarkers (methylmalonate [MMA] and total homocysteine [THcy]), the mitochondrial biomarker FGF21 and clinical trajectories over time in a cohort of patients with CblC defect. *Methods:* Nine patients with CblC defect diagnosed since 2000 were retrospectively reviewed. Baseline data, including clinical presentation, biochemical and molecular results were collected; subsequent progress (developmental assessments, eye reviews, biochemistry and medication dosing over time) was also reviewed. FGF21, a biomarker of mitochondrial function that has been reported as being elevated in organic acidemias, was also measured. *Results:* Over 250 MMA and THcy results were reviewed in this patient cohort. There did not appear to be any correlation between disease severity and these biomarkers. FGF21 levels showed a trend towards being higher in samples from patients with CblC defect when compared with controls. *Conclusion:* The standard biomarkers do not correlate with disease severity in patients with cblC defect, suggesting that alternative biomarkers are needed. FGF21 levels appear to be elevated in patients with CblC defect. Further analysis in a larger patient cohort over time may help establish whether FGF21 levels are also predictive of disease progression and therapeutic efficacy.

Delta (4)-3-Oxosteroid 5-Beta-Reductase Deficiency: Case Report and First-Tier Screening by Targeted Urine Tandem Mass Spectrometry Analysis

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Background: Delta (4)-3-oxosteroid 5-beta-reductase deficiency (CBAS2, OMIM 235555) is a disorder of bile acid synthesis caused by mutations in the *AKR1D1* gene. A female patient presented at 6 months of age with jaundice. Plasma conjugated bilirubin, ALT and ALP were increased with consistently normal GGT. There was a mild coagulopathy. Analysis of urine bile acids show increased excretion of 7α-hydroxy-3-oxo-4-cholenoic acid and 7α,12α-dihydroxy-3-oxo-4-cholenoic acid as glycine and taurine conjugates. Genotyping showed a homozygous pathogenic variant in AKR1D1. *Aim:* To assess the performance and specificity of bile acid biomarkers seen in CBAS2 for potential application in routine urine screening by tandem mass spectrometry (UMSMS). *Methods:* Negative ion electrospray ionisation tandem mass spectrometry analysis of 144 negative controls, 10 cholestatic controls and 1 CBAS2 patient. Analysis was performed by direct injection with targeted multiple reaction monitoring transitions. *Results:* UMSMS testing showed the individual CBAS2 bile acid conjugates were not specific as they were increased in some cholestatic controls. However, when expressed as a ratio to normal bile acid species, chenodeoxy-cholic as glycine and taurine conjugates, the CBAS2 patient was clearly distinguished from cholestatic patients and other controls. *Conclusion:* Patients with cholestatic liver disease have increased glycine and taurine conjugates of dihydroxy-oxo-cholenoic and hydroxy-oxo-cholenoic acids. UMSMS screening using these individual bile acids does not provide sufficient specificity to detect CBAS2. However, utilizing ratios of these bile acids to other species can be used to differentiate CBAS2 from patients with non-specific cholestasis in first-tier UMSMS.

Ethylmalonic Encephalopathy Detection in Newborn Bloodspot Screening

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Background: Ethylmalonic encephalopathy (EE, OMIM 602473) is a rare, severe, autosomal recessive metabolic disorder characterized by hypotonia, seizures, chronic diarrhea, petechia and orthostatic acrocyanosis. In severe cases, EE causes progressive neurological decline with death in the first few years of life. It is not usually included on newborn screening (NBS) panels. *Aim:* To compare the NBS results of three EE patients with varying phenotypes. *Methods:* EE can potentially be detected as part of the NBS tandem mass spectrometry metabolic panel. The biochemical profile typically shows an increase in C4 and C5 acylcarnitine levels. The NBS profiles were retrospectively reviewed for three confirmed cases of EE. *Results:* All three cases presented clinically

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with typical features of EE: case 1 at age 10 months with NBS C4 and C5 levels below cut-offs, hence no NBS follow-up was implemented; case 2 in the neonatal period with NBS C4 and C5 above cut-offs; case 3 in the neonatal period with NBS C4 and C5 levels above cut-offs. In all three cases urine metabolic screening was informative with increased thiosulphate excretion being a useful marker for EE. *Conclusions:* Although milder forms of EE may be missed by NBS, severe cases will be more evident and earlier diagnosis and treatment may prevent a fatal outcome. Detailed bioinformatic analysis of NBS results may be helpful in identifying milder cases at birth or assisting with the diagnosis when they clinically present.

Molecular Genetic Analysis of a Cohort of Patients With Glutaric Aciduria Type II in the Queensland Lifespan Metabolic Service

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Introduction: Glutaric aciduria type II (GAII) is a heterogeneous genetic disorder with variable clinical manifestations across the lifespan. Some patients, particularly those with late onset GAII, experience significant benefit from riboflavin therapy. Molecular diagnosis implicates a number of genes in the riboflavin/FAD pathway, but some patients reported in the literature do not have a confirmatory molecular diagnosis for their presentation, despite advances in next generation sequencing technology. *Aims:* The aim of this project was to determine whether Queensland patients with a clinical and biochemical diagnosis of GAII, have molecular variants within a targeted gene panel extracted from whole genome sequencing (WGS). The genes in the panel included: *ETFA, ETFB, ETFDH, SLC52A1, SLC52A2, SLC52A3, RFK, FLAD1, SLC25A32, MT-CYB, MT-CO2*. A secondary outcome was to assess for a preliminary association with riboflavin responsiveness. *Methods:* Eligible patients of ages across the lifespan were identified from the Queensland Lifespan Metabolic Service databases. Following whole genome sequencing, a custom gene panel was analysed for pathogenic variants and reported in the context of the individual patient's clinical presentation and response to riboflavin. *Conclusions:* Twenty-eight patients were enrolled. Only two (7%) had monogenic compound heterozygous variants (in *ETFDH* or *ETFA*). Of the remaining patients, nine had single gene mono-allelic variants (32%) and three patients (11%) had mono-allelic variants in two separate genes within the same metabolic pathway. The remaining 14 patients (50%) had no pathogenic variants detected within the gene panel. Specific correlation with riboflavin responsiveness was not consistent. Analysis of the complete genome is to follow.

Multiple Acyl-CoA Dehydrogenase Diagnosed on Carrier Screening in a Symptomatic Patient With Diabetes

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We report the case of a 38-year-old woman referred to our service who was diagnosed with MCAD deficiency on carrier screening at 21 weeks gestation. Two genetic variants in ACADM were identified c.985A>G (p.Lys329Glu) and the c.199T>C (p.Tyr67His), subsequent urine testing confirmed the presence of hexanoylglycine. This diagnosis occurred on a background of type 1 diabetes diagnosed at the age of 9 that had been complicated by brittle glycemic control with features of insulin sensitivity, frequent hypoglycemia and lack of ketone production during hyperglycemia. This case highlights some of the challenges surrounding the management of coexisting diagnoses of MCAD and diabetes and should raise awareness of the possibility of exploring for a defect in gluconeogenesis in diabetes with atypical biochemical features.

Developing a Graded Practical Approach for Dietary Fat Liberalization in VLCAD

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Background: VLCAD deficiency is typically managed via dietary restriction of long chain triglycerides (LCTs) to 10–20% of energy intake (% EI), substituted with medium chain triglycerides (MCTs). Milder phenotypes may tolerate dietary fat liberalisation; however a systematic and consistent approach is yet to be established. *Aim:* To (1) validate existing approach to dietary education against patient food diaries to determine contribution of LCTs to % EI; and (2) develop a practical graded approach for dietary fat liberalisation. *Methods:* Validation: $n = 16$, 24-hr recall food diaries were analyzed in Foodworks from existing patients with VLCAD across four age groups to determine % EI from LCTs. Serve sizes were adjusted to reflect energy NRVs for age and modern food supply. Liberalization modelling: Products high in MCT and/or carbohydrates within food diaries were incrementally substituted with higher fat options to maintain consistent energy intake. Number of 5g fat serves required to reach 20 and 30% EI from LCTs was determined. *Results:* Validation: Median % EI from LCTs ranged 4.8–7.2% across age groups with current diet approach, validating existing resources, and indicating patients may be able to include additional dietary fat. Liberalization modeling: Use of additional 5 g fat serves was determined as a practical teaching tool to gradually increase dietary fat comparable to non-VLCAD peers while emphasizing nutritious food choices. *Conclusion:* Existing dietary approach was validated and modified to reflect current food supply and permit additional LCT-containing foods to provide up to 10–20% EI. New resources were developed to guide fat liberalisation in patients with milder forms of VLCAD.

Modular Feeding with Triheptanoin in a Child With Carnitine Acylcarnitine Translocase Deficiency (CACT)

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Background: Triheptanoin is a synthetic medium chain triglyceride (MCT) used in long-chain fatty acid oxidation defects to reduce

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episodes of hyperammonia and rhabdomyolysis, requirements for high carbohydrate feeds and long term risks of cardiomyopathy. We report our experience in modular feeding with added triheptanoin for a child with carnitine acylcarnitine translocase deficiency (CACT). *Aim:* To introduce triheptanoin into modular feeds at 25 −35% of estimated total energy intake. *Methods:* Triheptanoin was initially introduced mixed into an oral modular formula at 10% total energy intake, without success due to refusal. An admission was required where a nasogastric tube was placed and Triheptanoin was introduced initially at 10% of total energy intake and gradually increased by 5% increments to a maximum tolerated amount of 23% total energy intake. *Results:* Before introduction of triheptanoin, the patient had higher average ammonia levels outside of illness, increased total carbohydrate intake (g) and a period of overfeeding of 115-150% of estimated energy requirements resulting in rapid weight gain. After introduction of triheptanoin, average ammonia levels were lower outside illness, intake of carbohydrate (g) was reduced, feeds provided 100% of estimated energy requirements and weight stabilised. *Conclusion:* Triheptanoin was incorporated into modular feeds providing 23% of total energy intake. Since the addition of triheptanoin into this patient's feeds, we have observed lower average ammonia levels outside of illness compared to pre-triheptanoin use and prevention of overfeeding. Total energy intake has reduced we have also observed a reduction in total intake of carbohydrate.

An 18-Month-Old Female With Ornithine Transcarbamylase (OTC) Deficiency Who Presented with Hyperammonemia Which Progressed to Acute Liver Failure

Anita Inwood[1,2], Tahlee Minto[1], Aoife Elliott[1], Joshua Eeles[1], Avis McWhinney[3], Sara O'Neill[1], Sally Smith[1,2], Janette Spicer[1], Catherine Atthow[1], Matthew Lynch[1], Michelle Lipke[1], David Coman[1,2], Nikhil Thapur[1], Carolyn Bursle[1], Richard Muir[4] and Jim McGill[5]

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Background: A 20-month-old DCDA twin, developmentally appropriate female with no family history of miscarriage or neonatal male death. And a history of recurrent vomiting and aversion to meat from 12 months with parents noting grisliness and ataxia with each episode of vomiting and return to baseline in between. *Case Study:* Investigations for abnormal liver function tests, included a urine metabolic screen which showed a mild elevation of glutamine, normal citrulline and an orotate of 1142μmol/L. *Results:* On admission, the toddler was well but cranky. Initial biochemistry showed an NH4 of 240μmol/L, elevated urea 6.6 mmol/L with marked deterioration in her liver transaminases, (ALT 2500U/L;AST 448U/L). Intravenous nitrogen scavenging medications (NSM) normalised the ammonia within 2 hours. She developed hypercalcemia, corrected calcium 3.86 mmol/L (2.20-2.70) peaking at 22 hours. Despite a protein-restricted diet and NSMs, her liver function continued to deteriorate; 30 hours after admission, she was in acute liver failure with an ALT of 25,900; AST 25,00; INR 3.0, normal NH4 and being worked up for a liver transplant. All symptoms resolved over the following 48 hours with only medical supportive liver therapy. She has remained stable on conventional treatment with diet and NSM medications. A diagnosis of OTC was confirmed by urine organic acids, plasma amino acids and molecular testing identifying a known pathogenic deep intronic variant (c.540+265G >A). *Conclusion:* This case demonstrates that acute liver failure can occur with later onset OTC, and that urea cycle disorders can present with rarely reported symptoms in developmentally appropriate females with episodic vomiting and agitation.

Improved Nutrition and High Dose Vitamins Prevent Metabolic Crisis in a Child With TANGO 2 Mutation

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Background: Metabolic crisis is the hallmark of TANGO 2 mutations. We present a child with multiple episodes of metabolic crisis and presenting with lactic acidosis, hypoglycemia and rhabdomyolysis. *Aim:* To evaluate the role of nutrition and high dose B group vitamins in a child with multiple metabolic crisis secondary to TANGO 2 mutations. *Methods:* A 10-year-old male presented with multiple episodes of rhabdomyolysis and life threatening cardiac arrythmias during the seventh year of life. Poor dietary intake was believed to be the trigger for these events. Energy and nutrition was optimised with intravenous dextrose and total parenteral nutrition, high dose B group vitamins and calorie dense feeds during the 4 hospitalisations which enabled full recovery. After insertion of percutaneous gastrostomy for optimal nutrition there have been no further episodes of metabolic crisis for 3 years. *Results:* Aggressive sick day management plan optimizing calorie and micronutrient needs improved the metabolic outcome during and in between episodes. Regular optimal management of nutrition through PEG feeds prevented any further hospitalisations or crisis. *Conclusion:* Optimizing calorie and nutritional needs along with high dose B group vitamins could help prevent metabolic crisis in children with TANGO 2 mutation.

Neurodevelopmental Outcome Following Lysine Restricted Diet in Preterm Twins With Pyridoxine Dependent Epilepsy: Case Studies from Western Australia

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Background: Pyridoxine dependent epilepsy (PDE) due to a genetic defect in *ALDH7A* is associated with refractory epilepsy and intellectual impairment despite adequate seizure control. Lysine restricted diet has been trailed in patients with PDE with favourable outcome. *Aim:* To evaluate the role of lysine restriction in the diet along with high dose pyridoxine in twin siblings with PDE. *Methods:* Twin

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children were born at 35 weeks to consanguineous Indian family. Twin 1 had seizures, metabolic acidosis and high lactate in the first week of life. Twin 2 had complex cyanotic congenital heart disease requiring 4 cardiac surgeries and prolonged hospitalisations. They were found to have a homozygous variant in *ADLH7A 1* gene. Treatment was commenced with high dose Pyridoxine and lysine restriction by day 10 of life. Regular blood monitoring and developmental assessment was carried out. *Results:* At 12 months corrected gestational age, the twins are doing well developmentally with age appropriate motor and language milestones, with no obvious neurological deficits in twin 1 and mild motor delay in twin 2 consistent with cardiac illness and prolonged hospitalizations. *Conclusion:* Restriction of lysine in preterm babies is difficult to monitor due to lack of available data. We present in a methodical way the close monitoring of lysine restricted diet to ensure optimal nutritional outcome with normal neurodevelopment.

Newborn Screening for GAMT Deficiency

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Background: Guanidinoacetate methyl transferase deficiency (GAMTD, OMIM 612736) is a defect in creatine biosynthesis that can result in intellectual disability, seizures and ataxia. Most cases have been clinically diagnosed as newborn screening is not widely available. *Aim:* To review the performance of testing for GAMTD in the Victorian newborn screening (NBS) program. *Methods:* Guanidinoacetate was included in the NBS metabolic panel for all babies from 2002 using a decision limit of 5.5 multiple of median (MoM). *Results:* 1.5 million babies were screened between 2002 and 2022. In 2022, a baby was identified with increased guanidinoacetate in the first and repeat DBS samples (25 and 8 MoM respectively). Urine and plasma biochemical testing was consistent with GAMTD. Diagnosis was supported by molecular genetic testing with compound heterozygous variants in the GAMT gene (c.327G>A pathogenic variant and c.563T>C variant of unknown significance) confirmed in trans. The patient was commenced on creatine monohydrate (400 mg/kg/day), L-ornithine hydrochloride (400 mg/kg/day), sodium benzoate (100 mg/kg/day) and a low arginine diet with protein restriction of 1.2 g/kg/day. At age 5 months they are thriving, seizure free and developmentally normal. *Conclusions:* NBS for GAMTD was easily incorporated into the existing NBS tandem mass spectrometry panel with minimal laboratory costs. The disorder appears to be rare in the Victorian population but is comparable to some other disorders included on the metabolic panel. Earlier diagnosis via NBS and treatment is likely to improve outcomes for GAMTD and NBS programs should consider inclusion of GAMTD in their screening panels.

Comparison of Screening Protocols for Congenital Adrenal Hyperplasia (CAH) in the New South Wales Newborn Screening Programme

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Background: Congenital adrenal hyperplasia (CAH) is a group of disorders with autosomal recessive inheritance and an incidence of approximately 1:14,000 to 1:18,000 worldwide. Since 2018, the NSW Newborn Screening Programme has screened all newborns in NSW and ACT for salt-wasting CAH by measuring 17α-hydroxyprogesterone (17αOHP) level using immunoassay, followed by a second-tier liquid chromatography tandem mass spectrometry (LC-MS/MS) steroid profile. Any newborn with a calculated ratio of (17α-hydroxyprogesterone (MS17αOHP) + androstenedione (A4))/cortisol > 2 or MS17αOHP concentration > 200 nmol/L was deemed screen positive and required referral for diagnostic testing and management. *Aim:* To determine the optimum newborn screening protocol to detect salt wasting CAH. *Method:* Three analytical techniques (fluoroimmunoassay, LC-MS/MS, and targeted next generation sequencing (NGS)) were compared. Furthermore, to determine whether performance indicators could be improved; (1) stratification of action limits for birthweight and gestational age, and (2) for the LC-MS/MS assay, additional steroids that could be measured on the same sample simultaneously, were evaluated. *Results:* There were 16 proven cases of CAH from 388,416 babies giving an incidence of 1:24,276. After assessing the screening efficacy, result notification time, and analytical cost for each method, fluoroimmunoassay and LC-MS/MS remained the preferred screening methods at this time in comparison to NGS. *Conclusion:* As a result of this study, we propose using a MS17αOHP action limit of 40.1 nmol/L in combination with ratios (MS17αOHP+A4)/cortisol >1.6 for detection of SW CAH.

Optimizing Second-Tier Newborn Screening for Congenital Adrenal Hyperplasia

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Background: The second-tier newborn screening panel for congenital adrenal hyperplasia (CAH) in Australasia uses the common three steroid panel, that is, 17-hydroxyprogesterone (17OHP), androstenedione, cortisol, and a ratio of (17OHP+androstenedione)/cortisol. *Aim*: The aim of this study was to investigate if additional steroids should be added to the panel for the screening of CAH. *Methods*: An eight-steroid LC-MS/MS panel of 17OHP,

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21-deoxycortisol, 11-deoxycortisol, cortisol, cortisone, androstenedione, testosterone, and progesterone was developed on the Waters TQXS system. For each patient sample, one 3.2 mm dried blood spot was eluted in a methanolic solution containing isotopically matched internal standards, and then separated chromatographically to ensure distinct elution of isobaric steroids to 17OHP. Data were interrogated using Stata-17.0 and MetaboAnalyst-5.0. *Results*: Steroid profile results were genera ted for 572 non-CAH baby samples (median gestational age 37 weeks, range 22 to 43 weeks) and 11 babies with 21-hydroxylase deficiency (nine archival and four current samples) and five archived samples from babies with 11-beta-hydroxylase deficiency. The ROC curves demonstrated 21-deoxycortisol to have the best sensitivity and specificity for the diagnosis of 21-hydroxylase deficiency with an AUC = 1.0. The heatmap showed the highest correlation ($r^2 = .89$) between 17OHP and 21-deoxycortisol. Concentration differences were observed for testosterone (varying with sex), progesterone (higher in the first 24 hours post-birth) and 11-deoxycortisol (significantly increased in preterm babies). *Conclusions*. Our data support 21-deoxycortisol as the superior marker for CAH due to 21-hydroxylase deficiency. We recommend that 21-deoxycortisol be incorporated into routine NBS panels, follow-up plasma steroid panels, and external quality assurance material across Australasia.

RNA Studies Resolve Molecular Diagnosis of Galactosemia

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Background: Galactosemia (Type I) is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase (GALT) deficiency, affecting galactose metabolism. We investigated two individuals (P1, P2) diagnosed with galactosemia on newborn screening but without a definitive molecular diagnosis. Atypically, P2 (34y) has normal neurocognition and no premature ovarian failure. Exome sequencing identified a homozygous GALT (NM_000155.3) c.821-23T>G variant of uncertain significance (VUS) in P1 and a single, heterozygous c.565-13T>A VUS in P2. *Methods:* Reverse transcriptase polymerase chain reaction (RT-PCR) and Sanger sequencing was performed using RNA derived from P1, P2 and control blood. *Results:* RT-PCR revealed the P1 c.821-23T>G variant results in four mis-spliced transcripts, and some residual normal splicing. The variant lies at a highly conserved position within the branchpoint motif. The P2 intron 6 c.565-13T>A variant creates a cryptic acceptor site that is used preferentially, causing a frameshift. Using primers that bridge the exon 6-7 splice junction (disrupted by c.565-13T>A), we selectively amplified transcripts arising from the allele in trans, revealing two mis-spliced transcripts retaining intron 3. gDNA sequencing detected a rare, heterozygous c.328+32G>A variant that weakened the donor splice site. Across both cases all detected mis-spliced GALT transcripts are predicted to be targeted for nonsense mediated decay or disrupt functionally important GALT domains. *Conclusion:* RNA studies can resolve molecular diagnosis for patients with biochemically diagnosed inborn errors of metabolism such as galactosemia. We aim to develop diagnostic RNA sequencing that will likely produce a high diagnostic yield in patients with a biochemical defect that implicates the causative gene.

Poster Presentations

'I Feel Much More Confident In Approaching Genetics In My Workplace …': A Short Course In Practical Medical Genomics

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Background: Using genomic information to guide disease diagnosis and management decisions is an increasingly important part of healthcare delivery. However, healthcare professionals report low confidence, knowledge, and skills in this area. A short continuing professional development course in practical medical genomics was developed at UNSW Sydney to address this growing area of need. *Aim:* To evaluate the impact of the short course on participants' perceived competence and confidence in incorporating genomic medicine into their clinical practice. *Methods:* The Capability, Opportunity and Motivation Model for Behaviour change (COM-B) underpinned the design and evaluation of the course. Participants could consent to providing researchers with access to their course activities, including an anonymous reflective pre- and post-course survey and their assessed self-development action plan. The surveys included questions on perceived competence in relation to the course objectives and perceived confidence in undertaking professional activities in genomics. The surveys were constructed using existing evaluation instruments. *Results:* Of the course participants who consented to research ($n = 23$ pre-course; $n = 14$ post-course; $n = 17$ action plan), 100% reported improvement in their understanding of topics covered. Participants' confidence in peer and patient genomic communication, and in developing evidence-based patient and family-centred care plans increased by 22% and 30% respectively. Perceived preparedness to incorporate genomics into practice increased from 26% to 86% at course completion. *Conclusion:* Participants' perceived confidence and competence in practicing genomic medicine improved across the cohort. These preliminary data provide insights for improving the effectiveness of future iterations of this course.

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You-Hoover-Fong Syndrome: Profound Growth Failure, Cataracts, and Dyslipidaemia

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Background: You-Hoover-Fong syndrome (YHF, OMIM 616954) is a rare autosomal recessive disease caused by a deficiency in the function of the telomere maintenance 2 gene (*TELO2,* (OMIM 611140). Less than 20 case reports are documented in the literature, with clinical manifestations including microcephaly, movement disorder, intellectual disability, hearing loss, visual cortical impairment, cleft palate, syndactyly, scoliosis and congenital heart disease. We report a female with YHF syndrome who presented at 21 months of age with bilateral cataracts, global developmental delay, deranged hepatic liver enzymes, profound growth restriction and hypertriglyceridemia. *Material and Methods:* Now 3.5 years of age the child continues to make developmental progress currently at the level of an 18 month old infant. Growth failure is extreme with height 80 cm and weight 10.25kg, both significantly below the 3rd percentile. Nutritional, primary gastrointestinal diseases, and growth hormone deficiency have been excluded. Hepatic enzymes remain mildly elevated in transaminitis, with normal hepatic synthetic function and normal ultrasound examinations. Dyslipidemia persists with triglycerides measuring between 3-12.8 (0.6-2.0mmol/L). *Results:* Trio based whole exome sequencing identified two pathogenic missense variants in the *TELO2* gene, c.1100G>T; p. Cys367Phe, and c.392G>A; p. (Gly131Asp). *Conclusion:* YHF syndrome is a rare disease, and our case provides further phenotypic expansion to include profound growth failure and dyslipidemia.

Adaptive Behavior Profiles of Children With Monogenic Neurodevelopmental Disorders

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Background: Deep neurodevelopmental phenotyping of children with monogenic neurodevelopmental disorders (NDDs) remains under researched, with specific neurobehavioral profiles often overshadowed by intellectual disability (ID). Yet the patterns of strengths and weaknesses in these profiles are of value for targeted clinical management. *Aim*: This study compared the adaptive behavior skills of children with a monogenic NDD associated with ID to delineate syndrome specific profiles. *Methods*: The study included 145 children with 6 monogenic NDDs (*CDK13*, *DYRK1A*, *FOXP2*, *KAT6A*, *KANSL1, SETBP1*) aged 1-17 years. Parents completed the Vineland Adaptive Behavior Scale to assess communication, daily living, socialisation, and motor skills. Diagnostic groups were compared using an analysis of variance, adjusting for ID. *Results*: Children with *DYRK1A* and *KAT6A* had flat adaptive profiles with skills severely delayed across domains. While children with *KANSL1* also had a flat profile, communication and socialisation skills were significantly higher compared to the *DYRK1A* and *KAT6A* groups. In children with SETBP1, communication skills were a weakness, but daily living skills were significantly better compared to the *CDK13* and *DYRK1A* groups. Motor skills were a relative strength in the profiles of children with *FOXP2*. *Conclusion*: This is the first cross-diagnostic comparison of multiple monogenic syndromes spanning a range of ID severity. Results confirm that distinct NDD profiles exist in these conditions. As anticipated, syndromes associated with more severe ID had flatter profiles across domains, whilst syndromes with milder ID were characterised by significant variability and more specific profiles of strengths and limitations.

Codesigning and Delivering a Journaling Study: Lived Experiences of the Genetic, Undiagnosed, and Rare Disease Community Through COVID-19

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Background: People with a genetic, undiagnosed, or rare disease (Guard) have been disproportionately impacted by the COVID-19 pandemic, due to challenges in accessing essential health and social care. The lived experiences of people within the GUaRD community, during this time of upheaval, provided a unique opportunity to gather an understanding of how COVID-19 affected their lives and how this will shape their future needs. *Aim:* i) to investigate how the COVID-19 pandemic impacted people in the GUaRD community in relation to wellbeing, resilience and accessing health and social care services and ii) what lessons can be learnt for future health and social care service provision. *Methods:* Co-designed and co-delivered with community leadership from a genetic community support group, we collected unstructured journals from people in the GUaRD community monthly from June 2020-May 2021. Data was cleaned before undertaking deductive data analysis using the Resilience Scale for Adults. *Results:* We recruited 29 people, with early journals focused on the importance of developing new structures for daily life, while later journals centred on mental wellbeing. A consistent message through the study was the challenge of accessing health and social care that was compounded by fear and concern about virus exposure. Journals highlight the need for reliable health information messaging (e.g., vaccinations). *Conclusion:* Waves of targeted support are needed for vulnerable communities through health crises, with frameworks to structure daily lives, followed by attention to mental wellbeing. Reliable health messaging throughout is essential.

CONSANG.NET 2.0: From Paper Report to Interactive Web Resource

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Consanguineous marriage, unions between couples related as second cousins or closer ($F \geq 0.0156$), is widely practised in many societies

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and it is estimated that 1100+ million people live in countries where intra-familial unions are strongly favoured. For more than 20 years the website *consang.net* has been a popular international academic resource detailing the prevalence, types and global distribution of consanguineous marriage. During that time *consang.net* has been a static repository of maps and publication reference lists. As a result, maps produced via ArcGIS, and more lately, QGIS have been used, with permission, in numerous genetic, epidemiological and demographic studies. Due to the static nature of the website there are, however, limitations in its capacity to update information on consanguinity in a timely manner, and in the ability of users to efficiently integrate recently published data into their own studies. To address these limitations, *consang.net* has been updated to a interactive web resource using open-source resources including QGIS, OpenLayers and qgis2web. The result is GIS-based data visualisation with user interactivity and where possible full DOI linkage for all appropriate publication references. This new web resource will allow country-, regional- and community-specific data visualization, that highlights changes in consanguinity levels over time and would be expected to influence the prevalence and patterns of distribution of Rare Diseases at community level.

Does Rare Genetic Variation Contribute to the Development of Multiple Sclerosis in Families?

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Background: Multiple sclerosis (MS) is a complex autoimmune and neurodegenerative disease with a significant genetic component. A family history of MS is reported in 15%-20% of people with MS and whilst rare, multi-case families do occur. Such families are an opportunity to discover rare genetic variants that may contribute to MS. Unlike several diseases that have overlapping features with MS (eg. leukodystrophies, ataxias, and others), where the impact of rare variation is understood, the role of rare variants in MS has not been explored and will need to be examined to establish their role in cell signalling and MS disease development. *Aim:* Study multi-case MS families to identify rare genetic variants segregating with disease. Determine how these variants affect cell signalling to establish or exacerbate MS pathology. *Methods:* WGS was conducted in four MS families with three or more affected first-degree relatives. A variant filtration strategy was implemented to identify population rare (MAF ≤ 0.001), potentially deleterious (CADD ≥ 15) variants segregating with disease in these families. Candidate variants were prioritised for *in vitro* and *in vivo* laboratory modeling based on the biological hypotheses for the potential of the dysfunction of the corresponding candidate genes to contribute to MS development. *Results:* Rare variant analysis completed in each family has implicated multiple candidates for further study including genes involved in glutamate signalling, type I interferon signalling and blood-brain-barrier integrity. *Conclusion:* MS families present a novel opportunity to identify rare genetic variants responsible for differential disease manifestation between MS cases and their unaffected relatives.

Predicting the Future: Parents' Views and Experiences of Receiving Prognostic Information About Their Child's Genetic Neurodevelopmental Condition

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Background: Highly sensitive genetic tests with potential to provide individualised prognostic information for neurodevelopmental conditions are in development. Insight into current practices about discussing prognostic information can inform the clinical integration of new prognostic genetic tests. This study aimed to explore how parents view and experience receiving prognostic information about their child's genetic neurodevelopmental condition. *Methods:* We conducted qualitative, semi-structured interviews with Australian parents ($n = 32$) of children with a variety of genetic neurodevelopmental conditions (e.g., Fragile X syndrome, Angelman syndrome, 22q11.2 deletion syndrome). We used reflexive thematic analysis to code and organise the transcribed data into themes to answer the research questions. *Results:* Some parents reported that receiving general prognostic information that was not specific to their child was of limited use. Conversely, some parents reflected on the benefits of a more open future for their child. Parents who received more detailed prognostic information at the time of diagnosis frequently felt overwhelmed, but some experienced utility in learning more detailed information. Parents discussed their disappointment when receiving deficit-framed prognostic information and expressed a need for more balanced information to be provided. Parents reported experiencing a range of psychological responses when receiving prognostic information including anxiety in the face of uncertainty, feeling overwhelmed or relieved. *Conclusion:* Our research can inform genetic health professionals having conversations about prognostic information with parents of children with genetic neurodevelopmental conditions. Our findings could be used to develop interventions to facilitate a balanced, strengths-based approach to such conversations while maintaining realistic expectations and providing accurate information.

Early Sample Collection Timing Due to COVID-19 Increases False Positive Results in Newborn Screening

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Background: The timing of sample collection is important for accurate interpretation of results for Newborn Screening (NBS) assays. It is recommended that samples are collected between 48 to 72 hours after birth, as current in-house thresholds to trigger result notification are optimised for analyte concentrations after 48 hours. Due to the COVID-19 pandemic, midwives have increasingly collected the newborns samples between 24 to 48 hours, in order to limit infection risk. *Aim:* This analysis examines whether the increase in samples

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collected between 24 to 48 hours during the COVID-19 pandemic has led to an increase in false positive results. *Methods:* The data was extracted from the NSW NBS database for samples collected at 24−48 hours and 48-72 hours during COVID-19, as well as for a comparable period preceding the pandemic. Biomarkers investigated include Thyroid Stimulating Hormone (TSH), Galactose/ Galactose-1-Phosphate, Immunoreactive Trypsin and 17-Hydroxyprogesterone. Analysis was conducted using Microsoft Excel, including calculation of false positive rate and p-values. *Results:* The analysis of 1,100,000 NBS results demonstrated that particularly TSH was impacted by early collection time with a marked increase in false positive results. *Conclusion:* False positive results cause unnecessary patient family anxiety, increased workload for staff and increased resource consumption. The results of this analysis indicate that midwives should be advised against collecting before 48 hours wherever possible.

A Pathogenic PINK1 Gene Variant is a Common Cause of Early-Onset Parkinson's Disease in People of Western Polynesian Ethnicities

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Background: Two unrelated patients with early-onset Parkinson's disease (EOPD), one Samoan, one Tongan, were found to be homozygous for a rare pathogenic *PINK1* variant, NM_032409.3(*PINK1*): c.1040T>C p.(Leu347Pro). *Aim:* To determine if the *PINK1*: c.1040T>C variant is a common cause of EOPD in Western Polynesian and Eastern Polynesian patients.
Methods: The *PINK1* gene of 23 unrelated EOPD patients was sequenced; patients included two Eastern Polynesian (Māori) and 21 Western Polynesian (Samoan, Tongan and Tokelauan) people. Control population studies also determined carrier rates. *Results:* Of the Western Polynesian group, 17/21 were homozygous for *PINK1*:c.1040T>C, while one was compound heterozygous; the two Māori patients were wildtype for *PINK1*. *PINK1*:c.1040T>C carrier-rates in control populations are as follows: NZ Western Polynesian ($n = 137$), 1 in 20; NZ Māori (part of Eastern Polynesia, $n = 126$), 1 in 126; Samoan (part of Western Polynesia, $n = 1285$), 1 in 16; Hawaiian (part of Eastern Polynesia, $n = 4150$) 1 in 143 (imputed with R^2 of 0.76). *Conclusion:* We report that *PINK1*:c.1040T>C homozygosity is a common cause of EOPD in patients of Western Polynesian ethnicities. In line with current testing strategies for relatively common recessive conditions, *e.g.* cystic fibrosis, Western Polynesian patients with EOPD should be tested for *PINK1* variants; if gene positive, cascade testing should be initiated. Community engagement and education via Parkinson's NZ and the Pasefika Parkinson's Support Group (South Auckland) is ongoing. Further research into the ancestral Pacific origin of this variant, patient impact and targeted therapies is underway.

Nonsyndromic Hereditary Hearing Loss In Multicultural Australia

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Background: Hearing loss (HL) is one of the most common sensory disorders in children and the WHO reports that 40% of childhood HL, worldwide, is due to genetic factors. Sensorineural hearing loss (SNHL) can be syndromic or isolated (nonsyndromic) and in Australia it is estimated that 2/3 of children with prelingual permanent SNHL have nonsyndromic hearing loss (NSHL). However, there is currently no Medicare funding for hearing loss testing and *GJB2/ GJB6* gene testing is the first-tier test, despite the low diagnostic utility. *Aim:* To determine the diagnostic yield of single gene *GJB2* testing vs a targeted hearing loss panel in our laboratory and investigate the ethnic diversity of causes of genetic hearing loss. *Methods:* DNA was extracted from peripheral blood, PCR amplification of the *GJB2* gene and Sanger sequencing was completed, and the data analyzed using Mutation Surveyor software. WES using Agilent SureSelect CREv2 exome was performed by an external laboratory and WGS was performed in-house with the Illumina PCR-free kit. Secondary and tertiary analysis (with a virtual HL panel) was performed in-house using DRAGEN germline pipeline software and VarSeq software, respectively. *Results:* Preliminary analysis shows a diagnostic yield of 12.8% for *GJB2* Sanger sequencing and 54.5% for WES/WGS with the virtual HL panel over a 10-month period in 2021. This data is not inclusive of copy number variants (CNVs); pathogenic CNVs contribute ~15-20% cause of inherited HL. *Conclusion:* In Australia, with such a multicultural population, the challenge is to provide comprehensive genetic testing that accounts for the heterogeneity of hearing loss, at a reasonable cost. Almost 30% of Australian residents are born overseas and although *GJB2* is still the most prevalent NSHL gene worldwide, testing only for this gene leaves ~80% of individuals with NSHL without an answer. Ethnic background of patients is not often included in clinical information; however this information could guide genetic testing, assist in clinical decision making and is important for variant curation.

Population Frequency Modeling Enables Gene-Specific Probabilistic Assessment of Large-Scale Population Data

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Background: The implementation of gene-disease attributes (such as penetrance and disease prevalence) into a quantitative algorithm for assessing variant pathogenicity is limited by data availability, presenting a significant barrier in maximizing the utilization of large population databases like gnomAD. Learning from more than 34,000 pathogenic or benign variants across more than 800 genes, a population frequency model was developed that contextualizes the allele frequency data based on >20 variant-, gene- and position-level properties of each variant. The algorithm quantitatively assesses how much a given variant allele frequency deviates from expectations about pathogenic variants. The information gleaned from the population frequency model was incorporated into *Sherloc* (an ACMG-guidelines based method for variant interpretation; PMID: 28492532) and the impact was measured. *Aim/Methods:*

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A machine learning approach was applied to develop a computational algorithm that estimates probabilities of pathogenicity based on allele frequency data in a gene-specific manner. *Results:* Population frequency evidence has been applied to 4 × as many variants compared to previous methods in *Sherloc*, leading to the resolution of ~15,000 unique VUS, impacting ~50,000 patients. Through simulation experiments we estimate that this tool will result in an approximately 2.5% reduction in future VUS rate compared to previous methodologies. *Conclusion:* The population frequency model represents a highly accurate, scalable and fully quantitative solution to determining the predictive value of variant allele frequencies in the context of a particular gene. Incorporation of this tool into the *Sherloc* interpretation system substantially increases the ability to classify variants accurately and confidently.

Carrier Screening Experience in 200k Patients: Optimal Strategies for Successful Outcomes at Population Scale

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Background: Multigene panels used in carrier screening (CS) have grown rapidly in size and complexity. Larger panels mean better diagnostic sensitivity in identifying at-risk couples. However, larger panels may: be more expensive; require more laboratory expertise; have more complex pre- and post-test consenting and counseling; raise ethical issues around low penetrance/milder conditions; and raise a question of the best strategy for testing and supporting couples. *Aim*: We reviewed our experience of >200,000 CS patients to explore if there exist optimal decision points regarding panel sizes, and result reporting strategies. *Methods*: CS was performed for patients in precurated panels (3, 47 or 289 genes), as single tests, or as customisable panels. Additionally, 13 common and/or variable genes were available as add-ons. Ordering patterns and positivity rates were assessed. A simulation was also performed to look at two additional panel sizes, a panel similar to the recent ACMG tier 3 guideline and a panel of over 550 genes. *Results*: Overall positive rates were 52%, with a carrier couple rate of ~13% (including variable and mild conditions). Reporting only severe conditions reduced the carrier couple rate to ~4%. Simulated panel results were compared to demonstrate clinical utility in couples and show how the various panels reach near-maximal diagnostic yield. *Discussion/Conclusion*: Reporting results as a reproductive couple with a couples' summary facilitates efficient triaging of high-risk couples in need of counseling resources. A panel of approximately 550 genes is predicted to optimise positive screening yield in a pan-ethnic population.

A Rare Splice-Site Variant in *TNNT2*: The Need for Population-Specific Reference Data

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Background: For individuals from ancestry groups not well represented in genomic reference databases, interpretation of rare sequence variants causing monogenic disease can be challenging. There are higher rates of uncertain variants, with a risk of misclassification potentially causing harm. *Aim:* Here, we illustrate the challenges in ascertaining variant pathogenicity in poorly represented ancestry groups. *Methods:* A rare variant in cardiac troponin T (*TNNT2*; NM_001001430.2: c.571-1G>A) was identified in three unrelated probands with cardiac phenotypes and diverse ancestries. The variant is located in the canonical splice acceptor site of intron 11, resulting in an in-frame deletion of one amino acid in a three amino acid exon. More than 25 probands with cardiac phenotypes, including hypertrophic cardiomyopathy and sudden cardiac death, have been reported with this variant across literature, collaborators and ClinVar. *Results:* >15 probands with the variant were determined to have Pacific ancestry raising suspicion of an ancestry-specific variant. Genomic reference population datasets are not publicly available for Pacific ancestry, so research groups were approached. We show the variant has a higher than expected allele frequency in Pacific population subgroups, ranging from 0.9–8.8%, and is too common to cause monogenic disease. *Conclusion:* There is a critical need for increased diversity within publicly available reference population datasets to more accurately inform variant interpretation efforts.

An Evaluation of Family History: An Old Concept in a New Genomics Era

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Background: Family history has been an essential part of clinical care to assess health risks. However, declining sequencing costs have precipitated a shift towards population screening programs using genomics as an initial approach with less emphasis on family history assessment. The value of family history collection for such

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population-initiatives has not been evaluated. *Methods:* Amongst 1750 individuals with no known pre-existing health conditions, a participant-led model to facilitate family history collection was initiated and three cohorts according to family history availability and assessment for cancer risk were formed: increased familial cancer risk (73 individuals), population risk (795 individuals) or unknown familial cancer risk (822 individuals). Whole genome sequencing data for each individual was curated and compared, focusing on 95 cancer genes. *Results:* One in 7 individuals assessed at increased risk of developing cancer carried a clinically actionable variant. This was at least a six-fold increase compared with individuals at population risk (1 in 46, $p = .00001$) or where family history was not unavailable (1 in 47, $p = .00001$). This enrichment was further pronounced (up to 18-fold) when assessing only the cancer genes in the American College of Medical Genetics (ACMG) Secondary Findings (SF) gene list. Furthermore, 63 (7.3%) individuals had an increased cancer risk according to their family history in absence of an apparent clinically actionable variant. *Conclusion:* The addition of family history information augmented the yield of detecting clinically significant variants and was critical for health risk assessment, emphasizing the significance of family history in this genomic era.

Exploring Individuals' Experiences of and Attitudes Towards Expanded Preconception Carrier Screening Prior to Receiving Results

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Background: Expanded preconception carrier screening (EPCS) can inform couples about the risk of future offspring inheriting severe recessive genetic conditions. Couples are able to explore reproductive options in line with their beliefs and values. *Aim*: To explore individuals' experiences of and attitudes towards counseling and testing for EPCS prior to its implementation into routine preconception care. *Method*: We conducted semi-structured interviews with 14 individuals. Participants were purposively sampled from 224 couples who had undergone pre-test genetic counseling and couple based EPCS, prior to receiving their results. Interviews explored experiences, knowledge, attitudes, and decision-making. Transcripts were analyzed using reflexive thematic analysis. *Results*: Participants were 10 females and four males. We identified four themes: (1) the value of EPCS is independently determined, highlighting the influence of lived experience and personal beliefs; (2) EPCS is about a couple and future offspring, emphasizing the importance of joint decision-making and the health of future children; (3) EPCS decision-making – 'let's talk about it', highlighting the importance of frank and open discussions in facilitating decision-making; and (4) EPCS for all – affordability, accessibly and equity, valuing the opportunities EPCS provided, and wanting it to be available to all. *Conclusion*: Participants valued genetic risk information for their future offspring based on their personal experiences and beliefs and believed it should be accessible to all. Pre-test genetic counseling facilitated conversations between couples and enabled wider discussion within families and with health professionals, influencing decision-making. These findings will help inform the roll-out of EPCS in Australia.

Factors Influencing Patients' Decisions to Transfer, Store or Discard Embryos With Mosaic PGT-A Results

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Background: A mosaic embryo can be defined as a single embryo containing at least two distinct cell lines. Whilst some mosaic embryos have resulted in healthy live births, there is an increased risk of implantation failure, miscarriage and potential of ongoing pregnancies with chromosomal abnormalities. It is not possible for health professionals to predict the outcome of a mosaic embryo transfer, therefore posing a decision dilemma for patients regarding the fate of their mosaic embryos. *Aim:* To gain an understanding of factors influencing patients' decisions to transfer, store or discard their embryos with mosaic PGT-A results. *Methods:* Participants were recruited from Number One Fertility via email. Ten semi-structured interviews were thematically analyzed, transcripts were co-coded and codes organised using a ranking system to identify emerging themes. *Results:* Of the 10 participants recruited; 2 transferred, 7 stored and 1 discarded their embryo with mosaic PGT-A results. Of those storing their embryo, 3 are unlikely to transfer, 2 will use it as a last resort, and 2 would transfer prior to another egg collection. All participants were unaware of what a mosaic embryo was before receiving their results. Influencing factors include; uncertainty/anxiety, specific mosaic abnormality, life experiences and rapport with the treating fertility clinic. *Conclusion:* Genetic counseling about mosaic PGT-A results should be guided by individual patient needs and unique life experiences to facilitate informed decision making. Results from this study emphasise the importance of establishing rapport to improve patient care and outcomes.

Homozygous CYP2C9*14 Allele Resulting in Profound Warfarin Sensitivity

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Background/Objectives: Rapid genomic testing facilitates early genetic diagnosis, while the data generated also provides opportunity for additional analyses in future, as clinical features evolve. We describe a neonate who initially presented with cleft lip/palate and congenital heart disease and underwent exome sequencing (ES) in 2018 without a diagnosis being made. Reanalysis of the ES data was performed after the clinical presentation evolved to severe dilated cardiomyopathy. Clinical management was complicated by profound sensitivity to warfarin and significant bleeding. *Methods:* Clinical rapid trio ES was performed in 2018 on DNA extracted from peripheral blood using Agilent Sureselect QXT CREv1 kit, following by sequencing on Illumina NextSeq500. Reanalysis using updated clinical information and updated phenotype-driven virtual gene panels was performed in 2021. *Results:* A homozygous pathogenic variant in *PPP1R13L* (c.1068dupC; p.(Ser357Leufs*49)) was identified as causing the primary clinical features (dilated cardiomyopathy and cleft lip/palate), this gene-disease association having been

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described in 2020 in five unrelated families. In addition, homozygosity for the well-established *CYP2C9**14 (p.Arg125His) warfarin sensitivity allele was identified, explaining the extreme warfarin hypersensitivity. Alternate anticoagulation with intravenous bivalirudin and low molecular weight heparin successfully preventing thromboembolic complications. *Conclusion:* Heterozygosity for the *CYP2C9**14 allele has been described in individuals with increased sensitivity to the anticoagulant effects of warfarin. This is the first case report of an individual homozygous for the *CYP2C9**14 allele with profound warfarin sensitivity. In addition to expanding the phenotypic spectrum associated with the *CYP2C9**14 allele, this case report highlights the value of genomic data as a healthcare resource.

Identifying Barriers for Increased Adoption of Genetic Testing in Cardiovascular Conditions

Peter Coleman and Tamsin Eades

Illumina Australia

Genetics plays a role in the etiology of many cardiovascular conditions. Genetic testing is recommended for particular inherited cardiovascular conditions by a number of professional cardiac societies as part of patient management. Despite this, the uptake of genetic testing by cardiologists remains limited. To better understand the barriers for increased adoption of guideline-directed genetic testing in inherited cardiovascular conditions, qualitative interviews were conducted with 24 cardiologists across Australia, New Zealand and Singapore. The 45-minute interviews were conducted by an independent third-party market research organisation, and then transcribed for analysis. Results from the study indicated that there are multiple barriers perceived by cardiologists for the implementation of guideline-directed genetic testing in cardiology. In addition to education, barriers and concerns identified in the interviews included, turnaround time of test results, access to testing and inability to directly order, implication for patient's life insurance, lack of clinical actionability and cost.

What Matters to Parents? A Scoping Review of Parents' Health Service Experiences of Genetic Testing for Rare Diseases

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Background: Genomic sequencing tests are increasingly available in pediatrics. As test ordering expands beyond the remit of genetics services, consideration for how care can be designed to enhance patient experience is needed. *Aim:* To inform key considerations for care by pediatricians, we conducted a scoping review to map what is presently known about the health service needs of parents in relation to genetic testing for rare diseases. *Methods:* MEDLINE, EMBASE, PsycINFO, PubMed and Web of Science were searched for empirical studies in nonacute settings reporting parent experiences of care throughout the patient journey. Extracted data describing aspects of care parents valued or considered lacking were mapped to an empirically-derived framework (the Picker Principles of Patient-Centred Care) adapted to context. Suggested strategies to meet parent needs were also recorded. *Results:* 28 studies met the inclusion criteria, most of which described experiences of care with genetics services. Aspects of care important to parents mapped to seven of eight Picker principles. In particular, parents valued empathic communication; concern for their emotional well-being; being kept informed while awaiting test results and signposted to psychosocial supports afterwards; and multidisciplinary care (with benefits to parents' understanding and feelings of being supported highlighted). Strategies to meet parent needs were reported in 19 studies, but most were intuitive suggestions from study authors. *Conclusion:* The absence of cited evidence for many of the strategies proposed highlights opportunities to improve the way in which interventions are identified and designed to enhance parent experiences of care and health and wellbeing outcomes in turn.

From Research to Resolution: Diagnostic RNA Splicing Studies Confirm Variant Pathogenicity in *PALB2*

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Background: A *PALB2* variant, c.2747_2748+4del was identified in a patient with breast and endometrial cancer enrolled in the ICCon study. This variant was confirmed in a diagnostic laboratory and predicted to affect abnormal splicing. RNA splicing studies were recommended, and the specimen received in our laboratory for assay. *Aim:* To evaluate the impact on normal splicing encoded by *PALB2:* c.2747_2748+4del. *Methods:* Blood was received in a PAXgene RNA tube. RNA was extracted and reverse transcribed to produce cDNA. Primers were designed to flank the exons upstream and downstream of the exon containing the variant. Results from bidirectional Sanger sequencing of the amplified products were analyzed and compared against a wildtype normal control. *Results:* Sequence analysis confirmed the *PALB2*:c.2747_2748+4del variant effects abnormal splicing. The allele containing the variant, a 6 base pair deletion at the end of exon 7, removes the canonical wild type donor site which results in the skipping of exon 7. This transcript encodes the in-frame loss of 54 amino acids within the highly conserved WD40 domain. Although our assay is not quantitative, comparison of relative allelic peak heights from the sequence traces indicate abnormal splicing is predominant from the allele containing this variant, thus supporting the pathogenicity of the variant. *Conclusion:* RNA studies confirm that splicing is abnormal from the allele carrying *PALB2*:c.2747_2748+4del. RNA splicing studies are an important supplementary assay which can aid variant classification and ultimately clinical management of the patient.

An Evaluation of the SMN1 Screening Techniques for Spinal Muscular Atrophy

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Background: Spinal muscular atrophy (SMA) is a neuromuscular disease affecting approximately 1 in 10,000 children. Timely

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identification of patients within newborn screening laboratories is crucial for rapid diagnosis and initiation of treatment prior to the onset of any disease symptoms. *Aim:* To assess the two methodologies, real-time quantitative PCR (RT-qPCR) and droplet digital PCR (ddPCR), used in the NSW Newborn Screening Programme for suitability of screening for SMA. *Methods:* Both the RT-qPCR and ddPCR techniques use DNA extracted from 3.2 mm dried blood spot discs using the PerkinElmer Eonis extraction kit. The RT-qPCR uses the PerkinElmer Eonis 4-plex SCID-SMA kit and examines exon 7 of SMN1. The ddPCR is based on water-oil emulsion droplet technology and uses BioRad's SMN1 copy number determination kit, QX200 droplet digital PCR system and thermal cycler. *Results:* The RT-qPCR is the faster of the two methods, taking 1.5 hours per plate to complete and requiring minimal sample handling. The ddPCR is the longer of the methods, taking 2.5 hours per plate, and sample handling is currently not automated; however the results obtained provide gene copy number, rather than presence/absence. Both methods use *RPP30* as a quality control reference gene in every sample. *Conclusion:* Both of the qPCR techniques have advantages and disadvantages, however the rapid turn-around, minimal handling and the ability to multi-plex make the RT-qPCR more ideal as a first tier high-throughput screen.

The Key Role the Laboratory Genetic Counselor Plays in the Stewardship Program in Queensland

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Aim: The number of requests processed by Pathology Queensland (PQ) for sendaway genetic testing more than doubled from 2016 to 2020 and ~50% of these tests were ordered by nongenetic clinicians. Metro North LINK funding supported the Genomic Institute/PQ partnership to run a demonstrator Genetic Testing Stewardship (GeTS) program which aimed to improve patient outcomes and use of healthcare resources by supporting appropriate genetic testing. *Methods:* The GeTS program reviewed genetic test requests from Metro North clinicians, from January 2022 to June 2022. The Senior Scientist performed a preliminary review and forwarded to the genetic counselor (GC) for review of appropriateness and clinical processes. Escalation to the genetic pathologist (GP) and clinical geneticist (CG) occurred when required. Ordering clinicians were offered support and education, and GC liaison enabled clarification of information when required. The outcome of review was tracked for each request to enable evaluation. *Results:* 141 in-scope requests were reviewed. Most requests (98/141, 70%) were reviewed for appropriateness and clinical processes by the GC and the remaining cases (43/141, 30%) required escalation to the CG and/or GP. GeTS intervention facilitated testing for 42% (59/141) of requests – commonly providing assistance with test and/or laboratory selection, requirement for consent, and clarifying insufficient clinical details. Following review, 22% (31/141) of requests were modified and resulted in savings of $16,945. Several cases will illustrate the key role the GC plays in stewardship review. *Conclusion:* Laboratory GCs play a key role in stewardship review of genetic tests and support positive working relationships with clinicians.

Harnessing Genetic Counseling Skills in the Rare Diseases Now (RDNow) Program: Genomic Diagnoses and Person-Centered Care for Children With Undiagnosed Rare Diseases

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Background: Rare Diseases Now (RDNow) is a multidisciplinary initiative to deliver genomic diagnoses and precise, personalized care to children at The Royal Children's Hospital, Melbourne. Drawing on the research and clinical expertise at the Murdoch Children's Research Institute (MCRI) and Victorian Clinical Genetics Services (VCGS), RDNow designs bespoke testing pathways for children who remain undiagnosed after clinical and research genomic testing. During the establishment of the program, barriers and challenges to rare disease research across these three institutions were identified with the basis often due to systematic complexity of communication. *Aim:* To harness transferable genetic counseling skills to address challenges to delivering person-centered molecular diagnoses in the RDNow program. *Methods:* Regular consultations involving key stakeholders including the RDNow Consumer Engagement Committee, VCGS and MCRI Bioinformatics teams, VCGS diagnostic laboratory and MCRI research laboratory teams, ethics and legal teams were used to open lines of communication and identify creative solutions to rare disease research on our campus. *Results:* Genetic counseling competencies, in particular relationship-building, communication, education, advocacy and a person-centered approach contributed to shaping the design, establishment and management of the RDNow program. Innovative use of study databases and software enabled streamlined communication between team members and with RDNow participants to deliver a program firmly focussed on optimal care for families affected by rare genetic diseases. *Conclusion:* Utilizing genetic counseling skills for end-to-end aspects of genomic research programs can rationalise processes and promote positive outcomes for the key stakeholders who include patients, their families, as well as research team members.

Targeted Approach for Non-Small Cell Lung Cancer – Is It Still Relevant?

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Background: Lung cancer is the leading cause of cancer death and fifth most diagnosed cancer in Australia with 13,810 cases diagnosed in 2021. Patients with non-small cell lung cancer (NSCLC) significantly benefit from companion diagnosis for specific variants. *Aim:* With the paradigm shift to using next generation sequencing (NGS) in laboratories, we review performance and relevance of a targeted approach by MassARRAY System (Agena Bioscience).

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Methods: This MassARRAY System is used to test for the presence of 70 actionable variants in five oncogenes: *EGFR*, *KRAS*, *BRAF*, *ERBB2* and *PIK3CA*. Performance of this assay from clinical referrals received in our laboratory over a period of 18 months was compared with NGS approaches from published literature. *Results:* Out of 1081 patients tested, 733 (68%) were positive for either *EGFR* (261), *KRAS* (412), *BRAF* (45), *ERBB2* (17) or *PIK3CA* (38) variants. Thirty-eight patients had multiple variants detected, with 2 patients having 3 variants detected. *EGFR* T790M was detected in 19 patients. The test failure rate was <0.2%. The average turn-around-time (TAT) was 3 days and cost per test is significantly lower compared to most of the NGS assays. *Conclusion*: There are distinct advantage NGS methodologies as to cover increased number of alterations simultaneously including gene fusions that improves sensitivity. A targeted approach like MassARRAY System with advantages of rapid TAT, low cost, and coverage of most of the molecular targets that are expected in standard clinical practice still offers an attractive approach for routine diagnostics.

Why the Low Y? Outcome Data for a Low Y Signal on the Genesyte Noninvasive Prenatal Screen (NIPS)

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Background: A low Y signal on NIPS is not infrequently reported. However, there are limited published data regarding causes, management and outcomes. *Aim:* We evaluated the cytogenetic and pregnancy outcome data (where possible) for 19 cases where a low Y value was reported on NIPS (Illumina NextSeq500/TruSeqv1.2/SaFER algorithm) to inform recommendations for genetic counseling and follow-up. *Methods:* NIPS reported with a low Y signal between 10-20 NCV were flagged for follow-up. Data requested from referring clinicians included pregnancy, prenatal and available cytogenetic outcomes. *Results:* Of 33 cases where a Low NCV Y value was reported, outcome data were ascertained for 19 cases with a fetal fraction ratio below 5:1. Prenatal diagnosis via amniocentesis was performed in 8/19, reporting 2 cases of 46,XY; 2 of 46,XX; 46,XX with a CNV on 3p; 46,XY with a chromosome 17 paternally inherited CNV; LCSH in a twin-pregnancy with a twin demise and co-twin with multiple congenital anomalies; and a case of triploidy 69, XXY. Others include: three cases with a likely demised twin; lung transplant from a male donor with a normal female fetus; low Y with lumbosacral myomenigocoele and hydrocephalus; three miscarriages; an NAD female and 2 NAD males. *Conclusion:* Here we present a case series of available outcomes for NIPS results showing a low Y NCV value. The most likely outcomes are 46,XY and 46,XX, and underlying causes being twin demise or Y artefact. Outcomes highlight we should not dismiss all such results as Y Artefact, given the relevance for counseling and follow-up.

A *KLHL40* 3' UTR Splice-Altering Variant Causes Milder NEM8, An Under-Appreciated Disease Mechanism

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Background: Nemaline myopathy 8 (NEM8) is an autosomal recessive disorder associated with variants in the kelch-like family member 40 gene (*KLHL40*). To date, only coding pathogenic variants have been identified and almost all NEM8 cases are reported with severe manifestations including fetal akinesia, fractures, contractures, respiratory failure, and neonatal death. *Aim:* This study examined the genetic etiology of a milder case of NEM8 and explored the pathomechanisms of a 3' untranslated region (3'UTR) variant identified. *Methods:* The affected patient was examined clinically followed by gene panel screening and exome sequencing. RNA sequencing and western blotting were performed from skeletal muscle. In vitro studies were performed to confirm that the 3'UTR variant reduces *KLHL40* expression. *Results:* Patient muscle biopsy revealed nemaline bodies and intranuclear rods and showed significant reduction in *KLHL40* mRNA and protein. Genetic studies revealed biallelic variants in *KLHL40*; a truncating 10.9 kb deletion in trans with a 3'UTR variant (c.*152G>T). The c.*152G>T variant was predicted by SpliceAI and Introme to create a cryptic donor splice site and was shown by RNA sequencing and in vitro analyses to induce multiple de novo splicing events. Puromycin assays suggested that the 3'UTR splicing likely provokes nonsense mediated decay of *KLHL40* mRNA, explaining the reduced *KLHL40* expression and protein abundance in the patient. Analysis of 3'UTR variants in ClinVar suggests that 3'UTR splicing may be an underrecognized pathomechanism in Mendelian disease. *Conclusion:* This study expands the genotypic and phenotypic spectrum of NEM8 and encourages consideration of 3'UTR variants during disease gene screening.

Epigenetic Regulation of Non-Hodgkin Lymphoma

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Background: miRNA biomarkers has been well established in some hematological malignancies so here we investigate the role of two miRNAs as drivers of lymphomagenesis in Non-Hodgkin Lymphoma (NHL) and assess their potential as diagnostic and prognostic biomarkers. *Aim:* Investigate the interplay between miRNA/mRNA regulation and DNA methylation by targeting Tet Methylcytosine Dioxygenase 2 *(TET2). Methods:* miRNA/mRNA expression was measured using RT-qPCR, along with methylation studies of CpGs promoter region CGIs of miR-29c and miR-210 and host genes *MIR29B2CHG and MIR210HG.* Samples included; 4 NHL cell lines, 24 patient peripheral blood-derived (PB) gDNA, 11 patient-derived tumors and 6 healthy control PB-derived leukocytes. Methylation data from pyrosequencing were correlated against expression levels of the individual miRNA as well as *TET2* mRNA. *Results:* Differential expression of miR-29c-3p and miR-210-3p was seen across 4 NHL cell lines compared to healthy controls and

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between DLBCL and FL tumor tissues. Differential methylation of CpGs in the upstream promoter of *MIR29B2CHG* and *MIR210HG* was observed across cell lines, and in DLBCL and FL tumor tissues, compared to controls. Differential methylation was not identified in either the MIR29B2CHG or MIR210HG promoter regions in patient PB gDNA compared to controls. Aberrant expression of *TET2* was seen in NHL cell lines and tumors, and disparate levels of dysfunctional promoter CGI methylation were seen across tissues. *Conclusion:* miR-29c-3p, miR-210-3p, and *TET2* may play a concerted role in NHL disease pathogenesis in specific tissues such as blood and solid tumors, with pronounced levels more commonly seen in DLBCL.

RNA-SEQ and WGS Analysis Uncovers a *DMD* Structural Variant and a *DIP2B* Repeat Expansion: A Case Report

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Background: Duchenne muscular dystrophy (DMD) is a rare progressive disease caused by pathogenic variants in the dystrophin gene (*DMD*). Hypermethylated CGG expansions within the 5'UTR of the disco interacting protein 2 homolog B gene (*DIP2B)* are associated with FRA12A type of intellectual development disorder. Here, we demonstrate the diagnostic utility of whole genome sequencing (WGS) and RNA sequencing (RNA-seq), used to identify a novel *DMD* structural variant and a *DIP2B* CGG expansion in a DMD patient for whom conventional diagnostic testing failed to yield a genetic diagnosis. *Methods:* We performed short-read WGS, skeletal muscle RNA-seq, and targeted long-read sequencing. OUTRIDER was used to detect RNA-seq expression outliers. *Results:* The proband had a typical DMD clinical presentation and clear features of dystrophinopathy on muscle biopsy. RNA-seq analysis identified six aberrantly expressed genes; *DMD* and *DIP2B* were the strongest under- and overexpression outliers, respectively. WGS analysis of the *DMD* locus revealed split reads in a pattern suggestive of a 216 kb paracentric inversion (NC_000023.11:g.33162217-33378800). Analysis of the *DIP2B* 5'UTR CGG expansion locus with Expansion Hunter indicated an expansion of 109 (80-186) repeats. Targeted long-read sequencing confirmed both the *DMD* structural variant and genotyped the *DIP2B* repeat expansion at 270 x CGG. There was no evidence of hypermethylation at the *DIP2B* promotor. *Conclusion:* Here, RNA-seq results heavily guided WGS analysis to resolve a complex *DMD* inversion and a likely *DIP2B* premutation; the clinical significance of the latter remains unknown and longitudinal follow up will be important for clarifying this.

Biochemical Variability In 3-Hydroxy-3-Methylglutaryl CoA Lyase Deficiency

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Background: 3-Hydroxy-3-methylglutarylcoenzyme A lyase deficiency (HMGCLD) is an autosomal recessive disorder of organic acid metabolism. HMGCoA lyase is a mitochondrial enzyme necessary for the catabolism of leucine, as well as for the synthesis of ketone bodies acetoacetate and 3-hydroxybutyrate. Affected patients typically present with hypoglycemia, metabolic acidosis, neurological symptoms and mild hepatopathy. Biochemically, HMGCLD is characterized by high urinary output and tissue accumulation of 3-hydroxy-3-methylgutarate (HMG), 3-methylglutaconate (MGC), 3-methylglutarate (MGL) and 3-hydroxyisovalerate (3IV). *Aims:* To distinguish presenting biochemistry from other leucine catabolic disorders and establish patterns of elevations longitudinally, when well and unwell. *Methods:* Data collection (urine organic acids and plasma acylcarnitines) from a cohort of seven HMGCLD patients over time was correlated with clinical status at the time of collection (i.e., presenting, monitoring, unwell/decompensated). Biomarker levels were also correlated with treatment initiation. *Results:* During metabolic crises, gross elevations of MGC and HMG were seen. Ketones were not detected in six of seven patients during crises. Additional elevation of MGL and 3IV was typically seen in crises. Most newly diagnosed patients had significantly increased plasma 3-hydroxyisovalerylcarnitine (C5OH) and 3-methylglutarylcarnitine (C6DCA), apart from one patient with low total carnitine levels. After commencement of treatment, C5OH and C6DCA levels decreased and most patients remained at typically twice ULN during routine monitoring. *Conclusion:* HMGCLD was always identifiable during metabolic crises, but there was biochemical overlap with other disorders when well. Plasma acylcarnitine biomarkers C5OH and C6DCA were consistently elevated. Correlation studies with urine biomarkers could help add to our knowledge of phenotypic variability.

Developing Evidence for a Polygenic Breast Cancer Risk Report: Consumers and Clinicians' Perspectives

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Background: Translating polygenic breast cancer information into health outcomes relies on effective communication to enable risk-appropriate decision-making. Effective communication is a key implementation challenge and evidence-based communication resources are lacking. *Aim:* To examine stakeholders' perspectives about communicating polygenic breast cancer risk to inform the development of a clinical report. *Methods:* The Theoretical

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Framework of Acceptability guided the study design. Data were collected using a mixed-methods approach examining stakeholders' perspectives on communicating polygenic breast cancer risk, including a comparison of four visual risk communication tools. Stakeholders included consumers and clinicians from genetics, oncology, and primary care disciplines. *Results:* Surveyed consumers ($n = 165/504$, response rate 33%) reported an icon array and a graph of cumulative breast cancer risk over age impacted their affective attitude but were less burdensome to understand and more effective at communicating risk compared to a skewed normal distribution curve ($p < .05$). Eleven consumers were subsequently interviewed and reported they would want to know their polygenic breast cancer risk if it were offered. They also wanted written information after a verbal discussion with a clinician. Six genetics, nine oncology, and ten primary care clinicians were interviewed. Most thought reports should be tailored to the recipients' genomic literacy, with separate reports for patients and clinicians. Suggested report content included a plain language summary explaining the polygenic breast cancer risk result, numerical risk with risk stratification categories, cancer risk management recommendations, and references to sources. *Conclusion:* This evidence will inform the development of a polygenic breast cancer report that will subsequently require evaluation.

The Development and Evaluation Of Educational Resources for Young Women With Neurofibromatosis Type 1 (NF1) Undergoing Breast Cancer Screening

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Background: Women (30-50 years) with NF1 have increased risk of breast cancer and poorer five-year breast cancer survival. Breast cancer screening is recommended from 30 years, compared to 50 years in the general population. Current breast screening resources may be inappropriate for this cohort due to an increased incidence of cognitive deficits, anxiety, and cancer worry. Limited access to patient-appropriate health screening information, and poor understanding of guidelines may contribute to lower uptake of cancer screening in this cohort. Simple, easy-to-understand educational resources increase patient knowledge and screening attendance. The aim of this study was to develop and evaluate patient resources targeted to this cohort. *Methods:* Informed by research design and evaluation principles, a brochure was developed with input from clinicians, support group representatives and interviews with women with NF1 who participated in breast screening. The content was further adapted to create a webpage and animation, evaluated through clinician and patient surveys. *Results:* Nine semi-structured interviews were conducted with women with NF1 after breast screening. All ($n = 9$) considered the brochure to be acceptable and useful with support for e-resources specific to NF1 and breast screening. The webpage and animation were also rated highly in terms of acceptability, usefulness, and relevance by clinicians ($n = 21$) and patients ($n = 10$). *Conclusion*: Information in three different media have been developed specifically for women with NF1 considering early breast screening, to increase understanding, provide reassurance and as a memory-aid to support clinician consultation. The resources are adaptable to local clinical services and may inform development of other condition-specific information.

Starting the Conversation on Including Genes Associated With Non-Syndromic Hearing Loss In Reproductive Genetic Carrier Screening

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Background: Some couples wish to avoid having a child born deaf, even though there are effective interventions and supports. There is no consensus on whether deafness should be included in reproductive genetic carrier screening (RGCS). This is problematic as governments consider implementation of population RGCS programs. *Aim:* This study explored stakeholder views on the acceptability of including genes associated with non-syndromic hearing loss (NSHL) in RGCS in Australia. *Methods:* Qualitative interviews were held with 27 participants: 14 who identified as deaf and 13 parents of a deaf child. Interview transcripts were analyzed thematically. A quantitative approach was used to survey 386 healthcare professionals (HCP) involved in RGCS or in the management of children with NSHL. *Results:* This study reveals the complexity of attitudes within these groups. The goal of supporting reproductive autonomy is in tension with concerns about potential harms, especially negative messages about deafness and an existential threat to Deaf culture. Deaf participants who supported carrier screening emphasised the need for accurate and current information on deafness. Most HCP agreed genes associated with NSHL should be included in RGCS. HCP working in hearing clinics and genetic HCP were notably more in favour than obstetricians and general practitioners. All stakeholder groups acknowledged the complexity of defining the severity of deafness, especially when compared to other conditions included in RGCS. *Conclusion:* The findings provide some support for inclusion of genes associated with NSHL but identified strong concerns that need to be addressed in the development of a RGCS program.

Variant Interpretation Training in the Genetic Counseling Workforce: Current Expectations and Education Opportunities in Australia

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Background: Genetic counselor education in Australia consists of a two-year equivalent Master of Genetic Counselling followed by training and certification with the Human Genetics Society of

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Australasia (HGSA). With the increased use of genomic technologies in healthcare, the role of the genetic counselor has expanded internationally to include laboratory, research and educational roles. Variant interpretation is the process of identifying and assessing the pathogenicity of genetic variants for use in healthcare settings. The extent to which genetic counselors currently practice variant interpretation in Australia is currently unknown. *Aim:* To assess the current expectations for training in variant interpretation in Australian genetic counselor education and the genetic counseling workforce. *Methods:* Consultation with key stakeholders in genetic counseling and genomics education in Australia. Assessment of current HGSA genetic counseling competencies and comparison with current Master of Genetic Counselling curriculum. *Results:* The current HGSA competencies for genetic counseling do not identify variant interpretation as a skill required of new graduates and the genetic counseling workforce. Consultation with key stakeholders, however, reflects the increased desirability of the skill. We describe the teaching approach taken at one Australian university for this skill and the types of genetic counselor roles supported by this. *Conclusion:* Variant interpretation is increasingly a desirable skill in the genetic counseling workforce and universities are well placed to lead with training the next generation of counselors.

Exploring Patients' Perspectives on Parameters of Uncertainty in the Provision of Clinical Genomic Testing

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Background: The expanding application and efficiency of genomic testing has increased the need to manage uncertainty in variant classification. The Clinical Genome Resource has developed evidence-based frameworks to standardize variant curation. Currently, patients' perspectives on these frameworks have not been explored. *Aim:* To explore patients' perspectives on uncertainty associated with three variant-specific test parameters: (1) contribution to total risk, (2) classification reliability, and (3) precision of variant-specific risk. *Method:* Six deliberative focus groups were conducted with 18 participants, who had undergone predictive testing for a familial cancer or cardiac disorder pathogenic variant. Focus groups were structured to introduce and explore three parameters in the context of a hypothetical scenario. An inductive thematic analysis approach was used to generate themes. These were mapped to the three parameters to investigate their influence on participants' acceptance of uncertainty. *Results:* Themes were captured in two domains: personal and clinical. Four themes were captured under the personal domain*: familial influences, personal control, informed understanding*, and *perception of risk* with the subtheme *individuality of risk*. The clinical domain included three themes: *actionability of results* and its two subthemes *severity of risk management* and *risk management options*, as well *as professional expertise* and *practicalities of testing*. The prominence of each theme, and how they influenced participants' acceptance of uncertainty differed between the three parameters. *Conclusion:* Patients' perspectives were found to be conditional and multi-faceted, indicating the inclusion of patients' values in framework development may provide benefits for managing uncertainty.

Enhancing Team Communication to Improve Service Delivery in a High Demand Clinical Genetics Service

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Background: Demand for clinical genetics services at Monash Health continues to grow rapidly at a volume the service is unable to fully meet, resulting in long patient wait times and staff pressures. Many members of the growing team work part-time and offsite resulting in fragmented communication. The department is always searching for ways to improve service delivery. *Aim:* To utilize the FamBIS database to enhance team communication thereby increasing effectiveness and efficiency in patient care. *Method:* A working group was formed with representatives from all staff groups to review and enhance FamBIS as a communication tool. Changes were made and comprehensive FamBIS training was provided to all staff. Individual staff review lists were cleared of backlog and team review lists were created, where applicable. Follow-up, feedback and improvements are ongoing. *Results:* Review actions were defined to encapsulate all patient related tasks from time of referral to discharge. This ensured that administrative tasks, clinic preparation, genetic testing, correspondence and patient follow-up were recorded and completed in a timely manner. New processes were implemented for team communication, and team review lists were created. *Discussion:* Overwhelmingly, staff feel more in control of their workload and confident that no tasks or patients are overlooked. Communication between team members has significantly improved without unnecessary phone calls and emails. Patient follow-up and handover has also improved. *Conclusion:* Through enhanced utilisation of the FamBIS database we have improved team communication, leading to improved effectiveness and efficiency in patient care.

Capillary Electrophoresis for the Screening and Diagnosis of Congenital Disorders of Glycosylation: A Thing of the Past

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Background: Congenital disorders of glycosylation (CDG) are a group of more than 130 disorders relating to defects in the glycan modification or synthesis pathways. A range of clinical manifestations are observed, including neurological abnormalities, cardiac disease, and developmental regression. Methods of screening and diagnosis include transferrin isoform (TFISO) analysis by capillary electrophoresis (CE), tandem mass spectrometry, and/or molecular genetic testing. The NSW Biochemical Genetics (BG) Service has been offering kit-based CE analysis for the screening of CDG types since 2004. *Aim:* We aim to assess the clinical utility of kit-based CE for the screening of patients with suspected CDG. *Methods:* TFISO-CE results and clinical data between January 2017 and June 2022 were extracted from the hospital's laboratory information

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management system. Clinical utility of this method was evaluated through exploration of data regarding number of CDG investigations relative to total BG requests, indications for testing, and positive test results. Positive CE results were correlated with molecular findings, when available. *Results:* Preliminary data showed that developmental delay, seizures, and hypotonia were the most frequent clinical indications for testing. After excluding false positives, the average test positive rate was 0.77%. *Conclusion:* Although serum TFISO analysis by CE has historically been utilized as a first-tier investigation, the low biochemical test positive rate determined by this study supports the cessation of this method and encourages the use of glycan structure analysis by mass spectrometry and/or molecular analysis for patients with CDGs. The NSW BG Service will cease CE based TFISO analysis in December of 2022.

Prenatal Diagnosis After 24 Weeks In Victoria, 1988–2021

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Background: Detailed information on all prenatal diagnostic procedures in Victoria has been collected for four decades. Annual reports and publications have focused on tests done ≤ 24 week gestation. After 24 weeks, the usual reason for prenatal diagnosis is a fetal structural abnormality, for which chromosome microarray analysis has become standard practice since 2012. *Aim:* To perform a state-wide analysis of late amniocenteses done after 24 weeks. *Methods:* Data were extracted from the Victorian Prenatal Diagnosis Database, 1988–2021. Chi-squared tests were used to describe trends in indications for and results of the procedures. *Results:* The annual numbers of late amniocenteses were consistently below 50 from 1988 to 2007 but subsequently increased to >180 by 2019. They increased as a proportion of all prenatal diagnostic tests from 1% to 10%. Over 90% were performed for fetal structural anomaly. Trisomies 21, 18, and 13 were diagnosed on average in 14.6% of tests from 1988-1991, 6.9% from 1992–1999, declining to <4% in the last decade ($p < .05$). The proportion of other abnormalities (unbalanced translocations, pathogenic copy number variants, mosaic abnormalities, sex chromosomal and rare autosomal aneuploidies) has remained stable at ~4.0%. Another 7% were variants of uncertain significance. *Conclusion:* The 3-fold increase in amniocenteses after 24 weeks coincides with advances in prenatal screening and availability of microarrays. Improved sensitivity of maternal screening and mid trimester ultrasound has reduced late diagnoses of the common autosomal trisomies. The average diagnostic yield of a late amniocentesis is one in ten.

Study 165-305: Interim Safety and Efficacy of Pegvaliase in Japanese Adults With Phenylketonuria

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Herein we present Part 1 interim data for an ongoing phase 3, open-label, multicenter, 2-part (Part 1: 52 weeks, Induction/Titration and Maintenance; Part 2: Long-term Extension, up to 156 weeks) study evaluating the safety and efficacy of pegvaliase (up to 40 mg/day) in Japanese adults with phenylketonuria who have blood phenylalanine (Phe) ≥600 µmol/L at baseline (BL). The majority (8/12) were male with a mean ± *SD* BL age and Phe of 29.4±8.1 yr and 1001.8±167.5 µmol/L. All patients completed ≥4 weeks induction followed by ≥5 weeks of titration with 10 mg/day. At week 52 mean Phe was 448.3 ±458.8 µmol/L, a mean absolute and percentage reduction from BL of 553.5±439.4 µmol/L and 56.4±42.3%; whilst mean percentage change from BL in intake of protein from intact food increased (41.9±67.2%) and medical food decreased (-32.5±55.0%). By week 52, 63.6%, 54.5%, 36.4% achieved Phe ≤600, ≤360, ≤120 µmol/L respectively. All patients experienced ≥1 treatment emergent adverse events (AEs), none CTCAE at severity grade ≥3. There were 12 hypersensitivity AEs, but no anaphylaxis events. Three patients had a dose reduction, and 5 patients had a dose interruption related to an AE. One patient developed nasopharyngitis (grade 2), requiring hospitalization, and was considered unrelated to therapy by investigator. There were no deaths, no AEs leading to discontinuation of study, and no treatment-related SAEs. The results support the efficacy of pegvaliase with a manageable safety profile.

A Multidisciplinary Approach to a Greener and More Sustainable Biochemical Genetics Laboratory

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Background: Medical laboratories produce large amounts of clinical/nonclinical waste and are reliant on natural resources and energy. Through engagement of laboratory staff and its served community, roadmaps to a net zero carbon future can be established. *Aims*: This initiative will review all facets of operations applicable to a biochemical genetics laboratory by: (1) determining the current state of sustainability practices and understand staff perception, (2) identifying the largest stream of waste/carbon footprint for targeted mitigation strategies, and (3) identifying opportunities to incorporate sustainability in laboratory operations. *Method*: Through surveys of staff, assess the level of understanding of 'greenlab'. Develop and implement laboratory specific and appropriate strategies based on recommendation by MyGreenLab®. Obtain MyGreenLab Certification and champion change in other laboratories by information sharing/mentoring. Participate in the International Freezer Challenge to promote best practices in cold storage management. Survey clients and patients to understand whether a sustainable laboratory will effect clinical service choice. *Results*: Baseline assessment against MyGreenLab criteria yielded a score of 53% and identified green chemistry, plug/energy load and waste management as main areas for improvement. Out of 102 opportunities identified, 53 strategies are already actioned on. We determined the largest streams of carbon emissions, and established protocols to reduce energy consumption and emissions by at least 9,200 kWh and 7.307 tones, respectively. *Conclusion*: This initiative highlights the key challenges the laboratories face pursuing greener practices. We have identified simple, yet

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impactful opportunities, and longer-term options to reduce emissions, and promote a culture of sustainability in the laboratory.

Mitokines as Markers of Mitochondrial Dysfunction in a *Mecp2*^{T158A} Mouse Model

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Background: Rett syndrome (RTT, OMIM #312750), the second most common cause of intellectual impairment in females, occurs due to pathogenic variants in the methyl-CpG-binding protein 2 gene (*MECP2*). Metabolic complications, mitochondrial dysfunction, and inflammation have been reported in individuals with RTT. Despite 66 clinical trials to date, including various medications hypothesized to be disease-modifying, treatment remains purely symptomatic. A significant impediment in determining treatment efficacy has been the lack of a clinical biomarker that correlates with affected status, disease severity and treatment efficacy. Mitokines, such as fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15), are established biomarkers of cellular stress and mitochondrial dysfunction, and so they may be of clinical utility for patients with RTT. *Aim:* We compared FGF21 and GDF15 concentrations in pre-symptomatic and symptomatic Mecp2-deficient mice and age-matched wild-type (WT) controls, to determine the suitability of these mitokines as biomarkers for RTT. *Methods:* Serum samples were collected from male and female WT and *Mecp2*^{T158A} mice at various ages. FGF21 and GDF15 concentrations were measured using a quantitative enzyme-linked immunosorbent assay. *Results:* Preliminary data suggests a significant elevation in FGF21 concentrations in female RTT mice compared to controls ($p < .05$); this was not observed in males. There was a trend towards increased GDF15 concentrations in female RTT mice compared to controls. *Conclusion:* We provide evidence that mitokines may be useful as biomarkers in female RTT mice. Further studies are required to determine whether the findings from this animal model are recapitulated in humans.

Inherited Metabolic Disease: A Journey Through the Ages

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Background: Inborn errors of metabolism (IEMs) are genetic disorders that alter biochemical pathways in the body, impacting on energy generation and/or utilization. The *Journal of Inherited Metabolic Disease* (JIMD) is a key resource for disseminating knowledge of IEMs. *Aim:* We assessed publishing trends in the JIMD, as a surrogate marker for developments in the diagnosis and treatment of IEMs over time. *Methods:* We reviewed published abstracts of articles from the JIMD between 1980 and 2019. Keywords (including disorders, biochemical pathways, study types, laboratory techniques and treatments) were generated from each abstract. Data wrangling was performed in Microsoft Excel and visualized using a custom script in Python3. Using a 'Word Cloud', keywords were then displayed based on their frequency in each decade. *Results:* Comparisons of Word Clouds amongst the decades identified multiple trends. Between the 1980s and the 2010s, there was a decrease in frequency of the keywords 'Tissue Culture' and 'Enzyme', with an upward trend in the use of keywords 'Treatment and 'NBS'. These observations suggest that earlier decades were more of an era of discovery and understanding of pathophysiology, subsequently leading to development of earlier detection and treatments in the field of IEMs. Unsurprizingly, there was an increasing trend of reference to 'molecular' analysis in more recent decades. *Conclusion:* Word Clouds are an under recognized tool for visualizing trending topics over time. The increasing prevalence of the keyword 'Gene Therapy' suggests a possible greater focus on this technology moving forward.

Patients With *FLNC* Truncating Variants Attending a Specialized Cardiac Genetic Clinic

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Background: FLNC encodes for filamin C, a protein expressed in Z-discs of cardiac and skeletal muscle, involved in intracellular signalling and mechanical stabilization. Variants can cause diverse phenotypes with skeletal (myofibrillar or distal myopathy) and/or cardiac (hypertrophic, restrictive and arrhythmogenic cardiomyopathies) manifestations. Truncating variants have recently been implicated in arrhythmogenic cardiomyopathy (ACM) without skeletal disease. *Aim:* Describe families with likely pathogenic/pathogenic (LP/P) truncating variants in *FLNC (FLNC*tv) seen in a specialized cardiac genetic clinic. *Methods:* Retrospective review of medical records, including cardiac investigations, was performed for families attending a specialized clinic identified to have a *FLNC*tv. Truncating variants included insertions or deletions leading to a frameshift, nonsense or canonical splice site variants. Variants were classified according to the ACMG criteria. *Results:* Of 6 families identified, 5 had primary cardiac phenotypes with frameshift variants predicted to cause nonsense mediated decay. 1 family had no cardiac phenotype, with a pathogenic c.3791-1G>C canonical splice variant identified as a secondary genetic finding. Of the 5 with cardiac phenotypes, proband age at diagnosis ranged 27−35 years (4 female). 3 families experienced sudden cardiac death (SCD) of a young relative (age range: 30-43y) and 1 patient is awaiting cardiac transplantation. Cardiac imaging was available for 4 affected individuals across 3 families, with left ventricular (LV) dilation and reduced systolic function reported in all (LV ejection fraction range: 30−51%). LV

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fibrofatty infiltration of the myocardium, demonstrated as late gadolinium enhancement on cardiac MRI or on postmortem histology, was seen in 4 families. *Conclusion: FLNC*tv cause a left-sided ACM phenotype with high risk of severe cardiac outcomes including end-stage heart failure and SCD.

Investigation of a Complex Familial Structural Rearrangement in a Neonate Utilizing Microarray, Cytogenetics and Fish

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Background: Microarray analysis was requested on peripheral blood from a neonate with multiple congenital abnormalities and two copy number variants of significance were detected. Conventional cytogenetic analysis visualized the copy number variants as an unbalanced structural rearrangement. Parental blood samples were requested to investigate the origin of the structural rearrangement. *Aim:* To investigate the extent of complexity of a structural rearrangement and utility of various cytogenomic technologies in familial risk assessment in case of unusual complex chromosomal rearrangements (CCRs). *Methods:* Whole genome single nucleotide polymorphism was performed using the Illumina GSACyto BeadChip and NxClinical software v6.1 on DNA extracted from peripheral blood. Conventional cytogenetics with G-banding and FISH analysis were performed on 72-hour synchronized blood cultures. *Results:* Microarray finding of a pathogenic terminal gain of 20p13p11.21 23.3Mb in size prompted conventional cytogenetic analysis, showing the unbalanced rearrangement was due to additional chromosome 20p material located on chromosome 15p .Surprizingly, parental testing revealed more complex familial rearrangement involving chromosomes 15, 20 and 22, resulting in the loss of the short arms of chromosomes 15 and 22 and formation of a stable dicentric derivative between chromosomes 20 and 22 in addition to the derivative described above. *Conclusion:* By using a combination of microarray, karyotype and FISH we were able to decipher the complex chromosomal rearrangements in this family and provide information that will be important for genetic counseling and assisting with risk assessment for any future offspring. This case expands the complexity of CCRs and invokes considerations for classification and nomenclature reviews.

Using a Custom Designed Capture to Provide Deep Sequencing for Detection of Low Level Mosaic Variants in Overgrowth Disorders

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Background: Overgrowth disorders are a heterogeneous group of disorders characterized by abnormal increase in size, which may be whole body or limited to a specific body part. Detection of pathogenic variants is often hampered by their being confined to a subset of cells within the affected tissue (somatic mosaicism). Methods such as whole exome or genome sequencing are not ideal for genetic diagnosis of overgrowth disorders as the average read depth is insufficient for the detection of variants with low allele fractions. *Aim:* To design a custom assay for deep sequencing of genes where variants are commonly reported in somatic overgrowth disorders. *Methods:* We used a custom Agilent SureSelect$^{XT\ HS}$ capture and library sequencing on an Illumina Miseq to sequence these 8 genes: *AKT1, AKT2, AKT3, MTOR, PIK3CA, PIK3R2, PTEN, RASA1*. *Results:* This method provided an average depth of coverage of at least 500x reads across coding regions with at least 95% of bases having at least 100x read depth, which yielded a sensitivity of >95% for variants with an allele fraction of >10%. It could detect somatic variants down to 3% allele fraction and was instrumental in providing a genetic diagnosis for patients with disorders associated with the genes in this panel. *Conclusion:* This method has the flexibility to improve clinical sensitivity for variants with allele fractions of less than 10% by varying the depth of coverage. Plans are underway to expand the panel to include other genes where mosaic findings are common.

Young People's Experiences of Managing Significantly Increased Risk of Gastric Cancer Due to a *CDH1* Pathogenic Variant

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Background: Currently, the most effective option for gastric cancer risk management in individuals with a *CDH1* germline pathogenic variant (PV) in Australia is prophylactic total gastrectomy (PTG). There is, however, increasing confidence in endoscopic surveillance as a risk management strategy, raising challenging decisions regarding gastric cancer risk management. For young people, this decision-making comes at a complex development stage of emerging and young adulthood. *Aim:* This qualitative study collates the first-ever Australian dataset of young people's (18−39 years) experiences of managing their gastric cancer risk, particularly focussing on exploring how young people with a *CDH1* PV make decisions about gastric cancer risk management, and how this decision-making impacts their normative young adult experiences. *Methods:* Thirteen semi-structured interviews were conducted. Data were analyzed using a team-based, reflexive approach to thematic analysis. *Results:* Participants' cancer risk perceptions were greatly influenced by their own lived and familial experiences. Perceived tolerance of uncertainty associated with surveillance, and desire for control over their cancer risk, were fundamental factors in their risk management decision-making. Nevertheless, the most complicating factor in their PTG decision-making was the concern that the physical implications after PTG would restrict or interfere with experiences and tasks that characterise young adulthood, including attending university, travelling and socializing. Further, participants described becoming or being parents as competing with and influencing cancer risk-management decisions. *Conclusions:* Findings can inform counseling approaches and conversations with this unique cohort. This preliminary study also provides the foundation for future research, particularly informing the development of a longitudinal cohort study.

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Experiences and Perceptions of Genetic Counselors Regarding Stem Cell Science: Exploring a Case for a Stem Cell Counselor

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Background: In light of the rapid emergence of stem cell clinical trials, conflicting online information, and unapproved and unregulated stem cell interventions (SCIs), there is need for trained professionals to support patients, research participants, and the public in being fully informed of these procedures and associated benefits and risks. The genetic counseling model, comprising of the 'teacher' and 'counselor' roles and the biopsychosocial dimensions, has been proposed as a promising approach to support those navigating SCIs in clinical and research settings. However, little research has explored this topic. *Aim:* To explore genetic counselors' (GCs') experiences on patient enquiries regarding SCIs, and/or their perceptions of if, or how, families can be supported when considering SCIs. *Methods:* Qualitative, semi-structured interviews were conducted with Australian-based GCs with or without experience in stem cell-related patient enquiries. Data were audio-recorded and transcribed verbatim, de-identified, and subsequently co-coded and thematically analyzed. *Results:* Fourteen virtual interviews were conducted between June and July 2022. The following themes have emerged from preliminary data: clinical utility, scope of practice, and the value of genetic counseling skills. Although many participants cited the limited clinical utility and resources in implementing stem cell-specialized GCs, some expressed optimism for this specialty to be more applicable in the future as demand grows. More in-depth analysis will be presented. *Conclusion:* This study is important in understanding the feasibility of expanding the genetic counseling profession to include stem cell science and how GCs can best support individuals when such concerns emerge for health and genetic conditions.

Percept NIPT Performance in Triplet Pregnancies

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Background: Triplet pregnancies are uncommon, occurring in approximately 3 per 10,000 pregnancies. Until recently, the only prenatal screening option for chromosome disorders in triplet pregnancies was first trimester ultrasound. Noninvasive prenatal testing (NIPT) could assist in assessing risk for chromosome conditions in triplet pregnancies. However, there is a lack of data and professional guidelines regarding the use and performance of NIPT in triplet pregnancies. *Aim:* We report on our experience and test performance of *percept*^{TM} NIPT in triplet pregnancies from December 2015–December 2021, with a focus on common trisomies 21,13 and 18. *Methods:* Triplet pregnancies that underwent *percept*^{TM} were included in this review. From December 2015, analysis was performed using the VeriSeq NIPT platform (Illumina Inc., San Diego) and updated in March 2019 to VeriSeq NIPT solution v2 (Illumina Inc). Secondary analysis was performed using WISECONDOR algorithms. Minimum fetal fraction requirements were based on chorionicity. Where possible, prenatal diagnostic test results and pregnancy outcomes were obtained. *Results:* 70/71 (98.6%) triplet pregnancies returned informative results. Twenty-nine pregnancies (40.8%) were trichorionic, 30/71 (42.3%) dichorionic, and 9/71 (12.8%) monochorionic. Three did not specify chorionicity. 68/70 (97.1%) were assessed as low risk for trisomies 21,13,18. One dichorionic triamniotic pregnancy (1.4%) was positive for trisomy 21 and all triplets were affected. There was one false-positive trisomy 18 result. One triplet pregnancy had persistent, low fetal fraction and an informative result could not be generated. *Conclusion:* Our preliminary experience suggests NIPT is a feasible option to complement ultrasound screening for chromosome conditions in triplet pregnancies.

'Language Matters': Parents' and Healthcare Professionals' Preferred Terminology for Pathogenic Variants in Childhood Cancer Predisposition Genes

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Background: Current literature/guidelines lack consensus regarding the most appropriate term for a cancer-related disease-causing germline variant in patients with childhood cancer. Guidelines also rarely address patient/family preferences, which are critical in the medically complex field of cancer genetics. *Aim:* To assess preferences of parents of children with cancer, genetics professionals, and pediatric oncologists for the most appropriate term to communicate a cancer-related disease-causing variant in children, and explore reasons for preferences. *Methods:* We collected qualitative data within larger studies (PRISM-Impact and GenPact). We asked participants their most/least preferred terms from four options; 'faulty gene,' 'altered gene,' 'gene change,' and 'genetic variant,' analyzing responses with directed content analysis. *Results*: Twenty-five parents, 6 genetics professionals, and 29 oncologists participated. Parents' preferences varied with an equal number of parents most preferring 'gene change,' 'altered gene,' or 'genetic variant' ($n = 8/25$). Parents least preferred 'faulty gene' ($n = 18/25$). Half the genetics professionals most preferred 'faulty gene' ($n = 3/6$); however this was least preferred for remaining genetics professionals ($n = 3/6$). Many oncologists most preferred 'genetic variant' ($n = 11/29$) and least preferred 'faulty gene' ($n = 19/29$). Participants across all groups perceived 'faulty gene' as having negative connotations and potentially placing

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blame/guilt on parents/children. Health professionals described challenges selecting a term that was scientifically accurate, easily understood, and not distressing to families. *Conclusion*: Explaining complex genetic information to families remains a challenge. Although a small sample, lack of consensus in our study highlights the need for conversations to be guided by families' preferred terminology, while providing accurate explanations regarding implications of genetic findings.

Prenatal and Health Outcomes of Children Born From Embryos at Risk of Chromosomal Mosaicism: Experience of a Melbourne IVF Clinic

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Background: Embryos at risk for chromosomal mosaicism can be offered for clinical use. Concerns exist regarding the potential for these embryos to result in true fetal mosaicism, however the literature suggests this is rare. Patients are advised to consider prenatal testing but limited information exists regarding child health outcomes. *Aim:* To determine if patients with a child born from the transfer of an embryo at risk of chromosomal mosaicism underwent prenatal testing, and whether concerns exist regarding health and development of children born. *Methods:* Clinical follow up was conducted by Melbourne IVF (HREC approval ID: 71/19). Patients who transferred between 01/01/2017 to 30/04/2021 and had a live birth were contacted to complete a phone survey regarding prenatal testing and their child's health and development. Medical records were accessed to clarify information provided. *Results:* 29 embryos were transferred to 28 patients (one patient had two transferred simultaneously). All eligible patients provided information. 19 had Percept^{TM} noninvasive prenatal testing (NIPT), of which two also had chorionic villus sampling or amniocentesis. Three patients had an amniocentesis only. 6 patients had maternal serum screening only or NIPT results are unknown. No aneuploidy was detected in patients with reports available. Children's ages ranged from 4 years and 6 months to 6 months old. Three children had mild speech delays and one child is undergoing investigations for ADHD. No parents were concerned about major motor developmental delays. *Conclusion:* Most parents had no concerns about their child's ongoing health and development, however further larger studies are recommended.

Contextual Control of Nonsense-Mediated mRNA Decay by UPF3A

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Background: Nonsense mediated mRNA decay (NMD) is a protective mechanism that degrades mRNAs encoding premature termination codons which underpin 30% of all genetic diseases. It is a major disease modifier and prized therapeutic target. NMD also degrades physiological mRNAs essential for development. While knockout NMD factors *UPF1* or *UPF2* is embryonic lethal, knockout of the third core factor *UPF3B* is not, and instead causes a neurodevelopmental disorder. *Aim:* Test the hypothesis that loss of *UPF3B* function is partially compensated by its paralog *UPF3A*. *Methods:* We modified the expression of *UPF3A* in cells with or without *UPF3B* and assessed impacts on *UPF3B* dependent functions in fibroblast, stem and neuronal cells. *Results:* The comparison of transcriptomes of stem cells lacking *UPF3A* or *UPF3B* unexpectedly suggested *UPF3A* antagonized NMD. This was confirmed in fibroblasts where *UPF3A* enhanced the abundance of NMD target mRNAs. Furthermore, *UPF3A* opposed cellular phenotypes caused by loss of *UPF3B*, including fibroblast proliferation, stem cell differentiation, and neuronal cell axon growth. *UPF3A* maintained these antagonistic NMD functions even in UPF3B depleted cells with one intriguing exception: UPF3A partially rescued the axon growth deficiency caused by loss of *UPF3B* in neurons. *Conclusion:* That *UPF3A* partially rescues axon growth caused by loss of *UPF3B* provides evidence of functional redundancy specific to neuronal cells, highlighting *UPF3A* as a potential modifier of *UPF3B* associated neurodevelopmental disorders. However, our data primarily align *UPF3A* as an NMD antagonist, which is both contrary to our hypothesis and of great significance to the NMD, and NMD-based therapeutic fields.

Pediatric Cataract Causing Variants Identified in an Australian Cohort

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Background: Pediatric cataracts (PC) are a rare heterogenous disease causing visual impairment or blindness in children. *Aim:* To identify disease-causing variants in Australian families with PC. *Methods:* Screen 63 known PC genes (for rare, coding variants) using whole-genome sequencing (WGS) data from individuals in 37 Australian families and determine those likely to cause disease. *Results:* Disease-causing likely pathogenic variants were identified in eight families. Novel variants were identified in genes *PITX3*, *BFSP1* and *GJA8, as well as previously reported* variants that were identified in genes *GJA3, CRYAA, COL4A1* and *HSF4. These results* expand the known genotype-phenotype correlations for these genes. In eight additional families, variants of uncertain significance (VUS) with evidence towards pathogenicity were identified in genes: *GJA3, GJA8, LEMD2, PRX, CRYBB1, BFSP2,* and *MIP,* but additional evidence is required to draw conclusions. A likely genetic cause was not identified in 21 of the 37 families. *Conclusions:* A molecular diagnosis has been achieved for eight families. An additional eight families with VUS are also likely to be disease-causing but cannot currently be returned to patients without further lines of evidence. These VUS reinforce the need for establishing robust pipelines for additional functional assessment of variants and classification criteria specific to PC genes to improve diagnostic rates. The genome sequencing data will enable further assessment of novel genes, noncoding regions and structural variants in the 21 unsolved families. These

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findings expand our current understanding of known PC genes and progress us towards better genetic testing outcomes for patients worldwide.

Are We 'Scid'ding in the Right Direction?

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Background: Severe combined immunodeficiency (SCID) is a primary immunodeficiency (PID) which is usually fatal by 2 years of age if left undiagnosed and untreated. Newborn screening for this disorder can effect timely diagnosis and, often curative, treatment if delivered under 3 months of age. In August 2018, the NSW Newborn Screening Programme commenced a 2-year pilot program screening for Spinal Muscular Atrophy (SMA) and severe PIDs simultaneously due to the availability of a multiplex quantitative PCR assay. The NSW Ministry of Health permanently added both to the panel of screened disorders on 1 July 2022. *Aim:* To investigate the outcome of babies detected on newborn screening (NBS), from 1/8/2018 to 30/5/2022, with an out of range PID result and therefore determined 'screen positive'. *Methods:* Data was extracted and sorted from the NBS database together with clinical information received from medical staff. *Results:* In this period 395,420 babies were screened, of which 310 were 'screen positive'. Most had normal repeat dried bloodspot results. 20 remained abnormal on the second sample and required additional tests to finalize screening. 16 babies were diagnosed with either SCID or another significant immunodeficiency, and offered prompt treatment. In addition, 22 babies were known to be from mothers taking immunosuppressant therapy and required follow up tests that subsequently normalized. There are no known false negative cases of SCID in babies who were screened in the first week of life. *Conclusion:* NBS for PID, especially SCID, is proving successful.

Developing Accessible Reproductive Genetic Carrier Screening for People Who Speak Languages Other Than English in Australia: Experiences From Mackenzie's Mission.

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Background: Reproductive genetic carrier screening (RGCS) gives prospective parents information about their chance of having children with a severe genetic condition. Couples across Australia were offered free RGCS by healthcare providers through a national study, Mackenzie's Mission (MM). Participants enrolled and consented to RGCS online. Tailored pathways were developed for people with limited English proficiency, who are underrepresented in prior RGCS research. *Methods:* MM is using a mixed methods approach to capture program wide longitudinal data. This substudy explores the experience of RGCS for people who use languages other than English, with a specific focus on participant characteristics, enrolment engagement, participant and healthcare provider experiences and perspectives. This data is being obtained through ongoing surveys, interviews, genetic counselor contact notes and facilitated discussions with study team members. Analysis of quantitative data uses descriptive statistics and qualitative data uses inductive content analysis. *Results:* Of 18,219 individuals who completed enrolment and accepted screening through MM, 2598 (14.3%) reported speaking a language other than English at home. Thirty-two individuals enrolled through a tailored pathway - fourteen with a study genetic counselor and interpreter, and eighteen using online written materials translated into Arabic (with or without interpreter support). The remaining 2,566 enrolled through the standard English pathway and preliminary interview data ($n = 9$) shows that participants appreciated being able to access clear online information. Other enablers included online translation tools and bilingual/bicultural healthcare providers, family, friends, and support workers. *Conclusion:* Findings demonstrate that RGCS can be made widely accessible through a multifaceted and supportive approach.

Exploring Women and Their Partners' Experiences of Preimplantation Genetic Testing for Inherited Cancer Syndrome.

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Background: Individuals with inherited cancer syndromes (ICS) have an increased chance of developing cancer and may seek to avoid passing the syndrome to future generations using preimplantation genetic testing (PGT). The recent introduction of Medicare funding may see a rise in PGT uptake. Exploratory research of the experiences of individuals and their partners who have used PGT for ICS is essential to facilitate best clinical practice. *Aim:* To explore motivations, decision-making, and experiences of individuals with ICS and their partners in using PGT to prevent their children from inheriting the ICS. *Methods*: Purposive sampling was used to recruit participants who have accessed PGT for ICS in the last 5 years. Semistructured telephone interviews were undertaken, and a phenomenological approach was used to guide reflexive thematic analysis. *Results:* Six semistructured interviews (3 dyadic, 3 singletons) with nine participants elicited experiences of PGT. Decision-making regarding use of PGT was motivated by genetic/parental responsibility, whereby individuals feel responsibility to protect their future children from passing on a familial variant. Participants' normative developmental experiences, including natural conception, career progression, and prioritization of financial resources for PGT rather than travelling or buying property, were interrupted. Further, participants were faced with ethical dilemmas throughout the PGT process about quality of life with the ICS and discarding embryos. *Conclusion:* The findings demonstrate the psychosocial impact on young adulthood for

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individuals using PGT and how cognizant individuals are regarding the ethical implications. These findings are vital to informing whether supportive care is needed for individuals using PGT.

The Psychosocial Impact of Receiving *BRCA1/2* Secondary Findings From Research Genomic Testing: Experiences of Elderly ASPREE Participants

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Background: Population-based genetic research can reveal clinically actionable secondary findings, such as pathogenic variants in *BRCA1/2*, which increase lifetime risk of cancer. Notifying participants of secondary findings can benefit them and their families. However, the value of returning results to older people has been questioned, given their low residual lifetime risk and concerns regarding their ability to cope with unexpected findings. *Aim:* To explore the experiences of participants in the Aspirin in Reducing Events in the Elderly (ASPREE) study who were notified of a *BRCA1/2* research result using a novel national research genetic counseling service. *Methods:* Semi-structured telephone interviews were conducted with nine ASPREE participants (five men and four women) who received *BRCA1/2* results. Interviews focused on experiences of receiving results and family communication. Transcripts were analyzed using inductive thematic analysis. *Results:* We identified three themes: (1) Dealing with the unexpected: the roles of age and life experiences; (2) The importance of family in receiving the *BRCA1/2* results; (3) Foundations of a positive return of result experience. Participants seemed curious when they received the notification letter and eager to share the result with their families. Participants had a positive relationship with the ASPREE study, which appeared to contribute to their satisfaction with the results return process. *Conclusion:* Older research participants coped well with unexpected secondary findings and ascribed value to the genetic information, particularly to benefit their family. Building a positive relationship with research participants may support the effective return of research results.

Nonreference Genome Transposable Elements (TES) Have a Significant Impact on the Progression of Parkinson's Disease

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The pathophysiology of Parkinson's disease (PD) is a complex process of the interaction between genetic and environmental factors. In the present study, we approached the complex genetics of PD by focusing on the nonreference genome transposable elements (TE) and their impact on the progression of PD using a longitudinal study design within the Parkinson's Progression Markers Initiative (PPMI) cohort. We analyzed 2,886 Alu repeats, 360 LINE1 and 128 SVAs that were called from the whole genome sequence data that are not within the reference genome. The presence or absence of these nonreference TE variants is known as a retrotransposon insertion polymorphism and measuring this polymorphism describes the impact of TEs on the traits. The variations for the presence or absence of the nonreference TE elements were modelled to align with the changes in the 114 outcome measures during the five-year follow-up period of the PPMI cohort. Linear mixed-effects models were used and many TEs were found to have a highly significant effect on the longitudinal changes in the clinically important PD outcomes such as UPDRS subscale II, UPDRS total scores and modified Schwab and England ADL scale. The progression of several imaging and functional measures, including the Caudate/Putamen ratio and levodopa equivalent daily dose (LEDD) were also significantly affected by the TEs. In conclusion, this study identified the overwhelming effect of the nonreference TEs on the progression of PD and is a good example of the impact the variations in the 'junk DNA' have on complex diseases.

Diagnostic Utility of Exome Sequencing in Malformations of Brain Development

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Background: Malformations of brain development (MBDs) are a broad spectrum of congenital anomalies resulting from disturbance of early brain development. MBDs are the major cause of neurodevelopmental delay, cerebral palsy, and epilepsy. Genetic causes underlie the majority of MBDs; however, the diagnostic utility of genomic testing applied to a wide range of MBDs ascertained through routine clinical practise is unknown. *Aim:* This study aimed to determine the genetic diagnostic yield currently achievable for MBDs utilizing exome sequencing (ES) in the Australian Genomics MBD flagship cohort. *Methods:* Affected children were selected through stringent inclusion criteria regarding age, imaging phenotype, and prior genetic testing. We performed singleton clinical ES on the probands. If the result was negative in the clinical setting, we followed up with a research re-analysis of the singleton data. For the individuals who remained unsolved, we performed ES on the parents, followed by a trio analysis. *Results:* 102 patients were recruited, and ten types of MBDs were ascertained. The diagnostic yield was 35.3% using clinical singleton ES, which improved to 42.16% with the research follow-up. The yield varied between different MBDs, with tubulinopathy and lissencephaly having the highest

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diagnostic rates and polymicrogyria and focal cortical dysplasia having the lowest. *Conclusion:* This study demonstrated the high utility of ES as a reliable method for investigating the genetics of MBDs. Nevertheless, the utility of trio analysis appears to outweigh singleton ES regarding the expended resources, time, and energy. Ultimately, a genetic diagnosis would end the diagnostic odyssey and improve prognostic and reproductive counseling for affected individuals.

Feasibility of Low-Burden and Scalable Approach to Measurement of Neuropsychiatric Outcomes in Female *FMR1* Premutation Carriers

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Background: Females with an *FMR1* premutation (PM) allele have increased risk for anxiety, depression, FXPOI and physical health issues. However, current understanding of relatedness across domains is low. *Aim*: To determine associations between physical health, anxiety, and depression in females with PMs aged 20-55 years old. *Methods*: An online health survey was administered in 2017 ($n = 140$). The survey captured lifetime diagnoses and current symptoms of a range of health outcomes and included a nested Liebowitz Social Anxiety Scale and Depression and Anxiety Stress Scale. We classified anxiety and depression using combined lifetime diagnosis plus current symptoms. Physical factors with occurrence >10% were entered into logistic regression models with anxiety/depression as outcome variables. *Results*: Anxiety occurred in 38% ($n = 53$) and depression in 30% ($n = 42$), both increased versus 2017 ABS female population data for anxiety (18%) and affective disorders (7%). In univariate analysis, anxiety associated with overweight/obese status ($OR = 2.35$, $p = .019$), irritable bowel syndrome (IBS) ($OR = 3.43$; $p = .006$), chronic migraine ($OR = 2.76$, $p = .027$), hearing loss symptoms ($OR = 4.0$; $p = .010$) and memory concerns ($OR = 4.61$; $p < .001$). Depression associated with most predictors that associated with anxiety, in addition with BMI ($OR = 2.35$, $p = .039$) and FXPOI ($OR = 2.93$; $p = .012$), but not with chronic migraine ($OR = 2.32$, $p = .067$). In multivariate analysis, only IBS and memory concerns remained significantly associated with anxiety, and IBS, hearing loss and FXPOI for depression. *Conclusion*: Approximately 1 in 3 females in the cohort had depression and/or anxiety. A holistic understanding of mental health in the PM that encompasses mental-physical multimorbidity may improve treatment and care of this cohort.

Attitudes and Training Needs of Oncologists and Surgeons in Mainstreaming Breast Cancer Genetic Counseling in a Low-To-Middle Income Country

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Background: With the advent of poly-ADP-ribose polymerase inhibitor (PARPi) therapies for breast cancer and shortage of genetic counselors worldwide, many countries adopted nongenetics healthcare professional (NGHP)-led mainstreaming models to deliver breast cancer genetic counseling. However, the feasibility of mainstreaming in healthcare settings with insufficient specialists, limited access to new therapies and where population health literacy is low remains unclear. *Aim:* To evaluate the attitudes, considerations, and self-efficacy of oncologists, breast and general surgeons in mainstreaming breast cancer genetic counseling in Malaysia. *Methods:* A 32-item survey was developed using a modified Delphi method and distributed to oncologists, breast and general surgeons who were recruited via purposive and network sampling. Participant characteristics and responses were analyzed using descriptive statistics and compared using chi-squared, Fisher's exact or Welch's t-test. *Results:* 21 oncologists and 32 surgeons responded to the survey. While 77% of respondents expressed interest in providing breast cancer genetic counseling, 85% preferred to refer patients directly to genetic services for genetic counseling. The main considerations for mainstreaming were the cost of genetic testing and PARPi therapy, and availability of support from genetics professionals. Respondents reported a lack of confidence in communicating genetic risk, particularly to patients with poor health literacy, and in the clinical management of patients with variants of uncertain significance. *Conclusion:* There is an urgent need to train more NGHPs in providing breast cancer genetic counseling in low-to-middle income countries. The mainstay for genetic counseling in this setting may be for risk management rather than access to PARPi therapy.

Identifying Disease-Causing Variants in Australian Families With Familial IPF

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Background: Interstitial lung disease (ILD) is a group of disorders characterized by chronic lung inflammation and/or fibrosis. Idiopathic pulmonary fibrosis (IPF) is one of the most common and devastating forms of ILD and is frequently diagnosed when patients have a life-expectancy of 2-3 years. There are now well established IPF genes that harbour rare, causative variants that contribute to familial ILD and 'sporadic' IPF alike. Here we report findings from the Genetic Research in Idiopathic Pulmonary (GRIPF) Study. *Aim:* to identify disease-causing variants in Australian families with familial IPF. *Methods:* Families with multiple cases of ILD, with at least one case of IPF, were recruited. Genome sequencing data for 28 families were generated and 30 IPF-candidate genes interrogated to identify putative disease-causing variants (segregate with disease, are

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rare, and predicted to be deleterious using in silico tools). These variants were curated using the American College of Medical Genetics and Genomics (ACMG) guidelines to determine if they had sufficient evidence to be considered disease-causing. *Results:* Four putative disease-causing variants were identified. A novel splice-site variant and a known missense variant, both located in *TERT*, were classified as likely pathogenic. Additionally, two novel missense variants of uncertain significance were identified, one in each of *SFTPA2* and *RTEL1*. *Conclusion:* Two disease-causing variants were identified in *TERT* in two families. Two putatively disease-causing variants were identified and assays to determine the functional impact of these variants are underway. Supportive functional studies would allow these variants to be re-classified as likely pathogenic and therefore disease-causing.

Exploring Attitudes and Biases Within Genetic Healthcare Towards Australian and New Zealand LGBTQIA+ Community

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Background: Australian and New Zealand (ANZ) genetic healthcare professionals (GHCPs) provide care to a number of patients who identify as LGBTQIA+. Research indicates that some LGBTQIA+ individuals remain worried about poor genetic healthcare provision or have experienced heterosexual biases from healthcare providers. Evidence is missing as to the level and nature of ANZ GHCP's explicit and implicit biases towards LGBTQIA+ individuals. *Aim:* (1) To assess the explicit and implicit biases of ANZ GHCPs and students; and (2) To explore differences within sub-demographics of ANZ GCHPs and students towards homosexuality and transgender identity (TGI). *Methods:* Data collection methodology follows from an American study with genetic counselors and students. GHCPs and genetic counseling students are being recruited through professional and education networks to complete an anonymous online survey. The survey elicits socio-demographics and explicit attitudes focusing on the individual's comfort and understanding of homosexuality and TGI. Embedded in the survey is an implicit association test (IAT) quantifying implicit bias towards homosexuality and TGI using timed responses. Statistical analyses include descriptive statistics and regression analysis. *Results:* Preliminary data from 29 respondents (Average age: 30–34; 81% female; 19% male), indicate an equal explicit preference towards gay/straight, and trans/cisgendered individuals. Some respondents demonstrated an implicit bias towards straight and cisgendered people. More in-depth data will be presented. *Discussion/Conclusion:* Our preliminary findings mirror results identified in American GHCPs and student cohorts. Recognition of ANZ GHCPs and student biases may provide the opportunity for future clinical policy updates and professional education for inclusive and diverse LGBTQIA+ healthcare.

Case Study and Ethical Analysis of Consent for Rapid Genomic Sequencing in Neonatal Intensive Care

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Background: The clinical utility of rapid genomic sequencing (rGS) in critically unwell infants has been consistently demonstrated, and there have subsequently been calls for rGS to be implemented as a first-line test in the neonatal intensive care unit (NICU). However, the complexity of information about genomic sequencing, together with the heightened emotional states of parents of children in the NICU, poses significant challenges for informed decision making in this context. *Aim:* To examine the ethical issues of obtaining informed consent for rGS in intensive care. *Methods:* We present an ethical analysis of a hypothetical case where the mother of an infant admitted to the NICU is herself under inpatient psychiatric care, and the father is urgently preoccupied with his wife's hospital admission. In their absence, the attending neonatologist must decide whether to proceed with rGS. *Results:* This case poses a number of ethical issues, including: (1) informed decision making and capacity, and the necessity to participate in pre-test genetic counseling; (2) explicit and implied consent in emergency contexts such as the NICU; and (3) whether it is in the patient's best interests to proceed with rGS without explicit, fully informed, written consent. *Conclusion:* As this technology is implemented around the world, clinicians will have to weigh up whether the benefits of potential cost-effective diagnostic certainty and timely intervention outweigh the potential harms of revealing complex health information, at a time when parents may not be able to process such information, to justify the use of rGS without informed consent.

Unusual Suspects in Hereditary Melanoma: *POT1*, *POLE*, *BAP1*

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Melanoma accounts for ~10% of all cancers diagnosed in Australia and contributes to 72% of all skin cancer related deaths. Ten percent of all melanoma cases report a positive family history, and 1% have familial melanoma. Of those, ~40% test positive for mutations in high-penetrance genes. 90% of these occur in *CDKN2A*, and consequently the genotype-phenotype correlations are well described in literature. However, less is known about genotype-phenotype correlations in rarer high-risk melanoma genes; *POT1*, *POLE* and *BAP1*. A systematic review identified 49 papers where skin phenotypic characteristics (e.g., number of nevi, nevi pigmentation and morphology, nevi location, and degree of sun damage) were variably, if at all, described. No standardized methods are developed for reporting skin phenotypes, and the degree to which variants in *POT1*, *POLE* and *BAP1* predispose to malignancies, particularly melanoma, was unclear. 248 variants were annotated from 67 sources to identify

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genotype-phenotype correlations across the three genes. *POT1* and *BAP1* showed high-cluster variant regions (≥3 variants within a 30 amino acid span) predominantly associated with cutaneous melanoma. Hereditary cancer variants in *POLE* were confined to the exonuclease domain and associated with a diverse cancer phenotype; however, one hotspot spanning 55 amino acids was associated with cutaneous melanoma. Genotype-phenotype correlations in *POT1*, *POLE* and *BAP1* can be used to identify patient disease predisposition based on mutation position and cluster regions. Better understanding of this association may guide future screening and surveillance for mutation-positive families.

A Clinical Experience of Recontacting Patients About a Change in Reproductive Risk After Reclassified Variant Results from Expanded Carrier Screening

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Background: Eugene genetic counselors (GCs) have delivered over 8000 expanded carrier screening (ECS) results, 90% as couples' results. Some couples have received a reclassified result that has led to a change in their reproductive risk. *Aim:* To report the clinical experience of recontact following variant reclassification to help inform best practice guidelines that support a sustainable clinical utility. *Methods:* Data were analyzed to determine variant reclassification rates and an online survey and focus group was conducted with 6 GCs at Eugene. *Results:* Of 8558 patients, 883 (10.3%) received a variant reclassification over a 3-year period. In 95.4% the variant was upgraded, and in 25 instances (3.4%) this led to a change in the reproductive risk for 19 couples. For 16/19, the risk increased for a condition with expected mild or later-onset phenotype, including 10 with a reduced penetrance variant(s) for GJB2 nonsyndromic hearing loss. On average, variant reclassification occurred after 47 weeks. At the point of recontact, seven couples had expanded their family and one had a child who was affected with the condition the reclassified variant was associated with. GCs reported challenges with reinitiating contact, mainly due to unknown patient circumstances post ECS result disclosure and time lapsed between results. However, when recontact was successful, they felt patients were generally appreciative. *Conclusions:* This research highlights potential patient implications of variant reclassification in an ECS context. Further research into the benefits of variant reclassification is required to help inform guidelines for sustainable patient recontact.

Secondary Use of Clinically Generated Genomic Data: Patients' Decisions and Perspectives to Inform National and International Data Sharing Efforts

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Background: As clinical use of genomic testing rises, so does the quantum of laboratory-governed genomic data. Patient trust must be maintained while managing availability of genomic data for clinical and research reanalysis. Research participant and public attitudes to genomic data-sharing are emerging but patients having clinical testing may have different perspectives. *Aim:* Identify patients' real-world choices and views on sharing their genomic data when consenting to a clinical genomic test. *Methods:* Data-sharing decisions at clinical consent of patients having genomic testing were ascertained. Postcounseling surveys were administered; quantitative data were analyzed using descriptive statistics, qualitative data underwent inductive content analysis informed by a systematic review. *Results:* Almost all patients (98%, 1480/1515) consented to share their data, with parents overrepresented among those who declined ($p = .047$). Most (90%) survey respondents (RR 73%) correctly recalled their decision, although those with English as an additional language were more likely to recall incorrectly (*OR* 3.11, $p < .001$). Most respondents (89%) desired some ongoing control over research use of their data. Of those willing to share data overseas (60%, 527/871), 23% indicated the researcher's country would influence their decision. *Conclusions:* The high uptake and understanding of genomic data-sharing is promising for efforts to make clinical genomic data available for reanalysis. Robust, ethical approaches are needed to achieve the level of control patients desire over research use, and transparency if/when this cannot be achieved. Our results are highly relevant for nation-wide data-sharing efforts; for example, the National Approach to Genomic Information Management.

Barriers to Pediatrician Use of Medicare-Rebatable Genome Sequencing for Specific Childhood Syndromes

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Background: From May 2020, Medicare Benefit Scheme (MBS) item numbers 73358/73359 allow pediatricians in consultation with a clinical geneticist, to request genomic testing for specific childhood syndromes. Providing rebates for nongenetics specialists to request genomic testing could improve timely, equitable access for patients. Use of these item numbers by pediatricians to date has been limited. *Aim:* To investigate barriers and enablers to pediatricians' use of the MBS item numbers. *Methods:* Phone interviews with pediatricians were conducted. A semi-structured interview guide developed from the Theoretical Domains Framework (TDF) captured data about barriers. Audio files were transcribed, validated and analyzed qualitatively. Authors deductively coded data to the 14 TDF domains. Thematic analysis explored pediatrician experiences and attitudes. *Results:* Twenty-six pediatricians (private and public practice in Victoria), were interviewed June-October, 2021. Barriers were grouped according to points of interaction: parent/patient-pediatrician (pre- and post-test) and pediatrician-clinical geneticist (consultation). Barriers mapped to TDF domains of knowledge, beliefs about consequences, skills, social/professional role and identify, beliefs about capabilities, environmental context and resources. Pediatrician/parent interaction barriers were perceived inadequate appointment time, competing clinical priorities, and limited experience discussing testing and consent: 'I'm fighting inside against the sinking feeling of oh gosh, there's another thing that we have to do now.' Private practitioners described challenges consulting a clinical

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geneticist: 'In private, unless you've got someone on your list you don't know where to start.' *Conclusion:* Pediatrician identified barriers at key interactions will guide co-design of interventions to support use of these MBS items by pediatricians.

Identifying Priority Areas for Research for People With a Variation of Sex Characteristics: An Exploratory Study

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Background: The views and experiences of people with a variation of sex characteristics are underrepresented in research. Barriers to research participation include diversity among groups that come under the 'umbrella' of variation of sex characteristics, medical trauma, and over-research creating research fatigue. We aimed to explore the views of key stakeholders to understand priority areas for research in this area. *Method:* We purposively sampled representatives from community advocacy organisations, researchers and clinicians. Data were collected using semi-structured interviews. Transcripts were analyzed using reflexive thematic analysis. *Results:* Eight interviews were conducted between December 2021 and May 2022 including 3 advocacy representatives, 3 researchers and 2 clinicians. We identified three themes: (1) Inadequacy of current research, focusing on researcher bias and lack of trust within the community; (2) Development of psychosocial as well as medical models of care and research; and (3) Educational and societal influences on decision-making. *Conclusion:* Voices of people with variation of sex characteristics are missing from existing research. Alongside medical care and research, investigation into long-term psychosocial impact is needed. Societal views and lack of education amongst health professionals influence decisions about the research that is/should be conducted. Working in partnership with people with lived experience of variation of sex characteristics to develop and under-take research is a priority.

Scoping Review of the Visibility of LGBTQI+ People and Relationships in Genetic and General Healthcare

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Background: Genetic health professionals are increasingly likely to provide services to people who identify as Lesbian, Gay, Bisexual, Transgender, Queer, Intersex and other (LGBTQI+). Although several studies have been conducted in general healthcare, little is known about the experiences of LGBTQI+ communities in their interactions with genetic healthcare. We aimed to identify and map research into the visibility of LGBTQI+ people and their relationships in genetic and general healthcare to inform practice and research. *Method:* We systematically searched five databases for published and grey literature. We included primary research studies reporting on visibility of LGBTQI+ people in genetic and general healthcare. Two reviewers independently screened the studies until an acceptable level of agreement was reached. We conducted a narrative synthesis and mapped the findings to a taxonomy of microaggressions. *Results:* Seventy-seven studies published between 1980 and 2022 were selected, of which four focused on genetic healthcare. We identified the following themes: respect, perception of health professional's knowledge and comfort, encounters of assumptions and stereotypes, reading the environment, and accessing and navigating through services. Findings suggest health professionals and support staff lack awareness of LGBTQI+ needs, and training in this area is inadequate. *Conclusion:* Despite growing societal acceptance of LGBTQI+ people, microaggressions still exist within healthcare. There is an urgent need to equip clinical services to increase the visibility of LGBTQI+ people and their relationships. Research to understand the experiences of LGBTQI+ communities who interact with genetic healthcare is warranted, and training is required to build staff confidence in those interactions.

The Use of Metaphor in Talking About Experiences of Being at Risk of Huntington's Disease

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Background: Understanding clients' use of metaphorical language can provide insight into their experiences and illness representations. Clients may use metaphor to communicate and process complex concepts and emotions. Little is known about client-generated metaphor in genetic healthcare. Aim: The aim of this study is to explore metaphor in communication by individuals at risk of Huntington's disease (HD). We asked: What types of metaphors do individuals use? And in what contexts are they used? We hypothesize that metaphors may be used to communicate lived experiences of HD by relating these to concepts more readily understood by others. *Methods:* The study design used a social constructionist epistemology and conceptual metaphor theory. A systematic metaphor analysis was conducted on transcribed pre-existing interviews from five HD support organisations with people at risk of HD. Rigorous qualitative coding for metaphorical expressions was followed by identification of overarching metaphor groups. *Results:* The three key categories of conceptual metaphors were: 'The Body/Mind is a Machine', 'Life/Disease is a Journey', and 'Huntington's Disease is a Collection of Diseases'. We highlight the domains of *machine* and *journey* as general aspects of disease representation and identify *a collection of diseases* as a metaphor unique to Huntington's disease along with a collection of novel metaphors unique to speakers' own experiences. *Conclusion:* Clients' choice of language reflects their lived experience. By responding to these choices, particularly metaphors, we propose that genetic health professionals can demonstrate advanced empathy and work with client language to facilitate narrative-based strategies for client meaning-making, decision-making and adaptation.

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Multiple ACYL-COA Dehydrogenase Deficiency: An Underdiagnosed Disorder in Adults

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Background: Multiple acyl-CoA dehydrogenase deficiency (MADD) is an autosomal recessive disorder of electron transfer flavoprotein or flavoprotein dehydrogenase that impairs the oxidation of fatty acids and branch chained amino acids. Three heterogeneous clinical phenotypes of MADD are observed: neonatal onset with congenital anomalies, neonatal onset without anomalies and mild or late onset MADD. *Aim:* There is a misconception that inborn errors of metabolism only occur in childhood leading to underdiagnosis of these disorders in adults. *Methods:* We describe seven cases of MADD diagnosed in adults, three in detail, and highlight the heterogeneity in presenting symptoms. *Results:* Case 1 presented with severe encephalopathy requiring intubation and ventilation prior to the finding of significant hyperammonemia requiring dialysis. Case 2 demonstrated progressive limb weakness and paresthesia resulting in wheelchair dependence. Case 3 displayed neuropsychiatric disturbances and encephalopathy presenting with behavioral disturbance, dysphasia, seizures and vomiting. Ammonia and plasma acylcarnitine profile together with urine organic acids profiles should be considered in adults with encephalopathy, severe acute or chronic muscular symptoms, acidosis and hypoglycemia. Significant clinical and biochemical improvements can be seen in the acylcarnitine profile within 2 hours of administration of 100mg Riboflavin. Acylcarnitine profiles are often normal when the patient is well. *Conclusion:* Raising awareness about first presentation of an inborn error of metabolism in adults is an important step in improving outcomes.

Developing a New Centre for Genetics Education Website to Meet Health Professional Needs

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Background: The NSW Health Centre for Genetics Education (CGE) website redesign was a partnership of CGE and NSW Ministry of Health. Following an internal gap and needs analysis of genomics resources, the requirement for a comprehensive website with easily accessible genomics education resources was identified. The analysis also identified the CGE website as a useful resource for health professionals. A project commenced in 2020 to rebuild and develop a new website for genetics education as a trusted source of information, aligning with the NSW Health Genomics Strategy. *Aim:* To develop a new CGE website using a co-design approach with key stakeholders to meet identified needs for NSW health professionals and patients. *Methods:* (1) eHealth NSW Human Centred Design team, eHealth NSW and an external web developer were engaged to develop the website alongside CGE; (2) Input was sought from key stakeholders, including consumer support organisations, through semi-structured interviews and workshops; (3) Prototype website was developed; (4) Feedback was sought from stakeholders via semi-structured interviews to enhance final website; (5) New CGE website launched. *Results:* After preliminary key stakeholder engagement (2 workshops; 12 interviews), a website prototype was developed. Following further feedback from 10 stakeholder interviews, the prototype website was enhanced. The new website was launched in May 2022 with a modern design, easy navigation, improved functionality, and new and increased capacity for resources such as videos and a genetic services map. *Conclusion:* Using a co-design approach with significant stakeholder input, a comprehensive new website with easily accessible genomic resources is now available.

Identification of Fetal and Neonatal Magnetic Resonance (MRI) Findings Alone Does Not Predict Clinical Phenotype and Outcome in Alexander Disease

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Background: Alexander disease (AD) is a progressive, autosomal dominant leukodystrophy caused by pathogenic variants in the *GFAP* gene. The clinical spectrum is broad, with neonatal, infantile, juvenile and adult-onset forms. Characteristic MRI brain abnormalities in AD include frontal-dominant leukodystrophy, T2 hypointense/T1 hyperintense periventricular rim, T2 hyperintensity and swelling or atrophy of basal ganglia and thalami, brainstem abnormalities and contrast enhancement of one or more structures. *Aim/Methods:* We describe the outcomes of two patients with AD with fetal/neonatal MRI abnormalities. *Results:* Case 1 had a fetal MRI at 33 weeks gestation demonstrating aqueduct stenosis with severe ventriculomegaly. MRI on day 2 of life showed frontal-dominant white matter changes and basal ganglia atrophy. Repeat MRI at 4 months (for severe global developmental delay, failure to thrive and refractory seizures) demonstrated a frontal-dominant leukodystrophy, caudate nucleus and brainstem T2 hyperintensity and swelling, and contrast enhancement of basal ganglia, frontal white matter, dentate nucleus, ventricular lining and brainstem. Genetic testing confirmed a pathogenic *GFAP* variant c.716G>A. The patient died at 6 months from neurological deterioration. Patient 2 had a head ultrasound at age 3 weeks showing enlarged thalami. MRI performed at 6 weeks and 4 months identified T2 hyperintensity and swelling of basal ganglia, and symmetrical frontal white matter changes. Neurological examination and neurodevelopment are normal at 5 years. AD was confirmed genetically (pathogenic c.236G>A *GFAP* variant identified.) *Conclusion:* This series shows that neonatal MRI changes alone do not predict the clinical outcome of AD. It also shows that AD can present with fetal aqueduct stenosis.

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Successful Management of a Neonate With an Antenatal Diagnosis of Carbonic Anhydrase VA Deficiency

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Background: Carbonic anhydrase VA (CAVA) deficiency (OMIM 114761) is an ultra-rare inborn error of metabolism with less than 20 cases described. Many affected infants present in the first days of life with hyperammonemia, lactic acidosis, ketonemia and encephalopathy. When CAVA deficiency is confirmed genetically, prenatal genetic testing can facilitate the diagnosis of subsequent affected siblings and permit proactive clinical management to prevent decompensation. *Aim*: To describe the clinical course of an infant antenatally diagnosed with CAVA deficiency who was carefully monitored and managed in the newborn period. The patient's brother had presented on day four of life with marked lactic acidosis (pH 7.18, lactate 11.7mmol/L,) hyperammonemia (450umol/L) and encephalopathy requiring hemofiltration and was subsequently confirmed to have CAVA deficiency (*CA5A* c.198_207delinsACCCGG/c.454G>A). *Methods*: The infant was born in a tertiary neonatal setting. He was managed from birth with regular 3-4-hourly breastfeeding with supplementary expressed breast milk and formula top-ups to ensure he received a full quota for gestational age and weight. In addition, he received carglumic acid at a dose of 100mg/kg daily for five days. Regular biochemical monitoring was undertaken with careful measurement of acid-base status and ammonium levels. *Results*: In contrast to his older brother, this infant had an unremarkable neonatal course with no significant clinical or biochemical concerns. He was discharged from hospital on day five of life with close follow-up arranged. *Conclusion*: In a neonate known to be affected with CAVA deficiency, careful management can be instituted to minimise the risk of metabolic decompensation in the neonatal period.

Process for Analysing and Returning Secondary Findings in Healthy Biobank Participants: The ONEK1K Study

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Background: The expanding use of genomic technologies in research is resulting in increasing numbers of research participants being identified with secondary findings. Many researchers and participants are in favour of returning these results. However, there are no standard methods for identification of secondary findings in healthy biobank participants in Australia. *Aim:* To develop a process for identification of secondary findings and determine the incidence of secondary findings within a cohort of healthy controls for the Tasmanian Ophthalmic Biobank. *Methods:* Samples underwent whole genome sequencing and bioinformatics analysis for pathogenic or likely pathogenic variants in 73 genes on the 'ACMG SF v3.0' list. Variant annotations (including VEP, REVEL and gnomAD allele frequencies) were used to find variants of interest which were then manually curated and reviewed by an expert committee for final classification. *Results:* To date, analysis has been completed for 354 of the 972 samples in the cohort, with 37 of these referred to our expert committee. Following review, 7 variants – *RYR1*, *PMS2* ($n = 2$), *TP53*, *FBN1*, and *HFE* ($n = 2$, homozygous) – were classified as reportable and approved for return to participants, giving a variant detection rate of 2.0%. Bioinformatics analysis is ongoing and more variants to be returned. *Discussion:* We have developed a pathway for identifying secondary findings in a cohort of healthy participants, adaptable for other cohorts. The rate of secondary findings identified is consistent with other studies reporting secondary findings (1–5%). This pipeline will be used to analyze and identify secondary findings for return in future studies.

Evaluating Performance of Fragmented Genomic DNA Using the Illumina DNA Prep PCR Free Protocol

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Australian Genome Research Facility Ltd

Background: Introducing the Illumina DNA Prep PCR-Free workflow at AGRF has enabled PCR-free sample preparation on samples with limited DNA, such as neonatal blood or small tissue (tumour) biopsies, due to the reduced starting inputs of the workflow. Data quality for intact gDNA was comparable to previously used methods however considering the variability in quality of clinical samples, we further tested performance using highly fragmented gDNA across multiple inputs. *Aim:* To evaluate the performance of lower quality gDNA with the Illumina DNA Prep PCR-Free workflow. *Methods:* Genome-in-a-bottle control DNA (HG001/NA12878), was mechanically fragmented to two mean fragment lengths of 1 Kbp and 400 bp to simulate degraded DNA prior to library preparation. Fragmented DNA was prepared in duplicate with inputs of 300 ng, 150 ng and 50 ng and compared to high-quality NA12878. Prepared libraries were sequenced using the Illumina NovaSeq 6000 system to a minimum depth of 10x. Samples underwent alignment and small germline variant calling using the Illumina DRAGEN DNA Pipeline. Variant calls were compared against a gold-standard variant call dataset using the hap.py tool from Illumina. *Results:* Simulated degradation led to smaller insert sizes, increased adapter content, and reduced variant precision and recall metrics compared to the high-quality DNA. *Conclusion:* The reduction in data quality correlates to the level of degradation, providing an indication as to performance of degraded material when using the Illumina DNA Prep PCR-Free for samples with limited recollection or re-extraction options.

Outcomes and Experiences of Clinical Genetic Testing in Congenital Heart Disease – A Single-Site Audit Study

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Background: Following genomic advances, genetic and genomic testing options for pediatric patients with congenital heart disease (CHD) have evolved significantly. *Aim:* A single-site audit was conducted to assess genetic/genomic testing outcomes and a survey was created to explore family experiences and preferences. *Method:* All genetic/genomic tests ordered in patients with surgically-corrected CHD at the Children's Hospital at Westmead between January 2017 and December 2021 were reviewed. Trisomy 13/18/21 diagnoses were excluded from analysis. Preliminary analyses included: demographic/clinical factors, genetic test ordered, diagnostic yield, presence of extracardiac anomalies (ECAs) and/or family history of CHD. Surveys will be sent to parents/carers of children included in the review who attended a consultation with a Clinical Geneticist. *Results:* Genetic/genomic testing was completed in 611 individuals (73 molecular testing; 538 cytogenetic test only). The most frequently ordered molecular tests were: trio (20/73) or singleton (6/73) exome (yield = 7/26; 27%); CHD panel (18/73; yield = 2/18; 11%); and single-gene/diagnosis-specific panel (11/73; yield = 9/11; 82%). Overall, the diagnostic rate using cytogenetic testing and molecular testing was 10% (56/578) and 37% (27/73), respectively. Diagnostic yields using molecular testing were highest in patients with obstructive lesions (5/10), functional single ventricles (4/8) or atrioventricular septal defects (2/4).The diagnostic rate was 32% (6/19) in familial forms of disease and 39% (23/59) in patients with ECAs. *Conclusion:* A genetic diagnosis is achievable in over a third of CHD patients with familial forms of disease and/or ECAs suggestive of a unifying syndromic diagnosis. Additional analyses, including survey responses, will provide insight into patient and family preferences and advances in genetic testing over time.

Breastfeeding Duration in PKU, the RCH Experience

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Breastfeeding is the biological norm for infants and there are few contraindications. The risks of not breastfeeding to mother and infant are well documented. Breast milk is safe and preferred for infants with PKU. Although exclusive breastfeeding in PKU is not possible in most cases, encouraging breastfeeding after diagnosis is usual practice for Metabolic clinics. Australian infant feeding statistics collected in 2020 indicate most infants (95.9%) have received some breastmilk. The proportion of infants receiving any breastmilk reduces by age with 88.6%, 79.5%, 73.8% and 51.1% still receiving breastmilk at 2, 4, 6 and 12 months respectively. There is limited Australian data on breastfeeding in PKU infants but reports from around the world indicate breastfeeding rates and duration are less than the general population. Records of PKU patients aged <5yrswere reviewed for documentation of any breastfeeding each month of life until 1 year. Data for 25 patients indicated76%, 64%, 56%and 28% of these children were receiving any breast milk at 2, 4, 6 and 12 months, markedly less that the general population. Barriers to maintenance of breastfeeding are many. Qualitative studies report mothers of infants with PKU have increased maternal stress, frequent interruptions to breastfeeding, difficulty maintaining supply and increased burden of expressing. Anecdotally, Australian metabolic services don't have adequate resources to breastfeeding support at time of PKU diagnosis Future research is needed to identify the specific barriers to breastfeeding duration in this cohort so appropriate education and support can be offered to these families.

Lipoprotein Lipase Deficiency: Considerations for Modular Feeds

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Lipoprotein Lipase deficiency causes significant hypertriglyceridemia. The mainstay of treatment is fat restriction to 10-26% of total energy. Currently no standard infant formula (SIF) provides restricted fat to 10% total calories. We report on a 10-week-old girl presenting with triglycerides of 140.8umol/L. She required a modular feed (MF) to transition from parenteral to enteral feeds. Here-in we discuss the considerations for creating this MF. MF are formulae of single macronutrient ingredients, in prescribed amounts, with addition of vitamins, minerals and electrolytes. In creating this MF we utilised Foodworks Online, with Nutrient Reference Values (NRV) interfaced and many formula products embedded. Macronutrient targets were fat10% total calories, protein<4g/kg/d, carbohydrate providing remaining calories. Micronutrients and electrolytes were set to meet adequate intake (AI) for <6months, which are based on intake of nutrients in breastfed infants. As the bioavailability of nutrients in human-milk differ from SIF, we also compared to infant formula per100mL. Challenges in creating this MF were vast. Fat restriction, whilst ensuring adequate essential fatty acids was difficult. Monogen, KeyOmega, Beneprotein, Polyjoule and Pediatric Seravit were used. In addition, single nutrients were needed, including Vitamin E, sodium, potassium. Meeting 100% AI wasn't possible with the ingredients available, some nutrients exceeded AI by up to 3000%. Comparing MF intake to SIF nutrient provision at target volume, it was comparable. Some ingredients aren't subsidized by the PBS, cost to the family needs to be considered longer term. This patient remains in hospital and the MF recipe adjusted as needed. We hope to provide future reports on progress.

Pediatric Cancer Genetics: An Emerging Subspecialty

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Aim: Children with suspected cancer predisposition syndromes (CPS) are an emerging patient group requiring specific skills for diagnosis, management and counseling, different from those involved in adult cancer genetics. Referral indications for pediatric cancer patients have rapidly increased in recent era, disproportionate to the overall cancer diagnoses due to widespread adoption of genomic technologies. We outline the unique requirements of this group and present a case for future proofing to ensure they receive skilled genetic input. *Method:* A review was conducted of all patients/family members referred to the CHW pediatric cancer genetics clinic between July 2020 and July 2022. Variables analyzed include patient/clinical demographics, referral source/reason, genetic testing uptake and results. The psychosocial impact of a CPS diagnosis is also explored. *Results:* Over 24 months 39 referrals were received, 22 in 2022 alone. Most probands had cancer (18/31;58.1%). Primary indication for referral was tumour type (14/39;35.9%), followed by

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existing genetics results (9/39;23.1%), often from research testing (5/9;55.6%). There was a high uptake of genetic testing (24/25;96%), which was offered to all previously untested individuals. A CPS was identified in 12 probands (12/31;38.7%). Predictive testing occurred in 21 biological parents and 5 siblings. *Conclusion:* Pediatric cancer genetics is a subspecialty requiring unique skill set. Concentrating clinical experience in this discipline via a tailored clinic with dedicated staff facilitates appropriate testing and optimal patient management. As a diagnosis of CPS is felt widely, supporting families through the implications, physical and mental is vital. The growth of this subspeciality needs to be planned for accordingly.

Focused Assays and Variant Reanalyses to Increase the Diagnostic Yield in the Inherited Retinal Dystrophies

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The emergence of TGA approved therapy and clinical trials for inherited retinal dystrophies (IRDs) heralds an increasing demand for accurate molecular diagnoses. The marked heterogeneity of the IRDs, however, makes variant identification challenging. Analysis is further complicated by regions of highly repetitive or homologous sequences, which are often under-investigated in routine clinical testing. We sought to investigate previously unsolved cases by utilizing targeted data reanalysis and focused assays, to increase the diagnostic yield. This study will discuss our experiences with a series of cases investigated within a diagnostic genomic laboratory setting. Focused Sanger sequencing assays were implemented to investigate the homologous *OPN1LW-OPN1MW* gene array and the highly repetitive GC-rich ORF15 locus within *RPGR*. These assays identified carriers of pathogenic complex hybrid *OPN1LW-OPN1MW* alleles as well as previously unidentified variants within the *RPGR* ORF15 locus. Furthermore, targeted high resolution chromosomal microarray analysis and targeted variant reanalysis facilitated new genetic diagnoses, including the consideration of a recently identified hypomorphic *ABCA4* allele p.(Asn1868Ile) previously considered benign due to a high control population allele frequency. The implementation of dedicated focused assays for exploring highly complex and clinically relevant loci in our laboratory was successful in providing genomic answers in previously unsolved families. As new therapeutic approaches emerge for an increasing number of IRD genes in clinical trial in Australia, this study highlights the need for incorporating systematic data reanalysis approaches and focused assays into the clinical diagnostic workflow to increase overall diagnostic yield.

Functional Genomics for Curation of Variants in Telomere Biology Disorder Associated Genes, a Systematic Review

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Background: Patients with an underlying telomere biology disorder (TBD) have variable clinical presentations and can be challenging to diagnose clinically. A genomic diagnosis for patients presenting with TBD is vital for optimal treatments. Unfortunately, many variants identified during diagnostic testing are variants of uncertain significance (VOUS). This complicates management decisions, delays treatment and risks nonuptake of a potentially curative therapies. Improved application of functional genomic evidence may reduce VOUS classifications. *Methods:* We systematically searched the literature for published functional assays interrogating TBD gene variants. Where possible, established likely benign/benign and likely pathogenic/pathogenic variants were used to estimate the assay sensitivity, specificity, positive predictive value, negative predictive value and odds of pathogenicity. *Results:* 3131 articles were screened and 152 met inclusion criteria. Sufficient data to enable a PS3/BS3 recommendation was available for *TERT* variants only. We recommend PS3 and BS3 can be applied at a moderate and supportive level respectively. PS3/BS3 application was limited by a lack of assay standardisation and limited inclusion of benign variants. *Conclusions:* Further assay standardisation and assessment of benign variants is required for optimal use of the PS3/BS3 criterion for TBD gene variant classification.

Monozygotic Twins With *QRICH1*-Associated Neurodevelopmental Disorder – Extending the Spectrum of This Rare Condition

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Background: QRICH1-associated neurodevelopmental disorder, also known as Ververi Brady syndrome (VBS), is a rare condition that was first described in 2018. Currently, there is limited data regarding the function of *QRICH1*. Recently, it has been proposed to play a role in dictating cell fate in response to endoplasmic reticulum stress. Individuals with VBS have been reported with varying molecular causes including nonsense, frameshift, missense and copy number variants in *QRICH1*. To date, thirty-eight cases have been published worldwide. The most consistent features include facial dysmorphism (92%), developmental delay / intellectual disability (71%; especially difficulties with language development), behavioral problems (42%) and autism spectrum disorder (30%). *Aims:* Here we describe monozygotic twin brothers with VBS of varying clinical severity, diagnosed after a 12-year-long journey. *Methods:* Trio whole exome sequencing was performed in a research setting, with data analysis and confirmatory Sanger sequencing undertaken in a NATA-accredited laboratory. *Results:* A novel de novo heterozygous frameshift variant in *QRICH1* was identified in both twins, consistent with a diagnosis of VBS. Their medical history and clinical features are described, and we document the evolution of their phenotype with age. We believe that their features are consistent with this rare condition.

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Conclusion: We describe *QRICH1*-associated neurodevelopmental disorder in twin brothers, and add to the growing body of clinical and molecular knowledge about this rare genetic condition.

A Maternally Inherited Deletion Within Imprinting Centre 1 (11p15.5) Resulting in Beckwith-Wiedemann Syndrome

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Background: Beckwith-Wiedemann syndrome (BWS) is a pediatric overgrowth syndrome with a susceptibility to tumour development. It is well known that molecular alterations of the imprinting control regions (IC) in the chromosome 11p15.5 region can result in the BWS phenotype as well as Silver-Russell syndrome, a disorder characterized by severe growth retardation. Deletions restricted to the distal IC1 are extremely rare with variable penetrance. Previous case studies suggest that clinical presentation is influenced by parental origin and size of the deletion. *Results:* We present a case of a 15 month old boy with overgrowth, macroglossia and a linear earlobe crease who was found to have a 28% gain of methylation at H19/IGFR2:IG-DMR due to a heterozygous deletion of 2 probes upstream of H19 within IC1 at 11p15.5. Subsequent testing found that the proband's brother who was similarly overgrown, also had the deletion within IC1 at 11p15.5 but no hypermethylation was seen. Familial testing demonstrated that this was maternally inherited from a mother with normal growth parameters. Given the predisposition to tumour development associated with BWS both children are currently receiving surveillance for Wilms tumor as per guidelines. *Conclusion:* This case highlights a rare familial form of BWS caused by a maternally inherited deletion within imprinting centre 1 resulting in hypermethylation in 2 brothers with features of BWS. Regulatory mechanisms of the imprinting centres are complex and clinical consequence of alterations in this area is dependent on the sex of the contributing parent and size and location of the alteration.

'In the Midst of Every Crisis, Lies Great Opportunity'

Angela Overkov

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Background: In recent years our genetic counseling community has been exploring further diversity of our unique skill set and its application outside of the traditional genetic counseling role. Moving from a traditional public health role to a laboratory-based industry role provided a plethora of lessons that have enabled me to 'level up' both professionally and personally. *Aim:* To convey my personal experience of 'moving to the dark side', the movement from self-doubt to self-assuredness and ultimately finding out that 'in the midst of every crisis, lies great opportunity'. *Methods:* I outline my career pathway within the public health system and the decision to take a risk to pursue an alternate employment opportunity. I share my thought processes underpinning this decision as well as the experience with industry that has allowed me to see opportunity where once I could only see barriers. *Results:* A shifted mindset as a direct result of new experiences, a change in surroundings and expectations. *Conclusion:* My 'why' is clear. To make a difference.

An Innovative Approach to Meeting the Unmet Information Needs of Rare Disease Families

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Background: Caregivers of a child with developmental and epileptic encephalopathies report poorer health-related quality-of-life than population norms. Unmet information needs in such a rapidly advancing genomic era may be contributing to this. GenE Compass is an information linker service that provides caregivers with personalized reports in response to their questions about their child's condition. *Aim*: We undertook a pilot evaluation of GenE Compass to determine acceptability, feasibility and impact on caregivers. *Methods*: Caregivers completed a baseline survey (Q1), received 3 months of access to GenE Compass, then completed a second survey (Q2). We also collected report-specific feedback. *Results*: From the 76 caregivers who completed Q1, we received 54 questions (from 37 caregivers). Most questions (43%) were regarding research opportunities such as available clinical trials and progress in gene therapy. On average, we returned reports within 27 days (range = 1–48). Of the returned Q2 to date ($n = 13$), most caregivers rated the quality of GenE Compass as 'good'/'excellent' ($n = 12$), and were 'mostly'/'very' satisfied ($n = 12$). All caregivers said they would use GenE Compass in the future and would recommend it to other families. Report-specific feedback ($n = 14$) showed that most parents felt that they understood the information at least 'moderately' well, and felt 'no change' or 'less' distress after reading the report ($n = 13$). Data collection is still underway. Conclusion: Although time-intensive, GenE Compass is acceptable and of high-value to caregivers. Further analysis is needed to determine impact. For sustainability, we will make reports of frequently asked questions freely available via our www.PENNSW.org.au website.

Collaboration, Complexity, and Codesign: Conversations About Awareness, Education, Support, and Training for Rare Disease

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Background: The estimated 2 million Australians living with over 7000 individually rare diseases (RD) face common challenges.

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These include symptom complexity, long diagnostic odysseys, and psychosocial challenges. Inequity in access to quality care is well documented, prompting the 2020 *National Strategic Action Plan for Rare Diseases*. *Aim:* The Rare disease Awareness, Education, Support, and Training (RArEST) program has been funded to codesign, deliver, and evaluate a suite of resources spanning mental health and wellbeing, clinician education, and advocacy. A multistakeholder network has been established to collaboratively identify the needs of those living with RD and those who currently provide care. *Methods:* Qualitative data were iteratively collected from stakeholder consultations including a reference group of 12 individuals representing RD communities, inclusive of priority populations. A survey of over 100 healthcare professionals is identifying current confidence and learning needs relating to RD practice. Data analysis has been informed by theoretical perspectives from codesign, knowledge translation, implementation science, and pedagogy. *Results:* Deep, multistakeholder consultations have been critical in ensuring project planning and evaluation aligns with needs. Data analysis has identified the importance of RD awareness in the general community, peer learning for health practitioners, a critical gap in mental health and wellbeing for those living with RD, and the need for trauma-informed care and partnership with RD advocates. *Conclusion:* Multidisciplinary communities of RD practice and reliable point of care resources are needed to address the training needs of healthcare professionals and RD organisation leaders. Codesign will continue to guide development of these initiatives.

Current Public Knowledge of, Attitude and Motivation Towards Genomic Medicine and Research: A Scoping Review

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Background: As genomics plays a more prominent role in healthcare and medical research, calls for greater public engagement with genomic technologies increase. Rogers' diffusion of innovation theory suggests that acceptance, adoption, and motivation to engage with technologies are reliant on public awareness, information-seeking and attitude formation. *Aim:* To examine current publics' knowledge of, attitude and motivation towards genomics in research and healthcare. *Methods:* A keywords search on Embase, Scopus and Proquest in September 2021, included peer-reviewed journals, theses, and conferences published in English 2016−2021. Populations were assigned to groups based on awareness of, familiarity with and/or involvement in genomics. Concepts included: attitude (genomics' favor or disfavor); motivation (wants/needs directing behavior toward a goal); and knowledge (technical, methodological, institutional, cultural) in a health research or clinical context. Relevant data from 91 articles were extracted and themes developed for attitude and motivation. *Results:* Literature was from 21 countries, including peer-reviewed journal articles (89/91). Eleven were mixed-methods studies; 36 qualitative and 44 quantitative. Fifty-six papers assessed knowledge; 52 attitude and 41 motivation. Thirty-nine papers reported on positive attitudes including: better health, lifestyle planning, altruism and personal gain. Forty-six papers reported on negative attitudes including: adverse psychological impact, fatalism, privacy, misuse, and discrimination/stigma. These themes were also noted as motivators and demotivators. *Conclusion:* Comparisons between papers were confounded by the use of different questions and scales across studies, specific to the context and time. However, the data provides insights into publics' conceptions, perceived benefits and concerns in relation to genomics in healthcare and research.

Efficacy and Safety of Sapropterin Before and During Pregnancy: Final Analysis of the Kamper Maternal and PKU-Moms Subregistries

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Background: Phenylketonuria (PKU), a rare genetic disorder, causes deficiency of phenylalanine (Phe) hydroxylase, leading to elevated blood Phe levels. Infants born to mothers with PKU have high risk of developing congenital defects if blood Phe levels remain uncontrolled (target, 120–360 μmol/L) during pregnancy. Sapropterin dihydrochloride (active synthetic BH_4) is effective in controlling blood Phe levels in individuals with PKU responsive to BH_4 therapy, but little is known about its risk-benefit ratio during pregnancy. *Aim:* This study investigated the use of sapropterin in pregnant women with PKU in the KAMPER and PKU-MOMs registries. *Methods:* Real-world data from two observational, maternal registries – KAMPER (NCT01016392) and PKUDOS (NCT00778206; PKU-MOMs sub-registry) – were assessed regarding safety of sapropterin in pregnant mothers and their infants. Pregnancy and infant outcomes were also assessed in this cohort. *Results:* Data from 57 BH_4-responsive women (79 pregnancies) exposed to sapropterin during pregnancy in KAMPER and PKU-MOMs are reported. Mean (SD) sapropterin dose during pregnancy was 11.5±5.9 (KAMPER) and 18.1±3.8 mg/kg/day (PKU-MOMs), with mean (SD) treatment duration being 247.5±52.1 and 270.2±61.6 days, respectively. Average blood Phe levels during pregnancy were maintained in 16/26 pregnancies in KAMPER and 43/53 pregnancies in PKU-MOMs. Most pregnancies (20/26 KAMPER, 46/53 PKU-MOMs) were carried to term, with the majority of the infants reported as normal at birth. Most adverse and serious adverse events were considered unrelated to sapropterin. *Conclusion:* Sapropterin has a favourable safety profile in pregnant BH_4-responsive mothers, enabling them to maintain blood Phe control during pregnancy, resulting in optimal pregnancy and infant outcomes.

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Personalizing Breast and Ovarian Cancer Risk Assessment in Clinical Genetics: Psychosocial Implications and Implementation of Polygenic Risk Scores

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Background: The risk of developing breast/ovarian cancer for women with a germline pathogenic variant associated with hereditary breast and ovarian cancer (HBOC) is modified by family history, environmental/lifestyle factors, and polygenic risk. The PRiMo Trial, a 5-year randomized control trial assessing the clinical effectiveness of providing personalized risk assessments, incorporates these factors alongside predictive genetic testing. *Aims:* PhD Project 1 (SL): To explore the experiences of women in PRiMo who receive a personalized risk assessment. PhD Project 2 (RP): To develop an evidence-based implementation framework for integrating personalized risk assessments into clinical genetics practice. *Methods:* PhD Project 1: Systematic review examining the psychosocial and behavioral impact of receiving personalized cancer risk information; Semistructured interviews ($n = \sim 30$) with women enrolled in PRiMo exploring their experiences of receiving a personalized risk assessment; Analysis of longitudinal participant-reported survey data regarding risk perception, risk management decision-making, adaptation, and family communication of genetic information. PhD Project 2: Systematic and scoping reviews to examine the use and success of implementation theories/strategies in clinical genetics, and review current practice guidelines/position statements on the implementation of polygenic risk information in healthcare; Interviews and focus groups with genetic healthcare providers and PRiMo participants regarding implementation determinants, priorities and needs; Process mapping and consensus activities to identify and tailor implementation strategies within a context-specific process framework. *Results/Conclusion:* These two PhD studies will be among the first to evidence how individuals experience this novel form of personalized risk assessment and how to implement them effectively in clinical genetics practice.

Implementing Polygenic Scores Into Clinical Healthcare Practice: A Scoping Review of Current Guidelines and Recommendations

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Background: Polygenic scores (PS) capture a proportion of the genomic liability for complex disease, with translational potential in numerous healthcare contexts. Guidelines and position statements on the clinical implementation of PS are being produced apace to keep up with rapidly mounting evidence of PS' clinical utility. To date, these statements have not been analyzed for concurring or discordant recommendations. *Aim:* To establish the scope and nature of professional guidelines and position statements pertaining to the implementation of PS in healthcare. *Methods:* The Arksey and O'Malley framework and the PRISMA-ScR checklist for scoping reviews informed the methodology. Data were collected through two search strategies across six databases and manual screening of 145 websites of professional organisations. Implementation frameworks informed descriptive and deductive content analyses. *Results:* 21 statements were included from 3,553 identified records. The predominant healthcare context represented was cardiovascular disease, with five statements. Cancer, prenatal, diabetes, neurology, obesity and chronic kidney disease were also represented. Most statements originate from Europe and the UK and have been published within the last two years. Statements range in detail but few include explicit strategies or methods for successful implementation. Many statements promote the implementation of PS largely once evidentiary thresholds for clinical utility are reached, and so outline necessary research avenues. Use of PS in reproductive decision-making is consistently not recommended. *Conclusions:* There is some consensus from professional societies on the forecasted value, research gaps and current limitations of PS. Yet, a lack of guidance regarding implementation approaches means the steps of translation to clinical practice remain ill-defined.

Using Record Linkage to Examine Perinatal Outcomes of Fetal Copy Number Variants in Victoria

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Background: Fetal copy number variants (CNVs) are of major clinical importance now that chromosomal microarray is the standard investigation for fetal structural anomalies. However, large studies reporting perinatal outcomes of fetal CNVs are rare. *Aim*: To determine the perinatal outcomes of fetuses diagnosed with a pathogenic CNV (pCNV) or variant of uncertain significance (VUS). *Methods*: Retrospective linkage study of all singleton pregnancies with prenatal diagnostic results from the Victorian Clinical Genetics Services from 2012−18 inclusive. Probabilistic record linkage between the prenatal diagnosis dataset and state-wide perinatal outcome data on all births ≥20 weeks was conducted by the Centre for Victorian Data Linkage. Chi-squared tests for proportions were performed. *Results:* We included 6945 prenatal microarrays; a pCNV was detected in 230 (3.3%) and a VUS in 483 (7.0%). A livebirth outcome was confirmed in 20.0% (95%CI:15.3-25.6%) of fetuses with a pCNV and 64.4% (95% CI [60.0, 68.5) of fetuses with a VUS. A perinatal death occurred in 2.2% (95% CI [1.4, 3.6[) of the total cohort. There was no birth recorded for 77.0% (95% CI [71.1, 81.9]) of pregnancies with a pCNV and 33.7% (95% CI [29.7, 38.1]) with a VUS, implying a spontaneous or induced pregnancy loss <20 weeks. Fetuses with an inherited CNV were more likely to be liveborn than those with a de novo variant (64.0% vs. 31.8%, $p < .01$). *Conclusion:* Data from this linkage study provides the first measure of the perinatal outcomes

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and birth frequency of infants with pCNVs and VUS in Australia. The PrenatAL Microarray (PALM) study is underway to examine the childhood outcomes of this cohort.

The Core Outcome DEvelopment for Carrier Screening (CODECS) Study: Results of an AUS/NZ Pilot Delphi Survey

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Background: The culmination of a core outcome development study is a consensus process in which all collated outcome domains from previous steps (systematic reviews and qualitative interviews) are reviewed and prioritised by key stakeholders. This process determines which outcomes will be defined as core outcomes (i.e., outcomes that should be reported in all future studies). *Aim:* (1) To determine the degree of consensus in an Australian/New Zealand (AUS/NZ) pilot Delphi survey and define a preliminary core outcome set for reproductive genetic carrier screening (2) To use the findings to inform a future international Delphi survey. *Methods:* We designed an iterative, online, 2-round pilot Delphi survey for participants with experience of, or expertise in reproductive genetic carrier screening from AUS/NZ, including patients, clinical geneticists, genetic counselors, researchers, and policy makers. Participants reviewed 83 outcomes from 21 domains in Round 1 and a refined list of 32 outcomes from 16 domains in Round 2. *Results:* A high degree of consensus was achieved and a preliminary core outcome set was developed based on the outcomes that were agreement among participants to be of critical importance. Four domains were included – primary laboratory outcomes, pregnancy outcomes, perceived (personal) utility, and resource use. *Conclusion:* The pilot Delphi survey resulted in a preliminary core outcome set to guide which outcomes should be considered for inclusion in all future reproductive genetic carrier screening studies. Conducting an international consensus process will ensure that the final core outcome set is relevant to contexts outside of AUS/NZ.

Impact of Germline Genetic Testing on Clinical Management of Prostate Cancer Patients

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Introduction: There exists limited data documenting real world recommendations post germline genetic testing (GGT) in prostate cancer (PCa) patients (pts). *Aim:* This study was designed to collect clinician reported outcomes from PCa pts who underwent GGT. *Methods:* Unselected PCa pts from 15 community and academic urology practices were prospectively recruited.84-gene panel test was utilized, with clinical outcomes collected via clinician-completed case report forms > 1-month post GGT. Genetic test results of a single pathogenic genetic variant (PGV) in a gene associated with autosomal recessive inheritance of cancer risk (e.g., *MUTYH*) were considered positive and included in all analyses. Statistical significance was determined by two-tailed Fisher's exact test. *Results:* 982 predominantly white (75.9%), nonmetastatic (80.7%) males with PCa were recruited; Average age was 65.3 years at PCa diagnosis. PGVs, most commonly CHEK2 (17) and BRCA2 (10), were identified in 100(10.2%) pts; 50(50%) of these did not meet NCCN GGT criteria. Among PGV positive pts, 243 recommendations were made. They were more likely to have changes to treatment (p <.0001), follow-up (p < .0001) and cascade testing recommendations (p <.0001) than those with negative/variant of uncertain significance (VUS) results. 13 pts either received a targeted therapy or were referred to a clinical trial. Among these, 3 (23%) did not meet NCCN GGT criteria. Referral to a genetic counselor was the most common follow-up recommendation for those with PGV (38 patients, 38%) and VUS results (66, 13.7%). Knowledge/reassurance was the commonest outcome for pts with negative results (38, 7.9%). *Conclusions:* GGT did influence PCa patient management. Appropriately, pts with PGVs received a greater number of recommendations for relatives, changes to follow up and treatment.

Identification of Actionable Genetic Variants Warrants for Universal Comprehensive Germline Testing in Uterine Cancer Patients

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Introduction: The prevalence of pathogenic germline variants (PGVs) in Uterine Cancers (UC) patients remains unclear, as a wide range of prevalences (4.5%–23%) have been reported in cohorts with limited sample sizes, varying eligibility for testing (including specificity of UC type), and differing numbers of cancer predisposition genes tested. Hereditary UC is traditionally associated with PGVs in Lynch syndrome genes or *PTEN*; however, growing evidence supports a significant role for other cancer predisposition genes that may reveal new clinical management options. *Aim:* The aim of this study was to assess the prevalence and potential clinical impact of PGVs identified in UC patients referred for comprehensive germline genetic testing. Methods: Prevalences of PGVs in patients referred for genetic testing with an indication of uterine or endometrial cancer were assessed and compared by syndrome type, patient age at testing, and self-reported ancestry. Potential clinical actionability of PGVs was based on established guidelines for clinical management, targeted therapies, and clinical trial eligibility. *Results:* PGVs were detected in 13.6% of the cohort (880/6,490). PGVs were most frequently observed in Lynch syndrome genes (60.4%) and *PTEN* (1.5%), with 38.1% in another cancer predisposition gene (i.e., *CHEK2, BRCA1/BRCA2)*. Nearly all PGVs (97.2%) were associated with guideline-recommended management, including family cascade testing; 60.5% were associated with U.S. Food and Drug Administration (FDA)-approved therapies; and 35.2% were associated with clinical treatment trials. *Conclusions:* Limiting germline testing to Lynch syndrome genes and *PTEN* could miss more than one-third of UC patients with PGVs (38.1%), many of whom have actionable results. Universal comprehensive genetic testing of UC

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patients could benefit many patients and at-risk family members medically.

Molecular Monitoring Following Thymic Transplant

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We report a patient who received a thymus transplant as treatment for severe combined immunodeficiency due to DiGeorge syndrome. This patient is one of very few Australians to undergo this procedure. The role of the thymus is in the development of mature naïve T cells from immature precursors produced by the bone marrow and is key in the adaptive immune response. Monitoring of T cells in the peripheral blood of the recipient is used to gauge the success of thymic transplantation. Multiplex STR assays are in frequent use as part of studies to identify maternal cell contamination, bone marrow engraftment success, and kinship, as well as sample identification. They may also be used to monitor T cell origin after transplantation. A successful thymic transplant will show only recipient genotype, as the donor thymus processes recipient immature T cells. A small population of donor T cells may be present due to incomplete depletion of donor lymphocytes from the donor tissue. An increase of donor T cells in the patient's peripheral blood may indicate a risk of autoimmune complications, graft versus host disease or acute rejection. Our patient was transplanted with sex-matched cultured donor thymus tissue. STR marker analysis showed 12 informative markers on the Promega PowerPlex 16 HS System. A peripheral blood sample, collected four months after transplant, was sorted into 2 populations: T cells and myeloid cells. The resulting STR marker analysis showed recipient genotype in the T cell fraction and therefore successful transplant with no evidence of donor engraftment.

Insight Into Diagnostic Yield Using Microarrays for Hematological Samples

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Background: As a high throughput laboratory offering cytogenetic testing for hematological samples across Queensland public hospitals, highly comprehensive testing is required. Current gold standard techniques in the malignancy setting are G-banded karyotype and FISH, however, several limitations are associated with these and therefore, a limited diagnostic yield. *Aim:* Literature suggests that incorporating chromosomal microarray analysis (CMA) for testing of hematological malignancies is expected to increase diagnostic yield. Therefore, we aimed to determine the CMA's ability to detect clinically relevant biomarkers in hematological malignancy samples. *Methods:* Our validation aimed to cover as many of the ACMG, ELN, R-IPSS, DIPSS, GIPSS and WHO described abnormalities (biomarkers) across six different disease types. The inhouse cytoSNP12 chip was used and the variant curation and reporting were done as per ACMG/CGC guidelines. Assay sensitivity, specificity, as well as limit of detection and the ability to detect amplifications were also assessed as part of the validation. *Results:* 63 samples (8 normal and 55 abnormal) were included in the validation. The 55 true positives were previously detected by other orthogonal assays. Based on our findings, the sensitivity for CMA performed in-house for hematological malignancies is established as ~99% for CNAs present in >20-30% of cells, with 100% repeatability. *Conclusion:* This validation managed to depict the strengths and limitations of CMA in the hematological malignancy setting. Upon completion of this validation study our laboratory has acquired NATA accreditation and CMA for hematological malignancies has been incorporated as part of routine testing.

New Conversations: A Consumer-Driven Pathway to Negotiate Genetic Testing Options for Breast and Ovarian Cancer

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Consumer-driven health care in genomics is inevitable in an age of unprecedented access to information and the advent of a variety of testing options. This and the availability of strong patient advocacy voices has meant that genetics health care providers must adapt and meet the changing needs of individuals and families. Pink Hope is a preventative health hub with the goal to give the community tools to assess, manage and reduce their risk of breast and ovarian cancer, while also providing personalized support for at-risk women. One consistent theme for those contacting Pink Hope is the difficulty readily navigating the genetic testing pathway and accessing genetic testing from a reliable service. NSW Government data estimates some genetic services having waiting periods of up to 12 months, which can lead to potential delays in diagnosis and preventative treatments. Using a consumer-focused process to empower the community, Invitae and Pink Hope developed a genetic testing pathway. The pathway is a way to fill this gap and define the way in which individuals concerned about hereditary cancer can access the most relevant information for their circumstances. This paper reports on the development of this pathway, its launch, evaluation and impact. Lessons learnt will guide future partnerships with advocacy organisations to support the provision of reliable genomic information for the community.

Rare Autosomal Trisomy of Imprinted Chromosomes Detected by Noninvasive Prenatal Testing and the Risk of Uniparental Disomy

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Background: Genome-wide noninvasive prenatal testing (gw-NIPT) can detect rare autosomal aneuploidies. Ongoing pregnancies with a rare trisomy result involving an imprinted chromosome are at risk of a uniparental disomy (UPD) syndrome following trisomy rescue. *Aim:* To review cytogenetic outcomes of pregnancies with an increased chance rare trisomy result involving imprinted chromosomes 6,7,11,14,15 and 20 screened via gw-NIPT at Victorian Clinical Genetics Services (VCGS). *Methods:* A laboratory audit was performed to identify eligible pregnancies screened at VCGS from April 2015-May 2022. Cytogenetic test results and pregnancy outcomes were obtained from VCGS laboratories and referring practitioners. *Results:* 242 pregnancies with an increased chance for a rare trisomy of an imprinted chromosome were identified (two trisomy 6 (T6), 59 T7, seven T11, 27 T14, 113 T15 and 34 T20). Outcome data

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was available for 78 pregnancies that underwent amniocentesis with UPD studies. Five were diagnosed with a UPD syndrome; one case each of matUPD7 (Russell-Silver syndrome), matUPD14 (Temple syndrome) and matUPD20, and two cases of matUPD15 (Prader-Willi syndrome). The risk of a UPD syndrome in ongoing pregnancies that underwent amniocentesis/UPD studies was 3.3% for T7, 20% for T14, 11.1% for T15 and 4.5% for T20. Over the audit time-period our laboratory was notified of four pregnancies with a low-risk NIPT result that were subsequently diagnosed with a UPD syndrome (three matUPD15, one matUPD14). *Conclusion:* gw-NIPT can detect some pregnancies at risk of a UPD syndrome. Where prenatal diagnosis is elected for pregnancies with an increased chance rare trisomy result involving an imprinted chromosome, UPD studies should be performed.

Jeffrey's Insights: Jeffrey Modell Foundation's Global Genetic Sequencing Program for Primary Immunodeficiency

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Background: Genetic disorders that impair the immune system, known as Primary Immunodeficiencies (PI), include over 450 inborn errors of immunity. Patients with PI are susceptible to frequent, severe, and sometimes life-threatening infections or autoimmunity. Suspected PI patients without a genetic diagnosis often endure a prolonged diagnostic odyssey. This diagnostic delay prohibits proper disease management and treatment. Next-generation sequencing (NGS) can shorten the diagnostic odyssey when implemented early, but because of cost and barriers to access, it is regularly unobtainable. *Aim:* To overcome these obstacles, the Jeffrey Modell Foundation (JMF), with Invitae, introduced 'Jeffrey's Insights', a no-charge genetic sequencing program, for patients within the Jeffrey Modell Centers Network (JMCN) with an underlying PI, but no genetic diagnosis, which expanded globally to more than 400 Centers in the JMCN in early 2020. *Methods:* Invitae's largest PI NGS Panel that simultaneously identifies sequence changes and exonic copy number variants was used for this program. Participating clinicians completed a questionnaire assessing prior barriers to access and post-sequencing alterations in disease management and treatment. *Results:* A total of 1,398 patients were tested from 45 countries, with an overall 20.3% molecular diagnostic yield, which varied depending on sub-geography (from 35.8% in Asia to 11% in the U.S./Canada). Results obtained from NGS led to an alteration of clinical diagnosis, disease management, treatment, and genetic counseling in 39%, 38%, 35%, and 53% of patients, respectively. *Conclusion:* The global expansion of this program highlights the impact of NGS for PI, including disease management, when ordered by an expert immunologist.

Periodic Automated Reanalysis and Reevaluation of Exome Data to Improve Its Clinical Utility

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Background: Although gene-disease associations and phenotypes are clarified over time and an individual's phenotype may evolve, reanalysis and reevaluation efforts for unsolved exome sequencing (ES) tests remain largely manual, limiting the utility of a ES test to the information available at the time of testing. *Aim:* We present an automated reanalysis pipeline that integrates up-to-date gene-phenotype associations and the evolving clinical phenotype of a patient. *Methods:* Probands undergoing exome testing between 18 December 2020 and 02 February 2022 are included. All exome testing provided by Invitae since December 2020 undergoes regular reanalysis and reevaluation every 6 months for 3 years unless opted out. Sequencing information, demographic information, updated clinical information (when available), and up-to-date internal data was provided to Invitae's Moon software 6 months after the initial report was provided and, for a subset of cases, again after 12 months. Moon-ranked variants were interpreted and assessed for clinical overlap and new findings were reported. *Results:* New reportable information was identified in 4% of over 1000 cases: positive or potentially positive (~0.5%); uncertain with clinical overlap and inheritance pattern match (~3.3%); other findings such as medically actionable incidental findings (~0.2%). Moon reduced initial exome analysis time by about 50% and reanalysis and reevaluation further to about 17%. *Conclusion:* Reevaluation and reanalysis of all clinical ES tests over 13 months resulted in 1 in 25 cases with new reports issued, indicating that this procedure for partial automation helps provide the best possible diagnostic utility of our ES tests.

Missense Variants in Mowat-Wilson Syndrome Cluster Around Exon 10

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Background: Mowat-Wilson syndrome (MWS) is an autosomal dominant disorder caused by pathogenic variants in *ZEB2*. Typical patients have distinctive facial features and severe intellectual disability, with variable associated features including epilepsy and congenital anomalies. For MWS patients in whom a molecular basis is identified, over 95% have deletions or truncating loss-of-function variants; very few have missense variants. *Aim:* In this study, we aimed to review the clinical and molecular results of patients with missense variants in *ZEB2*. *Methods:* Patients were ascertained by searching all published literature and the DECIPHER and ClinVar databases. Clinical data was compiled for patients where available, and all molecular variants were re-classified using the ACMG criteria. *Results:* We identified five pathogenic (P) variants, 18 likely pathogenic (LP) variants and 11 variants of uncertain significance (VUSs) from 34 variants reported as disease-causing. All 225 variants classified as VUSs in ClinVar were also reviewed, of which four were upgraded to LP, and six downgraded to likely benign. Of the 27 variants we classified LP or P by ACMG criteria, 63% occurred in the early part of exon 10 (a 50 amino acid region with striking lack of variation in population databases). *Conclusion:* The majority of VUSs reviewed could have been reclassified if missing phenotypic information and segregation data were available. From available data, we identified a predilection for missense variants in *ZEB2* causing MWS to occur in the early part of exon 10, but further studies of a potential genotype-phenotype correlation and underlying mechanisms are required.

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Involve Australia: Involving Community Members in Genomics Research

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Background: Involve Australia is a community-led project coordinated by Australian Genomics that aims to give the community a stronger voice in genomic research and its translation into clinical practice. There are several existing guidelines that promote community involvement in healthcare research, however none are specific to genomic researchers and very few report on all aspects of co-designing research with community. This project partners with patient support and advocacy groups, Indigenous community members, patients and carers, interested members of the public, genomic researchers and clinicians to keep community member voices at the forefront. *Aim:* To create a set of guidelines developed using co-design principles, which provides genomic researchers with useful tools to involve community members in their projects. *Methods:* We are interviewing community involvement program coordinators, researchers involving community members in projects, and institute leads from existing community involvement programs. Six semi-structured interviews have been conducted with 15 planned in total. Interviews will also be conducted with community members involved in these programs or projects. *Results:* Two clinician researchers, two community involvement program coordinators and two institute leads have been interviewed. Five of the six interviewees are female. Themes identified in our preliminary analysis include (a) the benefits of community involvement, (b) the importance of community involvement in research, (c) drivers of community involvement, and (d) barriers and enablers of community involvement. *Conclusion:* We hope that by learning from this group of informants we can develop a set of community involvement guidelines that will benefit and promote more meaningful genomics research.

Evolution of Prepair™ Reproductive Genetic Carrier Screening at VCGS

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Background: In 2012, Victorian Clinical Genetics Services (VCGS) began offering 'Reproductive Genetic Carrier Screen' (RGCS), now known as *prepair*™. VCGS was the first service in Australia to introduce this multi-disorder carrier screen for the three most common inherited conditions: cystic fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS). *Aim:* Report on our experience and evolution of *prepair*™ screening over the past 10 years. *Methods:* The fee-for-service *prepair*™ carrier screen is offered to individuals in pre or early pregnancy. In 2019, more comprehensive testing for CF (38 to 175 *CFTR* variant panel) was introduced and in 2021 AGG interruption analysis was added for carriers of small *FMR1* premutations (55-69 CGG repeats). An audit of service participation was performed in 2020. *Results:* Over 44,000 individuals at general population risk have been screened. One in 21 carried at least one condition (carrier frequencies – CF: 1 in 37, SMA: 1 in 55, FXS: 1 in 287). The 175 *CFTR* variant panel and *FMR1* AGG interruption analysis improved the clinical utility of this screening by identifying 46 additional CF carriers and reducing the proportion of *FMR1* increased risk results by 70%. Most screening was requested by obstetricians in metropolitan areas and 75% of those screened were in the top two socio-economic quintiles. *Conclusion:* Our experience demonstrates how service improvements have increased the clinical utility of *prepair*™ screening. A key consideration is inequity of access. The introduction of a Medicare item number (November 2023) should be instrumental in improving accessibility to screening.

Siblings With BH4 Responsive Phenylketonuria, Diagnosed on Newborn Screening: A Direct Comparison of BH4 Start Times

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Background: Diagnosis of phenylketonuria (PKU, OMIM 612349) has a direct impact on normal breastfeeding patterns. The Australian guideline for management of BH4 responsive PKU, suggests commencing BH4 over 6 months of age when phenylalanine (Phe) level is consecutively >360umol/L. Treatment under 6 months follows standard management, not inclusive of BH4. We present, *Sibling 1* managed according to the Australian PKU guidelines with BH4 (20mg/kg) commenced at 8 months and *Sibling 2* commenced BH4 (20mg/kg) at 2 weeks of age. *Aim:* Earlier initiation of BH4 can minimise disruption to breastfeeding, maximise natural protein and decrease intake of Phe-free formula. *Results:* Total protein requirements for PKU patients <12months is 2-3g/kg/day. At 1 month of age the percentage of daily protein from Phe-free formula was 45% for sibling 1 and 28% for sibling 2. Similarly, at 2 months of age the results were 42% for sibling 1 and 25% for sibling 2. At 4 months of age, sibling 1 received 35% of daily protein requirement from Phe-free formula and 22% for sibling 2. Between 0-6 months of age, the siblings had an average Phe of 328µmol/L and 283µmol/L respectively and had no compromise in growth, which was consistent along similar centiles. During this time, sibling 2 did not require an increased dose of BH4 in-line with weight gain to maintain Phe levels within range. *Conclusion:* Following the diagnosis of BH4 responsive PKU, an earlier initiation of BH4 can reduce disruption to normal breastfeeding patterns and maximise natural protein intake from breastmilk.

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Demonstrating the Value of Genome Sequencing in a Pediatric Neurology Cohort: A Successful Partnership Between a Patient Organization and Industry.

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Background: Evidence demonstrating utility of whole-genome sequencing (WGS) in rare disease continues to grow. In 2020, the Child Neurology Foundation (CNF) adopted an initiative focused on shortening the diagnostic odyssey. To aide in this initiative, industry partner Illumina, Inc., sponsored a WGS project for a small cohort of probands with suspected rare disease. *Methods*: An expert panel of neurologists selected by CNF developed inclusion criteria for case submission. WGS was completed by one of two CAP/CLIA approved laboratories. Clinical reports were sent directly to the ordering provider. IRB exemption was obtained retrospectively. *Results*: A total of 104 applications were received from 39 sites. The panel selected 25 cases from five geographically diverse sites in the U.S. with an average age of 9.04 years. All probands had multiple phenotypes, the most common being: seizures (18/25), global delay (17/25), hypotonia (13/25), and cognitive impairment (12/25). Prior genetic testing was reported in 23/25 (92%) probands, including 20 probands with prior whole-exome sequencing. The overall diagnostic yield for WGS was 24% (6/25). Information on medical management changes was available for a limited number of cases and included cessation of unnecessary imaging, introduction to support groups, and altered health screening. Clinician interviews conducted by CNF revealed positive feedback on the experience and perceived value of WGS. *Conclusions*: This experience demonstrates a unique way that industry and patient organizations can collaborate to engage patients and providers. Continued follow up on the impact of results on medical management is necessary to further highlight the value of WGS.

'Sometimes it worked extremely well, other times it was an absolute disaster.' Telehealth in Complex Genomics: The Clinicians' Perspective

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Background: The Covid-19 pandemic led to an immense shift from face-to-face provision of medical consultations, to provision of care predominantly via Telehealth where possible. Genomic medicine was not exempt from this adjustment. Genetic counselors and clinical geneticists experienced a major and rapid change to their work; genetics services shifted to mainly providing consultations via Telehealth, including multidisciplinary consults with more than one clinical craft group. *Aim:* We aimed to critically explore healthcare practitioners' experiences of using Telehealth in the context of complex genomics. *Methods:* We conducted semi-structured, qualitative interviews with 6 healthcare practitioners working during the first two years of the Covid-19 pandemic at a major clinical genetics service in Victoria, Australia. Data were thematically analyzed. *Results:* We developed four overarching themes: (1) barriers to positive outcomes of Telehealth interactions, (2) facilitators to positive outcomes of Telehealth interactions, and (3) healthcare practitioner's interest in continuing Telehealth into the future, and (4) how this can be optimized. Participants described feeling well supported by their colleagues and workplace to transition to Telehealth, however, technical difficulties, complexity of a case, translator requirements, or difficulties engaging the patient sometimes impeded a productive session. *Conclusion:* Our findings suggest that genetic healthcare practitioners are accepting of Telehealth for provision of consultations. Some patients are seen as not suitable for a Telehealth consultation; for example, those requiring physical examination, while others are seen as better candidates, such as some longstanding patients. A system of assessing case suitability for use of Telehealth may be of benefit going forward.

'The challenges are kind of inconveniences, but the benefits are potentially life-saving.' Patients' and Family Members' Experiences With Cascade Screening for Lynch Syndrome

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Background: Cascade screening for Lynch syndrome is critical for the identification of at-risk relatives who would benefit from early screening and risk-reduction strategies, as well as alleviate those without the familial variant. Uptake of cascade screening has consistently remained suboptimal, therefore it is important to consider methods of improving this uptake. Understanding proband and family members' experiences with cascade screening can inform appropriate strategies and interventions. *Aim:* We aimed to critically explore patients' and relatives' lived experience of cascade screening for Lynch syndrome. *Methods:* We used data from qualitative interviews with 20 patients with Lynch syndrome or their family members based in the United States of America. We analyzed data using reflexive thematic analysis. *Results:* We developed three overarching themes: (1) the variability of logistics of communication with family during cascade screening; (2) the variety of emotions and attitudes surrounding cascade screening; and (3) positive and negative reflections on cascade screening, including suggestions for improvements that could be made to the process. Genetic counseling was an important component of the cascade screening process, however, participants often described feeling under-supported. *Conclusion:* Our findings suggest that additional resourcing and alternative models of provision of genetic services are important considerations to optimize uptake of cascade screening. Furthermore, the needs of people at different stages varies across the cascade screening timeline. Intervention development should acknowledge these evolving needs to ensure a nuanced, time-sensitive approach to improve uptake of screening.

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Comprehensive Characterization of Skeletal Muscle Disease Gene Exon Usage Across Different Developmental Ages

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Alternative splicing is a normal post-transcriptional regulation process that facilitates the generation of multiple different protein isoforms from the one gene. There is an increasing body of evidence to suggest that disease-causing variants within exons that are 'used' (included within) all isoform RNA transcripts (100 percent spliced in exons) have a greater clinical impact than variants within exons that are not used by all transcripts. Our overall understanding of normal skeletal and cardiac muscle exon usage patterns is currently limited. This is adversely impacting our ability to understand how exon usage impacts clinical variability in the setting of cardiac and skeletal muscle diseases. Recent advances in bioinformatic technologies, and the increasing availability of high-quality healthy control and patient tissue-derived RNA sequencing (RNA-seq) datasets have, for the first time, made comprehensive exploration of this emerging research area now possible. In this study, we characterized the normal exon usage patterns of over 250 skeletal muscle disease genes in over 1400 skeletal and cardiac muscle transcriptomes across different developmental ages (fetal to adult). For some genes, exon usage patterns within specific regions of the transcript varied greatly across different tissues and/or developmental ages. Correlation of the usage of exons that harbour known disease-causing variants within these genes and clinical severity is now underway. Our study significantly expands our understanding of healthy straited muscle isoform biology. The outcomes of this study will greatly inform our understanding of the relationship between exon usage and clinical variability.

Verification of GSAV3 Assay to Detect Genomewide Changes in Solid Tumors

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Background: Single nucleotide polymorphism (SNP) arrays offer a genome-wide view of copy number alterations, and are increasingly used in oncology. In this study, we show the feasibility and limitations of a genome-wide assessment of copy number alterations and loss of heterozygosity (LOH) using formalin-fixed paraffin-embedded (FFPE) DNA from solid tumors on the GSAv3 platform. *Aim:* To verify the use of the GSAv3 assay to detect genome-wide changes in DNA extracted from tumor paraffin sections, in particular the amplification of the MDM2 locus. *Methods:* 10 tumor samples with different status for MDM2 amplification were selected. DNA was extracted and quantified. DNA quality was assessed by qPCR. SNP array was then performed using the GSAv3 platform and results were analyzed using NxClinical version 6.0. We compared the results obtained by FISH for the amplification of the MDM2 locus with the results obtained by the GSAv3 assay. *Results:* The results showed that genome-wide copy number variants and AOH can be detected by the GSAv3 platform, using DNA extracted from FFPE solid tumors. In particular, MDM2 amplification was accurately called in all samples, including those polysomic for chromosome 12. Microarray was also able to identify additional abnormalities that may be relevant for diagnosis and/or prognosis. imitations: some samples may not be suitable for microarray given DNA input requirements. *Conclusion:* This study showed that the GSAv3 platform is fit for clinical use on DNA extracted from FFPE solid tumors. This study was submitted to NATA and received accreditation.

A Scoping Review of the Psychosocial Issues That Occur for Individuals With Mixed Ethnocultural Heritages

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Background: Multicultural societies are becoming more common due to globalisation and migration. Dissolutions of social and cultural barriers has contributed to an increase of intercultural couples and families with mixed ethnocultural heritages. This impacts family structures, behaviors, and practices, including healthcare. All aspects of genetic counseling are influenced by an individual's ethnocultural heritage. Thus, genetic counseling must adapt to the changing demographics to provide culturally safe genetic counseling to clients of mixed ethnocultural heritages. *Aim:* This scoping review aimed to map what is known about the psychosocial issues that occur in genetic counseling for individuals with mixed ethnocultural heritages. *Methods:* We systematically searched five databases using the Joanna Briggs Institution scoping review method. We mapped areas of research to the Framework for Outcomes of Clinical Communication Services (FOCUS) and conducted a narrative synthesis. *Results:* Twelve studies were included. Of these discussed the psychosocial issues that occur for individuals with mixed ethnocultural heritages in genetic counseling. We identified psychosocial issues in the FOCUS domains of Communication, Patient experience, and Patient changes. The language and cultural barriers causing these issues may present more subtly for individuals of mixed ethnocultural heritages than those from specified cultural groups. No studies discussed the domains of Patient health or Family changes. Findings suggest an awareness of cultural nuances and cultural congruence helps facilitate the process of genetic counseling. *Conclusion:* Further conceptualization of 'mixed ethnocultural heritages' and research is required to understand the psychosocial issues that occur in genetic counseling for this cohort.

Is the New Better Than the Old? Comparison of CF Screening Follow Up Protocols

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Background: Cystic Fibrosis (CF) is one of the most common inherited disorders with a prevalence of 1:3200 live births in NSW and ACT. The NSW Newborn Screening (NBS) Programme aims to detect classical CF (inherited two mutated CFTR gene) only. Prior to May 2018, NBS screened for 3 common variants (detects >94%). The follow up protocol for a screen positive result for a baby who was a CF carrier was to refer the baby for a sweat chloride test to confirm diagnosis. Subsequently, a second tier Next Generation Sequencing assay was implemented using a targeted panel of 139 variants. The current follow up protocol is that all babies with 1 or 2 variant/s identified is to request a repeat NBS sample. If the IRT value remains elevated, those with 2 variants identified are referred to CF clinic while those with one variant are referred for sweat test. *Aim:* To compare the effectiveness of the current protocol to the previous

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protocol in terms of minimizing diagnostic investigations. *Method:* We performed a retrospective data evaluation of all CF referrals for babies born between May 2014 and April 2022. We compared the number of sweat tests performed, turnaround time (TAT), false positive and false negative. *Results:* The number of referrals for sweat tests has dropped significantly (from 373 to 56 tests) while the TAT for final diagnosis remained constant. *Conclusion:* The current protocol has resulted in fewer referrals for sweat tests, hence minimizing unnecessary anxiety for parents and stress on babies.

Views and Experiences of Australian Stakeholders Regarding the Use of Genetic Test Results in Life Insurance? The Australian Genetics and Life Insurance Moratorium: Monitoring the Effectiveness and Response (A-GLIMMER) Study

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Background: Genetic discrimination is an issue of international concern, and in Australia, the use of genetic test results in life-insurance underwriting is legal. In 2019, the Australian life-insurance industry implemented a self-regulated moratorium that applies only to policies up to certain financial limits until 2024. The Commonwealth government-funded study – Australian Genetics and Life Insurance Moratorium: Monitoring the Effectiveness and Response (A-GLIMMER) – is assessing the moratorium from the perspectives of various stakeholders. *Methods:* Our mixed-methods study targets four stakeholder groups: consumers/patients, health professionals, researchers and the financial services industry. We are using a combination of surveys, qualitative interviews, and document analysis to gather views and experiences regarding the use of genetic test results in life-insurance underwriting and its regulation. *Results:* In each of the four arms of the study, results are demonstrating a trend across stakeholder groups, indicating that while the moratorium is a positive step forwards, concerns about the moratorium remain. Main concerns are self-regulation by the insurance industry and lack of regulation, inadequate financial protection, poor understanding about the moratorium, and the uncertainty created by its temporary nature. Stakeholders overwhelmingly believe government oversight is required – very few patients (3%; $n = 9/326$), members of the public (6%; $n = 58/1002$), researchers (4%; $n = 2/52$) or health professionals (7%; $n = 10/139$) disagreed that the Australian government should introduce legislation to regulate genetic discrimination in life insurance. *Conclusion:* The findings of the A-GLIIMMER project so far indicate that across stakeholder groups in Australia, substantial concerns regarding the use of genetic test results in life-insurance remain.

Development and Evaluation of an Online Decision Aid to Support Individuals Eligible for Predictive Testing of Hypertrophic Cardiomyopathy

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Background: The decision to undergo predictive testing for hypertrophic cardiomyopathy (HCM) can be challenging for at-risk relatives, even with guidance from genetic counselors. Patient decision aids (PDAs) can support patients' decision-making. To our knowledge, no online PDAs have been published for HCM predictive testing. *Aims:* To develop an online PDA for HCM predictive testing and to explore the perspectives of genetic counselors and patients on the PDA's clarity and usability. *Methods:* The PDA was developed alongside an animation team, through an iterative process using the International Patient Decision Aid Standards framework. A prototype was presented to genetic counselor focus groups, with feedback incorporated. The amended PDA was presented to patient focus groups for feedback. Genetic counselors' transcripts were analyzed using inductive content analysis. Analysis of patients' transcripts is underway. *Results:* 10 genetic counselors and 8 patients attended the focus groups. Genetic counselor participants viewed the PDA as useful, indicating they would likely use it within clinics. They provided feedback on clarification of genetic concepts and maintaining neutrality in options for genetic testing. Preliminary analysis suggests patients viewed the PDA positively. Feedback included tailoring the PDA to parents deciding whether to test their young children and that the PDA would assist in family communication. The PDA will be further modified to incorporate patient feedback before implementing into clinical care. *Conclusion:* Through an iterative process, with genetic counselor and patient focus groups, we have developed an online PDA to support individuals considering HCM predictive testing.

Massimo's Mission: Closing the Gap From Diagnosis to Treatment for Leukodystrophies

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Background: Genetic disorders of the white matter, which includes the leukodystrophies, are often associated with early onset, severe

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symptoms, and lack of treatment options. Massimo's Mission aims to provide genetic diagnoses for Australian patients with white matter disorders and pilot the rapid development of cell and animal models for pre-clinical testing of candidate targeted therapies. *Methods:* Patients are recruited through clinical services, patient groups and online advertisements. Registry data is collected and managed using REDCap. Undiagnosed patients are provided clinical trio whole genome sequencing with a rapid turnaround if indicated. Patients that remain undiagnosed are triaged into our research program for further genomic analysis. Human induced pluripotent stem cell (hIPSC) and rodent models of leukodystrophies are being established and comprehensively characterized. These models comprise hIPSCs and transgenic mice carrying disease-causing mutations as well as conditional knockout mice. *Results:* Clinical, imaging and genomic data has been collected for patients recruited to the White Matter Disorders Registry ($N = 276$). Clinical whole genome sequencing has resulted in a diagnosis in 42% of cases. Analysis of unsolved cases is underway ($N = 45$). The clinical program and registry have played a key role in securing the Royal Children's Hospital as a trial site to deliver an industry funded antisense oligonucleotide therapy for patients with Alexander Disease. The stem cell and mouse disease models have significantly advanced the understanding of the pathophysiology underlying leukodystrophies and have enabled therapeutic proof-of-concept studies. *Conclusion:* This program is vital to facilitate timely genetic diagnosis and novel treatments for Australian leukodystrophies patients.

'How Many of Us Read the Terms and Conditions?' Public Perspectives on Consent for Genomic Data Storage and Sharing

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Background: Storage and sharing of genomic data following diagnostic sequencing is critical to the future of genomic medicine. Data sharing increases the chance of finding a diagnosis for both current and future patients and can benefit clinical and pharmaceutical research. Yet, few studies have explored public perspectives on how and where data should be stored, with whom it should be shared, and how to obtain meaningful consent to do so. *Aim:* To explore the Australian public's perspectives on genomic data storage and sharing. *Methods:* We conducted seven online focus groups with 39 members of the Australian public (mean age = 37 years; range 18-67). Focus groups transcripts were analyzed using inductive content analysis. *Results:* Participants were generally in favour of storing genomic data and were reasonably comfortable with data reuse to benefit the wider community, provided adequate consent had been obtained. Informed and explicit consent was key; many participants favoured a dynamic consent model to enhance autonomy and increase control over data uses. While specific consent was often favoured, participants recognised that being asked for consent for each individual data use could present a significant burden to individuals and a barrier to research. Consequently, many participants suggested consent should only be resought for new data uses, or when legislation or policies changed. *Conclusion:* Our findings reveal complexities associated with developing a one-size-fits-all approach to consent for data sharing and storage through the eyes of the Australian public. These results can be used to help guide policy development on these issues.

How to Select a Key Finding for a Syndrome Searching: A Systemic Approach

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Background: Out of 25,466 registries, 9176 entries in Online Mendelian Inheritance in Man (OMIM) have well-defined phenotypic details. Most of these syndromes have overlapping phenotypes, and reaching the precise syndromic diagnosis is challenging without a characteristic anomaly or key anomaly, which is likely an initiator for those anomalies. There is a paucity in the literature for a systematic way of identifying the characteristic anomaly or Key finding for a particular syndrome. *Aim:* Developing the checklist for systemic analysis of the clinical and lab data to find the most promising key finding/s for syndromic search. *Methods:* After analysis of the reported cases data from reference books of medical genetics and online database of inherited syndromes, predominant clinical and laboratory data are categorized, and the most practical and auguring features are mentioned systematically. *Results*: Overall, eight characteristics of a clinical or lab Key findings are based on the rationale or concept for syndromic searching. Each has a strong clinical or laboratory theme, and finally, the author summarizes features of that Key finding in each category. *Conclusion:* A structured checklist would help select the most characteristic clinical finding (Key anomaly) from all patient data for syndromic searching. It will help to confine the different diagnoses and will also save time.

Type 1 Diabetes National Screening Pilot: Feasibility and Acceptability Study

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Type 1 diabetes (T1D) is an incurable autoimmune condition for which three children in Australia are diagnosed every day. Children are often diagnosed too late, with 1 in 3 presenting with life-threatening diabetic ketoacidosis (DKA) and requiring hospitalisation in intensive care. Up to 90% of those who develop T1D have no family history of the condition. However, at-risk individuals typically harbour a genetic predisposition to autoimmunity with the strongest genetic determinant of risk being the HLA genotype. Evaluation of polygenic risk can determine those at an increased chance of T1D, allowing for early diagnosis, initiation of treatment, reduced trauma at diagnosis and improved long-term health. We aim to assess whether screening for T1D in the general population is feasible and acceptable, without causing significant parental distress. Children will either be recruited as: (1) new-borns for risk-stratified screening (polygenic risk score) with islet autoantibody follow-up screening in at-risk children at age 1 year ($n = 3000$); (2) infants aged 6−12 months for risk-stratified screening (polygenic risk score), with islet autoantibody follow-up screening in at-risk children at age 1 year ($n = 3000$); or 3) children aged 2, 6 and 10 years for islet autoantibody screening ($n = ,000$). Children with two or

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more islet autoantibodies will be identified as having early stage T1D. Parental anxiety will be monitored throughout, and support from a clinical diabetes educator and a genetic counselor is available. Our overarching vision is that all children will be routinely screened for T1D as part of a National Screening Program in Australia.

Metastatic Castrate Resistant Prostate Cancer – Genetic Counseling and Testing Issues

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Background: In April 2022, Medicare introduced new item numbers for genetic testing in men with metastatic castrate resistant prostate cancer (mCRPC) to determine eligibility for olaparib under the PBS. This change resulted in increasing numbers of men being referred for genetic testing. There are unique social and ethical issues that need to be considered in these men, who, until recently have been underrepresented in genetics clinics. *Aim:* This study aimed to determine the genetic counseling issues encountered by medical oncologists, when considering somatic and/or germline testing for this group of patients, and what support genetic counselors could provide. *Methods:* This pilot study, was conducted during July 2022. Clinicians were interviewed by a genetic counselor and asked to identify the issues they encountered when arranging genetic testing for mCRPC. The doctors also reported on the level of disease education and resources they provided to these patients. *Results:* The issues reported included: access to suitable tumor tissue for testing; decision to arrange another biopsy if needed; limitations of germline testing for treatment decisions; the cost of additional genomic testing; limited time for genetics education; and identifying appropriate resources to provide to patients. *Conclusion:* Genetic counselors can play an important role in providing support to medical oncologists and in counseling men with mCRPC who are undergoing mainstream genomic testing. This study confirms the results of other studies that show the importance of providing education to oncologists and patients regarding multigene next generation sequencing in tumor samples plus/minus subsequent germline genetic testing.

Evaluation of an Expanded CFTR Variant Panel: Spectrum of Variants Identified

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Background: Cystic fibrosis (CF) is a common inherited autosomal recessive condition with a prevalence of 1 in 2500 births and a carrier frequency of 1 in 25. Variants in the *CFTR* gene are responsible for CF and *CFTR*-related disorders. *Aim:* To evaluate the impact of the expanded *CFTR* variant panel on CF testing. *Methods:* In 2019 VCGS introduced an amplicon-based massively parallel sequencing assay. *This assay determines the presence or absence of a specific panel of 178 (diagnostic) or 175 (screening) variants in the CFTR gene. The diagnostic panel includes 3 variants of variable clinical consequences; c.350G>A (p.R117H) variant, polyTG tract (c.1210-34TG[11_13]) and polyT tract (c.1210-12T[5_9]). Results:* In 3½ years of offering this panel, 22,762 individuals have been tested; 1,267 with a family history (including 61 prenatals), 600 with symptoms suggestive of CF, and 20,895 with no family history or symptoms. There have been 599 population screening carriers identified (46 that would have been missed on the previous 38 variant panel) and 64 symptomatic patients that obtained a molecular diagnosis (6 of which would have been missed on the previous 39 variant panel). Sixty-two different variants have been observed in the nonfamily-history cohort, with p.Phe508del accounting for 74.3% of these. 90.9% of variants identified were in the ACMG recommended panel; however, 7 diagnoses and 51 carriers would have been missed if testing the ACMG variants only. *Conclusion:* The data indicates that the implementation of the expanded CFTR variant panel has been beneficial in both the diagnostic and screening settings.

Young-Onset Dementia: A Systematic Review of the Psychosocial Impact on Genetic Relatives

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Background: Young-onset dementia (YOD) describes a group of neurodegenerative conditions occurring before the age of 65, often caused by dominant genes such as *C9ORF72, PSEN1* and *MAPT*. The social context of YOD creates extra psychological and social challenges, yet the experiences of at-risk relatives are often overlooked in society and healthcare settings. A deeper understanding is necessary for effective genetic counseling about YOD. *Aim:* To identify the psychological and social impacts on asymptomatic relatives in families with YOD. *Method*: A systematic review of key databases for empirical studies published in peer-reviewed journals relating to the lived experience of individuals at genetic risk for YOD was performed. Data was collated and interpreted via a narrative synthesis. *Results*: Nineteen articles met the inclusion criteria. The majority of studies were qualitative and explored the experiences of children with a parent with YOD. Five themes were developed: (1) Onset of YOD disrupts family functioning (2) Emotional impact is significant and varied (3) Uncertain Future (4) Lack of visibility in health care and society (5) coping strategies include emotion-focused coping and distancing. *Conclusion*: Health professionals can explore the psychosocial needs of YOD for relatives and facilitate referrals and support to mitigate the effects of belonging to a family where YOD is present. We present a practical framework of questions and strategies for care of relatives, mapped to the self-regulation model of genetic counseling.

'Anything is better than nothing': Exploring Clinical Trial Acceptability in the Leukodystrophy Community

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Background/Aim: Leukodystrophies comprise a group of genetic white matter disorders that lead to progressive motor and cognitive impairment. Recent development of novel therapies has led to an increase in clinical trials for leukodystrophies. To enable recruitment of individuals with a Leukodystrophy into clinical trials, clinical trial acceptability should be ascertained. We sought therefore, to identify the motivations for and barriers to clinical trial participation in addition to clinical trial features that may be of concern to individuals

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with a leukodystrophy and/or their carers. *Methods:* Adults with a leukodystrophy and parents of individuals with a leukodystrophy were recruited through the Australian Leukodystrophy Registry and through online advertisements. Qualitative semi-structured interviews were used to explore participants views on what clinical trials involve, the risks and benefits of clinical trials, their desire to participate in clinical trials and their personal experience with leukodystrophy. Thematic analysis of data was performed with co-coding of interview transcripts. *Results:* Preliminary data ($N = 9$) suggests that motivations for clinical trial participation includes access to potentially lifesaving treatment and improvements in quality of life. The use of placebos and risk of adverse side effects are deterrents for clinical trial participation. Despite this, the majority of participants reported willingness to participate in first in human Leukodystrophy trials, with reference to clinical trials as the only source of hope. *Conclusions:* Interviewees demonstrated a strong desire to participate in clinical trials. Our findings suggest that inclusion of treating clinicans in the recruitment process may enhance participant enrolment into leukodystrophy clinical trials.

Noncoding Variants and High-Resolution CNV Analysis are Important Contributors to the Yield of Genetic Testing in Patients With Primary Immunodeficiencies

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Background: Primary immunodeficiencies, or inborn errors of immunity (IEIs), are a group of inherited disorders affecting the immune system development or function. Identifying the genetic etiology of an IEI can significantly impact patient management. Therefore, genetic testing is essential for these patients. *Aim*: We report results from over 4,800 patients who underwent multigene panel testing with 1 of 11 immunology-related panels. We demonstrate the importance of high-resolution copy number variant detection (CNV) and inclusion of clinically relevant noncoding variants for the indication of IEI. *Methods:* We retrospectively examined deidentified genetic test results from consecutive patients tested for the indication of IEI. Panel target regions generally included all coding exons, 20 base pairs at intron-exon boundaries, and select regions containing clinically relevant noncoding variants. Variant interpretation was performed using a point-based modification of the ACMG guidelines. *Results*: Median age at testing of the 4,894 patients was 16 years (range 0–90). Pediatric patients (<19 years) accounted for 62% of the cohort. A diagnosis was achieved in 547 patients (11.2%). The highest yield was for the Chronic Granulomatous Disease Panel and in patients who were less than 1 year of age. Diagnostic variants in 158 genes were reported. CNVs contributed to the diagnosis in 56 patients (10%), with 18 (32%) being 4 exons or smaller. Noncoding variants contributed to the diagnosis in 21 patients (4%). *Conclusion*: Small CNVs and noncoding variants contribute to 10% of diagnostic findings in a large cohort of patients with IEI who have undergone comprehensive, next-generation panel testing.

Noncoding and mitochondrial DNA variants are Disease Causing for 1 in 20 Patients With Monogenic Diabetes

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Background: Up to 4% of diabetes cases are caused by variation in a single gene. Comprehensive genetic testing is needed to maximize diagnostic potential for individuals with monogenic diabetes (MD); however, most multi-gene panel testing (MGPT) historically performed for this indication has not included analysis of noncoding regions associated with disease or the mitochondrial genome. *Aim:* In this study, we assessed the impact of including targeted coverage of noncoding regions associated with disease and mitochondrial genome analysis in next-generation sequencing (NGS)-based MGPT for patients with suspected MD. *Methods:* Clinical reports of 507 patients who underwent MGPT for an indication of suspected MD at Blueprint Genetics were examined. MGPT included both sequence and copy number variant (CNV) analyses of NGS data from a validated clinical exome assay targeting up to 30 nuclear genes, up to 72 disease-associated noncoding variants, and the mitochondrial genome. *Results:* A molecular diagnosis was established in 24.9% (126/507) of patients across 11 genes. Diagnostic CNVs were reported in 7.9% of patients with diagnostic findings ($n = 10$). One patient's diagnostic finding was a homozygous, likely pathogenic, noncoding variant in the *INS* gene, NM_000207.3:c.-152C>G. The pathogenic *MT-TL1* m.3243A>G variant, associated with maternally inherited diabetes and deafness (MIDD) syndrome, was identified as molecular diagnoses for six patients. *Conclusions:* MGPT that includes mitochondrial genome analysis and targeted sequencing of disease-causing noncoding regions resulted in molecular diagnoses for ~25% of patients with suspected MD. Noncoding or mitochondrial variants were causative for 1 in 20 of patients who received molecular diagnoses of MD.

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