Twin Research and Human Genetics (2025), **28**, 62–110
doi:10.1017/thg.2025.7

CAMBRIDGE UNIVERSITY PRESS

Abstracts

Abstracts for the 47th Human Genetics Society of Australasia Annual Scientific Meeting, Gold Coast, Queensland, Australia, 10–13 August 2024

Plenaries and Oral Presentations

PLENARY 1
Precision Phenotyping Through Artifical Intelligence Algorithms for Facial Analysis

Karen W. Gripp

Nemours Children's Health, Wilmington, DE, USA

Artificial intelligence tools can be used for precision phenotyping which may be combined with next generation sequencing to further patient identification and diagnosis. The Clinical Face Phenotype Space (CFPS) approach is typically used for facial image analysis. Several algorithms built upon the CFPS approach are available for evaluation of 2D facial images. In a clinical context, the DeepGestalt algorithm is a decision support tool that compares facial features of a patient image to those from previously established and trained syndromic conditions. The output of this tool is a ranked list of the pretrained conditions, with the syndrome most closely matching the patient photo in the top1 position. This DeepGestalt algorithm is used in the Face2Gene clinician tool and it has been studied in combination with genomic and feature data. In contrast, the GestaltMatcher algorithm compares a single image to another single image, using proximity in CFPS as a measure of similarity in facial features. The GestaltMatcher algorithm is a useful research tool as it can match undiagnosed patients based on similarity in their facial features. A third algorithm, D-score, evaluates the overall degree of facial dysmorphism in a patient image. D-score may be used by physicians with limited experience in syndromology to identify patients more likely to benefit from a referral to medical genetics or genetic testing. These computer aided facial analysis tools can support precision phenotyping in the era of next-generation sequencing and targeted drug therapies.

PLENARY 2
Applications of Artificial Intelligence for Complex Disease Genomics

Phillip Melton

Menzies Institute for Medical Research, Hobart, TAS, Australia

Medical research currently amasses a vast amount of patient clinical and large genomic datasets, making traditional data analysis approaches challenging. Artificial intelligence, specifically deep learning, offers a solution by efficiently integrating large and complex data to identify novel biological patterns. However, classic deep learning methods often act as black-box systems, making meaningful interpretation difficult. To address this, we utilised Kolmogorov-Arnold Networks (KANs), a recent alternative to classical methods. KANs allow for mathematical modeling of internal networks, yielding interpretable results. We used longitudinal early-life data with genomewide data from the Raine Study Gen2 cohort and integrative omic (genetic, epigenetic, lipidomic) data from the Busselton Health Study. These datasets were used to benchmark traditional statistical methods, machine learning, and KANs for performance comparison. In the Raine Study, we predicted body mass index (BMI) from age 5 to age 26 using genomewide genotype data and early life factors up to age 5, seven genetic risk scores for BMI, and our own genetic association results. Preliminary results show that KAN models outperform other models when groups include genetic data or genetic risk scores, with an area under the curve of less than 0.09. The most consistent predictors across all time groups were BMI at age 5 and genetic data. Integrative genomic results are still in progress. Our results highlight the potential of KANs as a powerful alternative to classical deep learning models.

PLENARY 5
The Experience of Implementing Genomics Into Clinical Practice Guided by Asian Ancestry-Specific Data

Yasmin Bylstra[1], Weng Khong Lim[1,7,11], Sonia Davila[1], Sock Hoai Chan[1,10], Jing Xian Teo[1], Sylvia Kam[10], Melody Menezes[4,5], Jan Hodgson[4], David Amor[4,6], Patrick Tan[1,7,9,11] and Saumya S. Jamuar[1,10,11,12]

[1]SingHealth Duke-NUS Institute of Precision Medicine, Singapore, [2]Cardiovascular and Metabolic Disorders, Duke-NUS Medical School, Singapore, [3]Cancer Genetics Service, National Cancer Centre, Singapore, [4]Department of Paediatrics, The University of Melbourne, Victoria, Australia, [5]Monash Ultrasound for Women, Victoria, Australia, [6]Murdoch Children's Research Institute, Victoria, Australia, [7]Genome Institute of Singapore, Singapore, [8]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, [9]Precision Health Research Singapore (PRECISE), Singapore, [10]Genetics Service, KK Women's and Children's Hospital, Singapore, [11]Cancer and Stem Cell Biology, Duke-NUS Medical School, Singapore and [12]Paediatric Academic Clinical Programme, Duke-NUS Medical School, Singapore

Background: While the principles of genomics delivery in healthcare are comparable worldwide, genomic reference datasets, health practices, costs and discrimination policies in Asian settings differ from

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

reported initiatives involving European-derived populations. For example, despite comprising over 60% of the global population, individuals of Asian ancestry remain underrepresented in large genomic datasets, posing challenges in variant interpretation and prioritising genomic health initiatives. Furthermore, data regarding clinically significant genomic variants and the experience of genomics screening in Asian communities is under-reported. *Methods:* To address these gaps, 9051 whole genomes from Chinese, Indian and Malay unrelated research consented participants were aggregated and curated, focusing on 4143 genes associated with Mendelian disease and 23 pharmacogenes. *Results:* This analysis identified individuals carriers and at risk of genetic conditions and has enabled tailored delivery of risk assessment for an extensive range of genetic conditions seen in clinical practice which were previously unknown. Characterising severe recessive disorders has resulted in the implementation of carrier screening to include individuals of Asian ancestry with guidance from community members, religious leaders and healthcare professionals regarding its acceptability. In parallel, a flexible learning framework was developed to return clinically significant genomic variants to this cohort. Following the delivery of these genomic findings, uptake in recommended health screening and predictive testing of family members has been notably inconsistent. *Conclusion:* These initiatives will help expand current understandings of genomic variation and implementation of genomic screening programs, opening opportunity for the provision of equitable access to genomic medicine for a wider population.

PLENARY 7
Increasing Equitable Representation in Genomic Resources

Daniel G. MacArthur[1,2], Samantha Croy[1,2], Luke Seesink[1,2], Rafal Shouly[1,2], Bindu Kanakamedala[1,2], Stuart Cantsilieris[1,2], Bronwyn Terrill[3,4,5], Mary-Anne Young[3,4,5], Zuong Dang[1,2] and Chris Richards[1,2]

[1]Centre for Population Genomics, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, NSW, Australia, [2]Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Clinical Translation and Engagement Platform, Garvan Institute of Medical Research, Sydney, NSW Australia, [4]School of Clinical Medicine, Faculty of Medicine and Health, UNSW Sydney, Sydney, NSW, Australia and [5]Australian Genomics, Melbourne, VIC, Australia

Background: Genomic medicine is rapidly accelerating, but existing genomic resources are currently missing information from many global communities. This underrepresentation limits the ability to translate genomic knowledge to those communities, and means the life-saving benefits of genomic medicine may not reach millions of Australians, many of whom already experience poorer health outcomes. *Aim and Methods:* The Our DNA Program at the Centre for Population Genomics is working with a number of diverse Australian communities to build genomic resources that are more representative of Australia's diversity. Our DNA is partnering with communities from the Pacific, South-East Asia, the Middle East and East Africa across Sydney and Melbourne to co-design locally relevant, culturally appropriate and scalable approaches for community engagement and outreach. This will allow Our DNA to recruit and assemble a resource of genetic variation data spanning 10,000 whole-genome sequences from participants of under-represented ancestral backgrounds in Australia. This program is challenging not just because of the scale and diversity of recruitment, but also the need to rapidly process blood samples to obtain live cells for functional genomics, and the goal of returning clinically actionable findings from genome sequencing. *Results and Conclusion:* This presentation will cover insights from the recent Our DNA pilot with the Sydney Filipino community, as well as ongoing community engagement with other Australian communities and translations to support participation in genomics research. We describe key principles and shared resources for community engagement in large-scale genomics projects.

PLENARY 9
The Relevance of Pharmacogenetic Testing in an Australasian Population

Luke B. Hesson[1,2,3]

[1]Douglass Hanly Moir Pathology, Sydney, NSW, Australia, [2]School of Clinical Medicine, UNSW Sydney, Sydney, NSW, Australia and [3]School of Life Sciences, Faculty of Medicine, UTS, Sydney, NSW, Australia

Pharmacogenetic testing can help optimise prescribing by predicting efficacy or toxicity of a wide range of medications for an individual patient. However, several challenges exist to the broad adoption of pharmacogenetic testing in the Australasian context. These challenges include uncertainty about when pharmacogenetic testing may be relevant, the paucity of data regarding genetic variation present in Australasian populations, and the absence of Medicare rebates. This presentation will describe the importance of pharmacogenetic testing in optimising the choice or dose of medication to improve efficacy and reduce the frequency adverse drug reactions, and describe recent work to address the above challenges.

PLENARY 10
Genomics-Guided Precision Treatment for Epilepsy

Lata Vadlamudi[1,2]

[1]Comprehensive Epilepsy Program, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia and [2]University of Queensland Centre for Clinical Research, Brisbane, QLD, Australia

Epilepsy is a serious neurological disorder affecting more than 50 million people worldwide. Epilepsy is a heterogeneous disorder characterised by recurrent, unprovoked seizures. The burden of disease is far more than just the seizure and can affect mobility, cognitive function and quality of life. More than 30% of people with epilepsy are resistant to current anti-seizure medications. Despite the enormous advances in genetic causes for epilepsy, precision therapies are not yet available for the majority of epilepsies, due to the complexity of the underlying biological mechanisms and challenges targeting them. Gene discovery in epilepsy has led to diagnoses; provided knowledge of the natural history; enabled pre-clinical drug discovery and clinical trials. Genomics-guided precision-based treatment in epilepsy utilises pharmacogenomics to improve anti-seizure medication selection and specific genetic variants can be targeted with disease-modifying treatments. We are in an exciting era of precision medicine in epilepsy and have an enormous opportunity to improve clinical care, with the exponential advances in genomic knowledge.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

PLENARY 11
Enhancing Genetic Counselling and Supervision in the Genomic Era: Drawing Ideas From Narrative Therapy (NT)

Rhona Macleod[1] and Mariangels Ferrer[2]

[1]Manchester Centre for Genomic Medicine/University of Manchester, Manchester, UK and [2]The Institute of Narrative Therapy, Cheshire, UK

Background: The genomics era has seen a rise in the number of people seeking genetic counselling and testing. This has led to changes in the way genetic counselling is practiced including enhanced multidisciplinary working. In turn, influences from the fields of clinical psychology and therapy are helping to inform how we think about wellbeing. Counselling supervision is recognised as an essential part of professional development in supporting genetic counsellors to accompany people as they navigate their genetic situation (e.g., Paneque et al., 2023). Here we consider how NT can contribute to genetic counselling supervision and practice. *Aims:* (1) To present some principals from NT (White and Epston, 1990) and consider how these align to the principles and practice of genetic and genomic counselling. (2) To outline a structure adopted for group counselling supervision and how narrative conversations are facilitated.
Drawing on cases from clinical practice, we will consider how a narrative position can help genetic clinicians to withstand and effectively support people in relation to grief and loss. In supervision the objective of the supervisor is to enhance and elaborate on the expertise of the supervisees in a way that provides them with novel avenues for addressing the concerns that arise during practice. *Conclusion:* A narrative position has the potential to shape how we practice and train genetic counsellors in the future, as well as moving families from a position of potential isolation.

PLENARY 12
Implementing Genomics and Models of Care for Inherited Kidney Disease — The KidGen Consortium

Andrew J. Mallett[1,2,3]

[1]Townsville University Hospital, Townsville, QLD, Australia, [2]James Cook University, Townsville, QLD, Australia and [3]The University of Queensland, Brisbane, QLD, Australia

Background: Diagnostic genomic sequencing has become the emerging standard of care in nephrology. How and why this has occurred in Australia in a multidisciplinary framework is important to consider *Aim:* To describe the past decade of multidisciplinary genomic implementation in nephrology across Australia *Methods:* Here we reflect upon and evaluate a national network of kidney genetics clinics developed and implemented over a decade in Australia. *Results:* We successfully established and expanded a nationwide network of 20 clinics over a decade, concurrently developing laboratory, research, and education programs to scale the clinical application of genomics in nephrology. Within this, we describe an Australian cohort of 1506 kidney patients encountered through this clinic, of whom 1322 received test results. Barriers to implementation in the nephrology context and applied real-time solutions to improve clinical processes are considered. *Conclusion:* Developing a multidisciplinary kidney genetics model across multiple health services nationally has been successful. The model has delivered optimal clinical care of individuals with inherited kidney disease in an economically responsible way whilst evolving with technological and service developments.

PLENARY 13
Flourishing in Healthcare – Taking the 'Eyeroll' Out of Reflection

Linda Humphreys

Griffith University School of Medicine & Dentistry, Brisbane, QLD, Australia

Background: The human capabilities are gaining increasing recognition as desired skills in the complex, dynamic and rapidly advancing landscape of workplaces. In the 2023 World Economic Forum Future of Jobs Report, self-efficacy skills (resilience, flexibility and agility), motivation and self-awareness, curiosity and lifelong learning are ranked in the top 5 core skills, with empathy and active listening ranked 8th. This recognition is mirrored in the health professions, with accreditation standards overtly requiring graduates and practitioners to demonstrate the human capabilities of person-centred care, leadership, and to support their own health and wellbeing.
I have integrated a communication skills contemplative pedagogy model into the Griffith University MD Curriculum. Coined 'MaRIS' (applying Mindfulness and affective Reflection through Impactful experiential learning in a psychologically Safe space), the model has established the foundations for building medical students' human capabilities and personal resilience for complex professional practice. *Aim:* The MaRIS model is designed to foster deliberate exploration of the value-laden aspects of healthcare, highlighting what matters to us through thoughtful reflection. However, in my experience, the concept of *affective reflection* is sometimes met with ambivalence, trepidation or outright resistance from students, educators, and health practitioners alike. I will discuss contemplative pedagogy, why reflection and emotional literacy matters for wellbeing at work with some ideas for practice.

PLENARY 14
Breast Cancer Genetics in Perspective: Increasing Knowledge Reveals Growing Complexity in Variant Interpretation

M. P. G. Vreeswijk

Human Genetics, Leiden University Medical Center, the Netherlands

Genetic testing to identify pathogenic variants in the high-risk breast-cancer susceptibility genes *BRCA1, BRCA2* and *PALB2* is routine clinical practice. While variants predicted to disrupt protein function, such as truncating variants and those at the canonical splice site, are considered to be associated with high cancer risk, the identification of Variants of Uncertain Significance (VUS), whose impact on protein function is unknown, complicates the interpretation of cancer risk and consequently, clinical management. The ENIGMA (Evidence-based Network for the Interpretation of Germline Mutant Alleles) consortium leverages expertise across analytical, splicing, functional, pathology and clinical working groups. ENIGMA's ClinGen Variant Curation Expert Panel has been instrumental in developing evidence-based ACMG/AMP aligned variant interpretation guidelines allowing the assessment of the clinical significance of VUS in *BRCA1* and *BRCA2.* For many variants, the lack of sufficient genetic and clinical data necessitates functional evaluation using quantitative functional assays displaying high sensitivity and specificity that meet international standards for VUS classification. Furthermore, quantitative functional analyses have unveiled unexpected biological insights for several variants, highlighting the complexity of variant interpretation. Notably, the default pathogenic

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

classification of truncating and canonical splice site variants may require reevaluation due the presence of alternative transcripts encoding functional protein isoforms. Additionally, functional analyses have demonstrated that many variants impact protein function to varying degrees. Establishing the quantitative relationship between residual protein functionality of *BRCA1, BRCA2*, and *PALB2* and breast cancer risk will enhance the precision of cancer risk assessment and inform tailored clinical management for individuals carrying these genetic variants.

PLENARY 15
Aboriginal Sovereignty and Benefit in Precision Oncology: What is Required?

Justine Clark[1,2], Jessica Buck[1,3], Amanda Richards-Satour[1], Louise Lyons[1] and Alex Brown[1,2]

[1]Telethon Kids Institute, Perth, WA, Australia, [2]Australian National University, Canberra, ACT, Australia and [3]University of Western Australia, Perth, WA, Australia

Aboriginal and Torres Strait Islander peoples are disproportionately affected by cancer and require equitable access to cancer care. An increasingly important part of cancer care in Australia is precision oncology: the utilisation of tumour genomic profiling to personalise cancer prevention, early detection, treatment and long-term disease management. Recent evidence demonstrates the unique genomic variation that exists among Aboriginal people in comparison to global reference datasets. Yet, Aboriginal and Torres Strait Islander peoples are absent from or underrepresented within the genome reference resources that support cancer clinical care as well as cancer studies spanning basic science to clinical trials. Here, we describe a set of requirements that are necessary to achieve Aboriginal and Torres Strait Islander benefit, equity and sovereignty in precision cancer research and precision oncology. We outline how these requirements can be operationalised through purposeful design of cancer research projects. Through initial research projects, we will develop an agenda for an Aboriginal and Torres Strait Islander precision cancer research program that is Aboriginal-led, data driven and aligned to community priorities. Our initial work will provide an opportunity to develop an understanding of the unique ethical and cultural considerations of precision oncology for Aboriginal and Torres Strait Islander peoples, as well as generate our first data on Aboriginal and Torres Strait Islander cancer genomics. We anticipate that building knowledge of Aboriginal and Torres Strait Islander cancer genomics and the translation of this knowledge into precision oncology will enable critical improvements to cancer clinical care and cancer health policy.

PLENARY 18
Enabling Clinical Translation of High-Throughput Functional Assay Data

Alan F. Rubin[1,2]

[1]The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia and [2]University of Melbourne, Melbourne, VIC, Australia

Background: A central problem in precision medicine is understanding the effects of individual DNA variants. Measuring their activity in the lab provides valuable evidence for clinical interpretation but can be both time- and resource-intensive. Multiplexed assays of variant effect (MAVEs) are a family of experimental techniques that allow researchers to measure many thousands of variants in a gene or other functional element in parallel, generating a large volume of high-quality functional evidence. *Aim:* Our aim is to increase the availability and discoverability of MAVE data for researchers and clinicians alike. *Methods:* We developed MaveDB, an open-source community-oriented database for MAVEs and other types of functional assays including those based on low- or medium-throughput approaches. MaveDB implements a user-friendly model for uploading and searching datasets, as well as a clinician-focused dashboard view that provides detailed information on individual variants. We are also driving the creation and adoption of international standards for functional assay data. *Results:* MaveDB has been embraced by the MAVE community as the database of record and already contains 1200 datasets comprising over 7 million individual variant-effect measurements. This includes MAVE data for several genes on the ACMG secondary findings list such as *BRCA1*, *CALM1/2/3*, *KCNQ1*, *MSH2*, *PTEN*, *SCN5A* and *TP53*. Availability of data standards has enabled integration of MaveDB data by diverse partners within Australia and internationally. *Conclusion:* As more functional data continues to be generated, increasing availability and promoting standardisation will help get this important evidence into the hands of clinicians quickly to improve patient outcomes.

PLENARY 19
CLINGEN Glaucoma Expert Panel Curation Guidelines Improve the Classification of MYOC-Associated Glaucoma Variants

Emmanuelle Souzeau[1], Patricia Graham[2,3], Johanna Hadler[1,4], Stuart W. J. Tompson[5], Kristina Whisenhunt[5], Jamie E. Craig[1], Alex W. Hewitt[2], Owen M. Siggs[1,6], Subhabrata Chakrabarti[7], John D. Hulleman[8], Francesca Pasutto[9], Terri L. Young[5], David A. Mackey[2,3], Kathryn Burdon[2] and Andrew Dubowsky[4]

[1]Flinders University, Flinders Medical Centre, Adelaide, SA, Australia, [2]University of Tasmania, Hobart, TAS, Australia, [3]University of Western Australia, Perth, WA, Australia, [4]SA Pathology, Adelaide, SA, Australia, [5]University of Wisconsin-Madison, Madison, WI, USA, [6]Garvan Institute of Medical Research, Sydney, NSW, Australia, [7]L V Prasad Eye Institute, Hyderabad, India, [8]University of Texas Southwestern Medical Center, Dallas, TX, USA and [9]University Erlangen-Nuremberg, Erlangen, Germany

Background: Pathogenic variants in *Myocilin* (*MYOC*) are the most common cause of Mendelian adult-onset glaucoma. Genetic testing can lead to early diagnosis of at-risk individuals and interventions to minimise vision loss. However, accurately classifying genetic variants remains a key challenge in clinical genetics. *Aims & Methods:* ClinGen Variant Curation Expert Panels (VCEP) aim to develop guidelines for variant curation specific to genes or diseases. The Glaucoma VCEP previously published rule specifications for *MYOC* to improve variant classifications. All *MYOC* variants published and identified in cases have since been curated by the Glaucoma VCEP using the specified rules. *Results:* A total of 265 variants classifications have been published in ClinVar with Expert Panel status, including 44 as benign /likely benign, 191 as variants of uncertain significance (VUS), and 30 as likely pathogenic/pathogenic. The classifications confirmed all pathogenic variants are located within the conserved olfactomedin domain. A prior ClinVar classification was reported for a third of the variants, of which a two-third reached classification concordance, while 10% were downgraded with clinical impact. Functional evidence was available for 24% of variants, of which 67% reached a clinically conclusive classification. Additional or new functional evidence could lead to the reclassification of over a third of VUS. *Conclusion:* The refined *MYOC* variant curation guidelines from the Glaucoma VCEP have improved variant classification and the number of variants curated in ClinVar. Data sharing and additional functional

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

evidence have been identified as critical factors to improve further variant classifications.

ALLIED HEALTH WORKSHOP

Use of Ketogenic Diet Therapy (KDT) in Paediatric Pyruvate Dehydrogenase Complex Deficiency (PDHCD) — A Case Series

Tessa Bollard[1], Kiera Batten[1,2], Katherine Lewis[1], Amanda Owers[1], Dinusha Pandithan[1], Jacqui Russell[1], Sue Thompson[1,3] and Kaustuv Bhattacharya[1,4]

[1]Genetic Metabolic Disorders Service, Sydney Children's Hospital Network, Sydney, NSW, Australia, [2]School of Health Sciences, Faculty of Medicine and Health, The University of New South Wales, Sydney, NSW, Australia, [3]School of Nursing, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia and [4]Clinical School and school of Clinical Sciences, University of New South Wales, Sydney, NSW, Australia

Background: PDHCD is a disorder of carbohydrate metabolism causing neurological compromise. KDT, an established treatment for PDHCD, is purported to provide ketones as an alternative substrate for the brain. However, published data is limited. *Aim:* Report current KDT practices in paediatric PDHCD in NSW. *Methods:* Retrospective review of living PDHCD cases under the care of the NSW paediatric metabolic team. *Results:* Five cases were included, aged 18 months to 16 years. Age of diagnosis ranged from five months to three years. Types of KDT utilised included 'Classical', 'Modified Atkins', and 'High-Fat, Low-Carbohydrate'. KDT was commenced in the inpatient setting in three cases. Frequency of ketone monitoring varied from daily to when parents deemed necessary e.g. during illness or suspected hypoglycemia. Broader biochemical surveillance and nutritional supplementation also varied. Two cases were supplemented potassium citrate prophylactically, one case was supplemented multivitamins prophylactically, whereas others commenced supplements when deemed necessary. One case suffered a transient hyperkinetic movement disorder following KDT commencement, resolving within 12 weeks. No other significant side effects were reported. Four cases were reported by parent(s) and clinician(s) to have improved alertness and development progression after KDT commencement. The parents, but not the clinicians, of the fifth case reported improved alertness and development progression. *Conclusion:* KDT in PDHCD appears effective but inconsistently managed in NSW. Given extensive KDT experience in refractory epilepsy, standardisation of implementation and monitoring should be considered, to optimise outcomes for these patients. An Australasian review of practices would provide a larger cohort to inform standardisation.

Outcome of a 4-Year-Old Boy With Carnitine-Acylcarnitine Translocase (CACT) Deficiency Following Elective Adenotonsillectomy and Subsequent Multiple Episodes of Cardio-Respiratory Arrest

Kalliope Demetriou, Drago Bratkovic, Sarah Donoghue, Alice Rogers, Stephanie Oates, Melissa Colombo and Annabelle Comerford

Women's and Children's Hospital, Adelaide, SA, Australia

Background: A 4-year-old with CACT deficiency (OMIM 212138) underwent elective adenotonsillectomy for obstructive sleep apnoea. He had first presented in the neonatal period with hypoglycemia, hyperammonaemia and pulseless ventricular tachycardia. His management included modular feeds of polyjoule, Beneprotein and vitamins, walnut oil, sodium-D3-hydroxybutyrate and triheptanoin. His regimen provided 61Cal/kg/day (7.5% from protein, 64% from carbohydrate, 24.5% from triheptanoin, 4% from essential fatty acids). At baseline he had chronically elevated ammonia, CK, lactate and troponin levels and mild LV hypertrophy. *Aim:* Describe the metabolic and critical care management that resulted in sustained biochemical stability but did not prevent acute deterioration in cardiorespiratory status. *Methods:* Throughout the admission 15-25% glucose concentrations were used to provide glucose infusion rates of 6.5mg/kg/minute (37.4Cal/kg/day). Enteral ketone therapy was continued but triheptanoin could only be provided intermittently. Additional measures to reduce metabolic demand during management for acute respiratory distress syndrome included active thermoregulation to normothermia, deep sedation, non-depolarising agents for muscle paralysis and dexmedetomidine to counter tachycardia. Management of subsequent unpredicted episodes of cardiorespiratory arrest included standard cardiopulmonary resuscitation. *Results:* Despite stable and improved plasma levels of troponin, lactate, ammonia and CK, without metabolic acidosis, there was rapid progression in left ventricular hypertrophy and parenchymal lung disease. Acute intermittent left ventricular outflow tract obstruction was considered a contributing factor to his multiple arrests. *Conclusion:* Glucose and ketones provided apparent metabolic stability and critical care measures to reduce metabolic demand were beneficial. Unpredicted outcomes included acutely progressive cardiac muscle hypertrophy and new dependence on non-invasive ventilatory support.

OXFORD NANOPORE TECHNOLOGIES INDUSTRY SESSION

Motif Diversity and Repeat Expansion Instability in Familial Adult Onset Myoclonic Epilepsy

Mark Corbett

University of Adelaide, Adelaide, SA, Australa

Familial Adult Myoclonic Epilepsy (FAME) is characterised by cortical tremor, myoclonus and myoclonic and/or generalised tonic-clonic seizures with onset in the 2nd to 3rd decade. FAME is caused by noncoding, intronic expansions of a reference TTTTA DNA motif adjacent to an inserted and repeated TTTCA motif in one of seven different genes with unrelated molecular functions. Guidelines for clinical molecular tests for FAME are currently not available and the pathogenic limits on repeat length or the effects of different motifs within the repeat are not known. We previously showed that the age of disease onset significantly decreased over three successive generations in a large Australian/NZ family with FAME2. We hypothesised that this anticipation correlated with the length of the TTTTA and TTTCA repeat expansion. We measured the length of FAME TTTTA and TTTCA repeats in DNA extracted from blood of 94 affected individuals from 10 FAME2 families using long-range PCR and Oxford nanopore DNA sequencing. The average length of the entire repeat increased in successive generations in multiple FAME2 families and correlated with younger age of onset of myoclonus ($r = -0.329$, $p = .05$). There were no significant differences in the magnitude of changes in repeat lengths between maternal or paternal inheritance. Changes in numbers of both TTTTA and TTTCA repeats over successive passages of patient-derived lymphoblastoid and primary skin fibroblast cell lines were dynamic: potentially modeling somatic instability. High levels of motif and repeat length variation at FAME loci were observed in population controls from the gnomAD database and individuals we sequenced. Our results collectively suggest that TTTTA and TTTCA repeat expansions are

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

dynamic during both meiosis and mitosis, with longer overall length correlating with earlier disease onset and motif structures that may lead to false negative results using some diagnostic methods.

The Long and the Short of Establishing a Clinical Nanopore Sequencing Facility for Acute Care in New Zealand

Justine O'Sullivan

University of Auckland, Auckland, New Zealand

There are ~200 children in high dependency neonatal acute care in New Zealand at any one time, requiring a scalable distributed solution for acute care genomics. We have established an expandable acute care clinical pipeline based around the PromethION2 solo system with connection to Fabric GEM™. In the establishment phase, we have performed benchmarking using GA4GH benchmarking tools and Genome in a Bottle HG002 - HG007. Evaluating ~3.3x106 truth SNVs and ~500x103 INDELS at read depths of between 24-42X coverage identified SNV recalls = 0.992 ± 0.001, precision = 0.997 ± 0.0006, and F1 = 0.995 ± 0.0008 over a minimum of two runs completed by different technicians and analysts. INDEL identification approached recalls = 0.838 ± 0.043, precision = 0.922 ± 0.019, and F1 = 0.874 ± 0.032 over the same runs. Subsequent analyses indicated that the observed variation in recall, precision and F1 was largely limited to correct copies of falsely duplicated regions and areas of collapsed errors with clusters of CHM13 hets in GRCh38. Rarefaction analyses up to 80X coverage identified that SNV identification plateaus at ~20X coverage, while INDEL identification plateaus at ~40X coverage. Analyses of samples from Coriell CNVPANEL01 demonstrated that large scale genomic variations can be reliably detected after ~2M reads, equivalent to ~2hr sequencing time. Application of the pipeline in acute care genomic diagnosis is ongoing. We present the preliminary results from the pipeline validation phase, performed in parallel with established International accredited facilities available to New Zealand's clinicians

Why is Population Health the Future of Medicine?

Katheleen Barnes

Oxford Nanopore Technologies, USA

A paradigm shift in genomics is upon us. As DNA/RNA sequencing improves in breadth and accuracy and becomes more cost efficient, global health systems and diagnostic industries are slowly realising that the benefit of genomic and other omic screening to patients is finally aligning with the economics of making it available more broadly. The significant benefits of third-generation sequencing, or long-read sequencing, include richness of data, speed, accuracy, affordability and an accessible design, all of which have a profound opportunity to make an impact. But this ambition is not without its challenges, and scaling this technology across health systems will require a population health approach. Broadly defined, population health refers to the health status and health outcomes of a group of people, rather than just the individual. Population health includes consideration of health determinants, such as health inequalities and distribution of health across subpopulations, and the interventions and policies that link health outcomes with health determinants. A goal of population health is to improve health by reducing risk of disease through early detection, in part through broad deployment of precision medicine tools, throughout the life journey. As the technology improves and the economics of sequencing shift, so do the opportunities to engage health systems on a mass scale.

Poster Presentations

Evaluating the Implementation of Complex Genomic Profiling Using Circulating Tumor DNA to Patients with Advanced Cancer

Laura Forrest[1,2], Kim An[1], Kortnye Smith[3], Michelle Tew[4], Jo Cockwill[5], Bonney Corbin[5], Victoria Sharp[5], Christine Goulter[3,5,6], Lavinia Tan[3], Melissa Martyn[5] and Jayesh Desai[3]

[1]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [2]Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, VIC, Australia, [3]Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [4]Centre for Health Policy, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [5]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia and [6]Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia

Background: Complex genomic profiling (CGP) — a pan-cancer somatic test using circulating tumor DNA — has the potential to detect actionable tumor variants and individualise treatment. Cancer Statewide, funded by Melbourne Genomics Health Alliance, is evaluating delivery of CGP to patients with advanced cancer in regional and metropolitan oncology services in Victoria, Australia. *Aim:* To examine the preliminary experiences of oncologists delivering and patients receiving CGP within the Cancer Statewide program. *Methods:* This effectiveness-implementation hybrid study is guided by the updated Consolidated Framework of Implementation Research (2022) and Proctor's Implementation Outcomes Framework. The mixed methods approach recruits oncologists and patients to complete T1 surveys after offering/being offered CGP. 5-point Likert scale responses are analysed by describing the mean (standard deviation) and are also collapsed into three categories (disagree, neutral, agree). *Results:* From August 2023 to March 2024, 36 oncologists and 112 patients responded to T1 surveys. More oncologists reported needing educational resources to implement CGP (69.4%) compared to training (58.3%), and 80.6% reported needing access to information about CGP while delivering this test ($\mu = 3.94$, $\sigma = 0.66$). 80.6% of patients preferred having CGP discussions with their usual oncologist rather than another oncologist with specialised CGP knowledge. A greater proportion of patients at regional hospitals preferred discussing CGP in person instead of Telehealth, compared to patients at metropolitan hospitals (84.8% *cf* 66.7%). *Conclusions:* Educational and point of care resources are needed by oncologists to deliver CGP and patients' preference about the model of care they receive must be considered in implementation evaluation outcomes.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Multi-Omic Newborn Screening: Perspectives From South Australia

Lucy T. Anastasi[1], Jovanka King[2,6,8], Carol Wai-Kwan Siu[2,3], Ayesha Chowdhury[1], Alex Ashenden[3], Tomas Rozek[3], Khoa Lam[2,3], Enzo Ranieri[4], Drago Bratkovic[6], Ben Saxon[6], Nicholas Smith[6], Christopher Barnett[2,6], Hamish Scott[1,2], Jennie Louise[2,7], Tracy Merlin[5] and Karin S Kassahn[1,2]

[1]Department of Molecular Pathology, SA Pathology, Adelaide, SA, Australia, [2]Adelaide Medical School, Faculty of Health and Medical Sciences, The University of Adelaide, SA, Australia, [3]Department of Biochemical Genetics, SA Pathology, SA, Australia, [4]Present address: Sydney Children's Hospital at Westmead, Sydney NSW, Australia, [5]School of Public Health, The University of Adelaide, SA, Australia, [6]Women's and Children's Hospital, Adelaide, SA, Australia, [7]Present address: South Australian Health and Medical Research Institute, SA, Australia and [8]Immunology Directorate, SA Pathology, Adelaide, SA, Australia

Background: Newborn bloodspot screening (NBS) is a very successful public health initiative. Infants are currently screened for 31 conditions in the South Australian NBS program. The NewbornsInSA research study offers families genomic screening for over 600 additional conditions. This research program will be most successful if designed in collaboration with families, scientific and health professionals, and with support from the South Australian community. *Aims:* Explore the feasibility and acceptability of the NewbornsInSA research model among a range of stakeholders. *Methods:* A mixed-methods approach was adopted to explore stakeholder acceptability of the research design. Health care professionals, the general public and patient advocacy groups were identified as key stakeholders to engage. *Results:* Health care professionals were engaged by circulating a short video, followed by an online survey. This was distributed via snowball sampling initiated by research staff, heads of departments, community of practice groups, and education leads. We present preliminary findings from respondents, regarding perceived acceptability, anticipated change in management pathways, anticipated concerns of parents, foreseeable operational barriers, ethical concerns, and conditions of interest. Focus groups with families investigated the acceptability of the screening model and reviewed the consent strategy and materials. Patient advocacy groups were consulted and reviewed study materials for readability and acceptability. *Conclusion:* Active engagement with a wide range of stakeholders, including the general public, health care professionals and families is essential to evaluate overall study design, safety and acceptability of a research program exploring a novel approach to NBS.

Whole Exome Sequencing in the Differential Diagnosis of Neurodevelopmental Disorders AND Extending the Clinical Spectrum of Okur-Chung Neurodevelopmental Syndrome

Anna Antonets, Michael Gabbett, Angharad Webb and Simon Villegas

Genomics for Life, Brisbane, QLD, Australia

Introduction: Neurodevelopmental disorders manifest at any age and encompass a wide range of severity and associated symptoms. Identifying the aetiology of neurodevelopmental disorders has been challenging given the diversity of genetic and non-genetic causes. *Clinical History:* The proband, a 15-month female with global developmental delay and facial dysmorphic features, was clinically examined. She initially presented at two months of age with jaundice and was found to have a generalised hepatitis and conjugated hyperbilirubinaemia, both of which spontaneously resolved. At 15 months of age, she was hypotonic, was unable to walk, and had no speech. Normal investigations included a skeletal survey and an exome panel investigating neonatal jaundice. A cranial ultrasound demonstrated a bilateral echogenic focus in the basal ganglia, immediately subjacent to the caudothalamic groove, suggestive of calcification. The combination of neonatal hepatitis and basal ganglia calcification raised the possible diagnosis of Aicardi- Goutières syndrome. *Methods/Results:* Sequencing of the whole exome in the child and parents (trio analysis) identified a de novo CSNK2A1 c.593A>G; p.(Lys198Arg) pathogenic variant in the proband. Pathogenic variants in CSNK2A1 are associated with Okur-Chung neurodevelopmental syndrome (OCNDS) which is inherited in an autosomal dominant manner. *Conclusions:* Here, we present evidence that OCNDS may present as a phenocopy of Aicardi Goutières syndrome, thus extending the previously reported phenotype of OCNDS. Whole exome sequencing (WES) is an effective tool to diagnose patients with phenotypically similar and aetiologically diverse neurodevelopmental disorders and to discover new genetic causes

Differential Alternative Splicing of Skeletal Muscle Following Two Weeks Limb Immobilisation In Young Men

Aliah Aziz, Vernon Coffey, Kevin Ashton and Paul Dunn

Bond University, Gold Coast, QLD, Australia

Background: Muscle atrophy caused by skeletal muscle inactivity (disuse) or unloading, can often be a result of injuries or extended illnesses. While previous studies have characterised large-scale differential gene expression (DGE) responses in skeletal muscle induced during atrophy, the contribution of other regulatory mechanisms such as differential alternative splicing (DAS) during skeletal muscle atrophy has yet to be determined. This study aimed to identify global changes in DAS genes associated with disuse-induced muscle atrophy. *Method:* Twenty-one male participants (25.4 ± 5.5 y, 81.2 ± 11.6 kg) underwent 14 days of unilateral knee-brace immobilisation with standardised dietary provision and four-weeks of exercise training. RNA-sequencing was performed on vastus lateralis muscle samples from pre-immobilisation, day 3 and day 14 of immobilisation. Several bioinformatics methods such as rMATS software package were used to identify differential alternative splicing events and determine their gene functions. *Results:* DAS events mainly occurred in the gene's coding domain sequence region and after filtering, 699 DAS events were found at day 3 and 1005 DAS events were found at day 14. DAS genes were enriched in pathways involved in atrophy such as morphogenesis, ubiquitin-proteasome pathway and developmental processes. *Conclusions:* The study identified many genes that regulate the (mal)adaptation response to disuse-induced muscle atrophy through alternative splicing, which may have an important role in regulating protein content by generating different isoforms that exhibit divergent physiological and functional properties. Imbalance of RNA splicing is associated with pathological changes with skeletal muscle disuse and our findings provide novel data on the mechanistic response during muscle wasting.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Functional Analysis of an *FHOD3* Founder Variant Causing Hypertrophic Cardiomyopathy IN the Balkan's Population

Serena Li[1], Ginell Ranpura[1], Mira Holliday[1], Bernadette Hanna[2], Jodie Ingles[3,4], Saurabh Kumar[5], Christopher Semsarian[1,4,6], Seakcheng Lim[1] and Richard Bagnall[6,7]

[1]Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, NSW, Australia, [2]Department of Medical Genetics, Westmead Hospital, Sydney, NSW, Australia, [3]Genomics and Inherited Disease Program, Garvan Institute of Medical Research and University of New South Wales, Sydney, NSW, Australia, [4]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia, [5]Department of Cardiology, Westmead Hospital, Sydney, NSW, Australia, [6]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia and [7]Bioinformatics and Molecular Genetics Group at Centenary Institute, The University of Sydney, Sydney, NSW, Australia

Background: A c.1646+2T>C donor splice site variant at the cardiac-specific exon 12 of *FHOD3* is the second most common cause of hypertrophic cardiomyopathy (HCM) in the Balkans population, occurring in 16% of probands with a known genetic cause. *Aim:* Functionally evaluate RNA splicing outcomes due to the pathogenic c.1646+2T>C variant and two neighbouring variants of uncertain significance (VUS) using transcriptome sequencing of patient-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CM). *Methods:* iPSC-CMs were derived from three unrelated people with HCM who have *FHOD3* exon 12 donor splice site variants, and three controls. We performed transcriptome sequencing on patient-specific and control iPSC-CM, with and without cycloheximide treatment, and control myectomy. Splicing outcomes were quantified and confirmed with Sanger sequencing of RT-PCR products. *Results:* Transcriptome sequencing of iPSC-CMs with a pathogenic NM_001281740.3:c.1646+2T>C variant, or c.1646+1G>A or c.1646+1G>C VUS, showed skipping of exon 12, which did not occur in three control iPSC-CM or control myectomy tissue. Exon skipping led to an in-frame deletion of 120 amino acids (FHOD3 p.Lys430_Ser549del) encoding a domain of formin-homology-domain 3 protein that directly interacts with myosin binding protein C3. Sanger sequencing of RT-PCR products revealed that exon skipping was allele-specific. *Conclusions:* Donor splice site variants at the cardiac specific exon 12 of *FHOD3* are pathogenic and cause HCM through loss of a myosin binding protein C3 binding domain. iPSC-CMs are useful to investigate cardiac specific RNA transcripts when primary heart tissue is unavailable and support the classification of variant pathogenicity.

Molecular Classification of Adult Diffuse Gliomas Using a Glioma-Tailored Gene Panel at Sullivan Nicolaides Pathology

Narelle Barton, Victoria Jones, Rachael Chambers, Lauren Kalinowski and James Harraway

Sullivan Nicolaides Pathology, Brisbane, QLD, Australia

Background: Diffuse gliomas are primary central nervous system (CNS) neoplasms, which constitute 24% of adult brain tumors. Survival rates and treatment are dependent on histological and molecular biomarkers which have been incorporated into integrated classification by the World Health Organisation. The objective of this study was to assess the frequency of variants detected by our glioma-tailored gene panel, and to correlate them with histopathological features. *Methods:* 104 adult diffuse gliomas were tested in 2023-2024. Histology and Immunohistochemistry (IHC)-based molecular detection was performed for IDH-1, ATRX, Ki-67, EGFR and p53. A somatic glial tumor panel was performed by Massively Parallel Sequencing (Illumina) and analysed with NxClinical software (Bionano). SNP microarray (Illumina) was performed to confirm copy number abnormalities (CNAs). *Results:* IDH-1 or IDH-2 variants were present in 31.7% (n = 33/104) samples, with 13 of these also having an 1p/19q co-deletion. Of the IDH wildtype samples, 70% (n = 54/77) also had a trisomy 7/monosomy 10 profile, with 51.9% (n = 28/54) of these with EGFR amplification, and 98% (n = 53/54) with a TERT promoter variant. TP53 variants (n = 33/104), CDKN2A/B deletions (n = 56/104) and the BRAF *p.*(Val600Glu) variant (n = 4/104) was detected in 31.7%, 53.8% and 3.8% of samples respectively. *Conclusions:* 85/104 (82%) samples were able to classified based on molecular profile and histological features, indicating that is an effective diagnostic technique that facilitates integrated histological and molecular glioma classification.

Reverse Phenotyping Informing Variant Pathogenicity in Reproductive Carrier Screening

Cara Beck[1], Alison Archibald[1,2,3], Edwin Kirk[4,5,6], Nigel Laing[7,8,9] and Martin Delatycki[1,3,10]

[1]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia, [4]School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia, [5]NSW Health Pathology Randwick Genomics Laboratory, Sydney, NSW, Australia, [6]Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia, [7]Department of Diagnostic Genomics, PathWest Laboratory Medicine, Perth, WA, Australia, [8]Centre for Medical Research, University of Western Australia, Perth, WA, Australia, [9]Harry Perkins Institute of Medical Research, Perth, WA, Australia and [10]Bruce Lefroy Centre, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background/Aim: A particular challenge of variant classification in reproductive carrier screening is the need to assess variants in the absence of a proband with a phenotype. Familial segregation can provide additional evidence for or against pathogenicity, particularly for X-linked variants. The Australian Reproductive Genetic Carrier Screening Project (Mackenzie's Mission) screened 9107 couples for >1300 genes that underlie ~750 serious childhood onset conditions. We report on three X-linked variants, initially classified as Likely Pathogenic, that were found to segregate in unaffected males. *Methods:* Mackenzie's Mission methods and gene selection processes have been described previously. When a likely pathogenic variant was identified in an X-linked gene, genetic counselling included a discussion around testing male family members. If a male was identified with the variant, phenotypic assessment, including biomarker analysis where possible, was undertaken. *Results:* Likely Pathogenic X-linked variants IDS, COL4A5 and F8 were identified in multiple couples. Males in the families were tested and some were found to carry the variant without a significant phenotype. The male carrying the IDS variant had reduced iduronate-2-sulphatase levels with no clinical evidence of Hunter syndrome. Biomarker evaluation of males who carried the COL4A5 and F8 variants was normal, therefore ruling out Alport syndrome and hemophilia respectively. *Conclusions:* Segregation and reverse phenotyping provided additional information, and in some cases, reproductive reassurance to the couples. This approach will become more important as increased numbers of genes are included in expanded reproductive carrier screening.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Personalised Mental Health Care and how Pharmacogenomics Could Revolutionise Management in Australian General Practice: Case Study Discussions

Cristina Beer[1], Annalese Semmler[2], Fiona Rae[1] and Joanne Voisey[1]

[1]Centre for Genomics and Personalised Health, School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia and [2]School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia

The utilisation of precision medicine in clinical practice is a growing science that promises to better guide management, particularly in mental health care. One of the main tenets of precision medicine is genetic testing. Identifying genetic variation in key enzymes and proteins may impact a patient's response to medication. For example, identifying single nucleotide polymorphisms (SNPs), gene deletions or amplifications in CYP450 enzyme encoding genes that are responsible for the metabolism of medications, namely CYP2D6, CYP2C19, CYP2C9, CYP1A2, may help determine treatment response. Several organisations have established clinical guidelines for pharmacogenomic (PGx) testing, including The Clinical Pharmacogenetics Implementation Consortium (CPIC and The Dutch Pharmacogenetics Working Group (DPWG). These guidelines are being implemented across Europe, US, Canada, and Asia. However, pharmacogenomic testing, is currently underutilised in Australia as a management tool for mental health conditions in the clinical practice setting. SNPs in CYP450 genes are particularly useful in helping to guide response to medications as well as predict potential adverse reactions and interactions with other medications and possibly nutraceuticals, which are increasingly utilised in clinical practice. Actual case studies will be presented in a clinical practice setting, showing the clinical use and availability of genetic testing. How PGx may be utilised to assist in guiding medication choice and dosing will be discussed and how this could potentially revolutionise the way mental health conditions are managed.

Empowering Combined Pharmacogenomic and Monogenic Disease Analysis Using a Multi-Platform Approach

Steven Bentley[1], Sangavi Sivagnanasundram[2], Jacqui Montgomery[1], Holly McLean[1], Rachel Di Conza[1], Eleise Britt[1], Skyla Bowley[1], Jessica Silver[1], Jordan Lee[1], Matt Stevens[1], Lokman Pang[2], Karl Vaz[3], Stephanie Kuo[2], Susan Fisher[2], Gina McLachlan, Amy Clarke[4], Melanie O'Keefe[1], Melinda Zino[1], Christopher Noune[1], Linda Ciccarelli[3], Christy Atkinson[2], Michael Christie[2], Bryony Thompson[2] and Paul James[2]

[1]Australian Genome Research Facility, Melbourne, VIC, Australia, [2]The Royal Melbourne Hospital, Melbourne, VIC, Australia, [3]Austin Health, Melbourne, VIC, Australia and [4]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia

Background: The reducing cost of genomic analysis has improved the opportunity to provide personalised genomic information surrounding response to drug-based therapies. However, the cost to perform a 30X whole genome sequencing analysis on each patient is still prohibitive. As part of the Melbourne Genomics Health Alliance's multisite clinical change projects (CCP), this study aimed to develop an economic and robust workflow to facilitate monogenic disease analysis and identification of pharmacological actionable genetics variants. *Method:* Variant calls were generated from low coverage PCR-free whole genome sequencing, WGS-based imputation using Illumina DRAGEN (Glimpse), as well as genotyping using the Illumina Global Screening Array. These variants were then combined and used to call pharmacogenomic star alleles in 18 genes using PharmCAT and Illumina DRAGEN. Monogenic variants of interest were validated through Sanger sequencing. *Results:* The accuracy was determined by comparing the variant calls to 30X WGS samples. A reduction to 5x WGS was found to have an F1 score of 0.983 for SNVs and 0.592 for Indels. The pharmacogenomic star alleles calls were consistent between 30x and 5x coverage, except for HLA and CYP2D6. Additionally, there was an increased risk of uncalled haplotypes at lower depths. *Conclusions:* Low pass WGS, accompanied by imputation and array data provides a valid methodology to economically inform pharmacogenomic variants. However, caution around indels and uncalled haplotypes are warranted; additionally, complex genomic regions were not accurate.

Mainstreaming Cancer Genomic Testing: Acceptability, Efficacy, and Impact

Jennifer Berkman[1], Emily de Bortoli[1], Julia Steinberg[2], Tatiane Yanes[1] and Aideen McInerney-Leo[1]

[1]Frazer Institute, The University of Queensland, Dermatology Research Centre, Brisbane, QLD, Australia and [2]The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council NSW, Sydney NSW, Australia

Background/Objectives: A genetics workforce shortage and rapid expansion of cancer genomic testing has driven the development of mainstreaming models-of-care for genomic testing: specifically genetic counsellor-embedded (GEM) and upskilled-clinician (UPC) models. To determine the feasibility, acceptability, and cost-effective of mainstreaming in cancer settings we conducted a scoping review of the literature. *Methods:* Relevant records published in English between 2013-2023 were identified by searching PubMed using key terms covering three areas: cancer, genetics/genomics, and mainstreaming. *Results:* 37 articles (5 GEM; 32 UPC) across five cancer types were identified. In both models-of-care, testing uptake was >90% and referral/testing rates increased 1.2-6.7-fold, while the time from diagnosis to receipt of results decreased 1.5-6-fold. Although eligibility criteria varied, pathogenic variant detection rates were typically ≥10%. GEM model studies did not evaluate cost-effectiveness, physician attitudes or patient outcomes. UPC models were found to be cost-effective, primarily through reducing the number of genetics-related appointments. Physicians found the UPC model workload acceptable and reported improvements in knowledge and confidence. Patients' acceptance and satisfaction were universally positive and decisional satisfaction was high. Patient distress in the UPC model was low overall and comparable to traditional testing models and the continuity-of-care of the UPC model was appreciated. *Conclusions:* We concluded that mainstreaming cancer genomic testing is feasible, cost-effective, acceptable to cancer physicians and beneficial to patients, physicians, and the healthcare system. More studies are needed to capture the GEM model impacts and to directly compare the GEM and UPC models.

Reproductive Genetic Carrier Screening: Observations in the First Six Months Since the Introduction of a Medicare Rebate

Lisa Bickley and Melanie Smith

Victorian Clinical Genetics Services (VCGS), Murdoch Children's Research Institute, Melbourne, VIC, Australia

The Victorian Clinical Genetics Service was the first to offer reproductive genetic carrier screening in Australia, covering the three

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

most common recessive conditions: fragile X, cystic fibrosis and spinal muscular atrophy. RANZCOG and RACGP have long recommended carrier screening be offered to women in preconception and early pregnancy. From November 2023, the cost of testing has been subsidised by the Australian Government on the Medicare Benefits Schedule (MBS), enabling individuals and couples to determine their reproductive risk with no out of pocket expenses. Since the introduction of the Medicare rebate, a shift in referral numbers and demographics has been observed. Previous studies have determined access to screening inequitable based on socioeconomic status, with the removal of financial barriers we review the key demographics and carrier outcomes across 10,000 individuals. Our experience to date, the rate of preconception screening has improved from 31% to 46%, with 449 individuals identified as carriers (1 in 21) of at least one condition: 277 CF (62%), 159 SMA (35%), 13 FXS (3%) and 6 carriers of 2 conditions (1%). 8 partners were identified as carriers of the same disorder (6 CF, 2 SMA: 0.09% of individuals screened). Of the 8 increased risk couples identified, 6 were pregnant at the time of testing. 4 couples went on to have prenatal testing, identifying 3 fetal carriers (2 CF, 1 SMA) and 1 CF affected. Continued rates of referrals will enable more couples in broader socioeconomic backgrounds to be informed of their reproductive risk and pregnancy management options.

Pathogenic Biallelic Variants in *VPS52*, Encoding an Intracellular Trafficking Protein, Cause Impaired Brain Development

Sankalita Ray Das[1], Ruby Gummer[1], Rosie Sullivan[1], Austin Larson[2], Jennifer Friedman[3], Julie Jones[4], Naif A Almontashiri[5], Hanan Shamseldin[6], Fowzan Alkurya[6], Stephanie Hughes[1] and Louise S. Bicknell[1]

[1]University of Otago, Dunedin, Otago, New Zealand, [2]University of Colorado School of Medicine and Children's Hospital Colorado, Aurora, CO, USA, [3]University of California San Diego and Division of Neurology, Rady Children's Hospital, San Diego, CA, USA, [4]Greenwood Genetic Center, Greenwood, SC, USA, [5]Center for Genetics and Inherited Diseases, Taibah University, Madinah, Al Madinah, Saudi Arabia and [6]King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Background: Vacuolar protein sorting-associated protein 52 (VPS52) is a core protein subunit of both the Golgi-associated retrograde protein (GARP) and the endosome-associated recycling protein (EARP) complexes. Both are heterotetramers involved in the intracellular vesicle trafficking network in eukaryote cells. *Aim:* Confirm pathogenicity of variants identified in *VPS52* as a novel disease gene. *Methods:* Exome sequencing was followed by both molecular and zebrafish model experiments explored the pathogenicity of hypomorphic loss-of-function variants in *VPS52*. *Results:* Through exome sequencing, we discovered two affected sibs in a New Zealand family are compound heterozygous for variants in *VPS52*. Both affected sibs have microcephaly, seizures and developmental delay. Through international collaborations via Genematcher, we have identified a further seven families with biallelic variants, including four families from Saudi Arabia segregating the same missense variant. Affected cases have both neurological and non-neurological abnormalities, ranging from ventriculomegaly to microcephaly with arthrogryposis and cholestasis. Through studying patient fibroblasts and reporter cell models we confirmed that variants act in a loss-of-function manner to reduce VPS52 transcript or protein levels, with a subsequent cellular effect on complex stability, lysosomal levels and lysosomal localisation in the cell. Genome editing targeting *vps52* in a zebrafish model confirmed similar developmental effects. *Conclusions:* We have identified that *VPS52* is a novel disease gene, where biallelic variants act through a loss of function mechanism to disrupt intracellular trafficking. Our findings add further insight into the consequences of impaired vesicle trafficking, and the importance of this cellular function in brain development.

The Diagnostic Utility in Expedited Prenatal Exome Sequencing: Early Identification of Acrodystosis Type 2

Sunita Biswas[1], Abhi Kulkarni[1], Lucas Dejong[1], Shannon Le Blanc[2], Louise Cilento[2] and Christopher Barnett[2]

[1]SA Pathology, Genetics and Molecular Pathology, Adelaide, SA, Australia and [2]Women's and Children's Hospital, Paediatric and Reproductive Genetics Unit, Adelaide, SA, Australia

Background: A nonconsanguineous G1P0 couple with no significant family or medical history were referred to Clinical Genetics 2 in the setting of increased nuchal fold translucency (INFT) and growth restriction. Current literature suggests that the likelihood of a monogenic disorder in the setting of INFT is less than 2%; however, if the INFT persists and/or a second ultrasound abnormality is identified, this risk increases to 20%. In this family, expedited prenatal exome sequencing made the diagnosis of acrodystosis type 2 (OMIM 614613). *Aim:* Present the diagnostic utility of early prenatal exome sequencing, and discuss the diagnostic approach of variant curation in the setting of broad phenotypic information. *Methods/Case:* Microarray performed at 12 weeks gestation was normal, ruling out aneuploidy and copy number variation. The couple were counselled around the possibility of a monogenic disorder due to persistent INFT and growth restriction at 16 weeks, and consented to early trio whole exome sequencing from CVS derived DNA. *Results:* A heterozygous pathogenic PDE4D variant was identified, associated with autosomal dominant acrodystosis type 2. This result allowed the couple to consider and opt for termination. *Discussion:* This case demonstrates the powerful diagnostic utility in early identification of a pathogenic variant in the prenatal setting. Importantly, phenotypic markers of acrodystosis, such as brachydactyly and maxillary hypoplasia, are not evident by ultrasound until greater than 20 weeks gestation. This case illustrates an example of where additional abnormalities should generate a clinical suspicion for a monogenic disorder and thus prompt early genomic testing.

Understanding the Australian Public's Awareness of Pharmacogenomics

Richelle Breed[1,2], Joanne Voisey[2], Esther Lau[1,3], Yasmin Antwertinger[1] and Annalese Semmler[1]

[1]School of Clinical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia, [2]Centre for Genomics and Personalised Health, School of Biomedical Sciences, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia and [3]School of Pharmacy, University of Queensland, Brisbane, QLD, Australia

Background: Pharmacogenomics studies how a person's genes impact their likely response to medicines. Genetic variation can

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

result in altered therapeutic outcomes; for example, poor response, or adverse reactions to medicines. Identifying these variations early has the potential to optimise drug response. Despite this knowledge, pharmacogenomic implementation has been slow in Australian clinical practice. One major factor thought to contribute to this delay is the lack of public awareness and education about pharmacogenomics. Compared to international studies, knowledge of the Australian public's current understanding of pharmacogenomics is largely unknown. *Aim:* To explore current knowledge and perception of pharmacogenomics among the Australian public. *Methods:* A 54-item, mixed-method online survey asking participants for their thoughts on genetic testing and pharmacogenomics was distributed from November 2023 to March 2024. Recruitment was obtained through an Australian marketing agency and advertisement. Quantitative data was analysed using descriptive and inferential statistics, while qualitative data analysis was thematically analysed. *Results:* 853 participants completed the survey. Gender, age, or geographical location did not statistically correlate with prior pharmacogenomics awareness or knowledge. However, prior genetics education correlated with a statistically significant increase in pharmacogenomics awareness ($p \leq .001$). Interestingly, 83.2% ($n = 709$) of participants were unaware of the difference between direct-to-consumer and health-service-related genetic testing. A greater understanding of pharmacogenomics was recorded from those participants aware of the differences between the genetic testing services ($p \leq .001$). *Conclusions:* Overall, understanding of pharmacogenomics amongst the Australian population is lacking, highlighting the need for public education if pharmacogenomics implementation into Australian clinical practice is to be successful.

Introduction of Food Allergens to Infants With Inborn Errors of Metabolism

Rachel Brennan[1], Maureen Evans[1], Jordan Brockett[1], Angela Harris[1] and Vicki McWilliam[2,3]

[1]Department of Metabolic Medicine, The Royal Children's Hospital, Melbourne, VIC, Australia, [2]Allergy and Immunology Department, The Royal Children's Hospital, Melbourne, VIC, Australia and [3]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia

Background: Australasian Society of Clinical Immunology and Allergy (ASCIA) guidelines advise on food allergen prevention for infants. Compliance with these guidelines is challenging in metabolic disorders requiring protein or fat restrictions. Carer uncertainty regarding introduction of common food allergens and limited dietary options may result in avoidance during a key window of opportunity. Delayed introduction has been shown to increase the chance of developing a food allergy. *Aim:* To develop a practical resource for solids introduction compliant with ASCIA guidelines and within the constraints of a restricted diet. *Methods:* A literature review was conducted to investigate relevant evidenced-based practice and guidelines, in conjunction with expert consultation. *Results:* An evidenced-based resource guiding solids introduction containing common food allergens including type, amount, frequency, and duration of exposure was developed for restricted diets. *Conclusions:* The balance between risk and benefit of introduction of allergens based on predicted longer-term restriction is critical. In severe protein restrictions, introduction of some allergens may be impractical without comprising intake of other important foods. Furthermore, without their ongoing inclusion, this may lead to a higher risk of food allergy. Longer-term dietary restrictions required for metabolic control is unknown in the first year of life and may subsequently change over time with new treatments or clarity of phenotypic spectrum, confirming the need to mitigate the risk of food allergy development when possible.

Involving Consumers from Non-English-Speaking Backgrounds in Genomics Research: Pakistani Perspectives

Julia Broadbent[1,2], Keri Finlay[2,3], Isabella Sherburn[2,3], Zoe Fehlberg[2,3], Fiona Russo[4] and Stephanie Best[2,5]

[1]University of Melbourne, Melbourne, VIC, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Australian Genomics, Melbourne, VIC, Australia, [4]University of Southern Queensland, QLD, Australia and [5]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Partnering with consumers in research is a well-established method of creating higher quality, patient-focussed healthcare systems. Meaningful involvement is especially critical for consumers from non-English speaking backgrounds (NESB), whose underrepresentation in genetics services has contributed to unequal genomic healthcare access and outcomes. *Aim:* Our study aimed to explore perspectives of Australian consumers from NESBs, particularly Pakistani communities, regarding involvement in genomics research. *Methods:* Previously collected survey data — regarding perspectives towards consumer involvement in health research — were analysed via descriptive statistics. Survey findings informed focus group discussion which further explored barriers and enablers to involvement in genomics research for Pakistani consumers. Inductive content analysis was undertaken, and results were synthesised with survey findings. *Results:* A range of interlinked factors were identified from the survey ($n = 1155$) and focus group ($n = 3$) as influencing NESB consumers' involvement in genomics research. Barriers to involvement for Pakistani consumers included fear of judgement and being unaware of involvement opportunities and/or potential benefits of genomics research for their community. Factors supporting these consumers' involvement in genomics research included: researchers establishing reciprocal relationships with culturally diverse communities; clearly communicating research goals and outcomes; and consumers' lived experience and desire to help others in their communities. *Conclusions:* This study constitutes an initial step investigating influences and needs of Pakistani consumer partners in genomics research. Future research should explore which findings are applicable to consumers from other NESB communities. We hope our findings will help future genomics research to become more inclusive and consumer-focussed.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Aetiological Insights Into Young-Onset Colorectal Cancer Tumourigenesis Through Genomic Tumor Mutational Signature Profiling

Peter Georgeson[1,2], Eric J. Joo[1,2], Khalid Mahmood[1,2,3], Romy Walker[1,2], Mark Clendenning[1,2], Sharelle Joseland[1,2], Julia Como[1,2], Susan Preston[1,2], Natalie Diepenhorst[1,2], Julie Toner[1,2], Yen Lin Chu[1,2], Aaron L. Meyers[1,2], Evelyn Yang[1,2], Christabel Notowidjojo[1,2], Marci Chai[1,2], Alysha Prisc[1,2], Steven Gallinger[4,5,6], Robert Grant[4,5,6], Dylan E. O'Sullivan[7,8,9], Darren R. Brenner[7,8,9], Finlay Macrae[10,11,12], Christophe Rosty[1,2,13], Ingrid M. Winship[10,12], Mark A. Jenkins[2,14] and Daniel D. Buchanan[1,2,10]

[1]Colorectal Oncogenomics Group, Department of Clinical Pathology, The University of Melbourne, Melbourne, VIC, Australia, [2]University of Melbourne Centre for Cancer Research, Melbourne, VIC, Australia, [3]Melbourne Bioinformatics, The University of Melbourne, Melbourne, VIC, Australia, [4]Lunenfeld Tanenbaum Research Institute, Mount Sinai Hospital, The University of Toronto, Toronto, ON, Canada, [5]Ontario Institute for Cancer Research, Toronto, ON, Canada, [6]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada, [7]Department of Oncology, University of Calgary, Calgary, AB, Canada, [8]Department of Community Health Sciences, University of Calgary Cumming School of Medicine, Calgary, AB, Canada, [9]Department of Cancer Epidemiology and Prevention Research, Alberta Healthy Services, Calgary, AB, Canada, [10]Genomic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Melbourne, VIC, Australia, [11]Colorectal Medicine and Genetics, Royal Melbourne Hospital, Melbourne, VIC, Australia, [12]Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia, [13]Envoi Specialist Pathologists, Brisbane, QLD, Australia and [14]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia

Background: The incidence of young-onset colorectal cancer (YOCRC; diagnosed ≤50 years of age) is increasing in Australia and globally, the cause of which is unknown. *Aim:* We characterised the tumor mutational signature (TMS) landscape of YOCRC and young-onset-adenomas (YOAds) to identify the spectrum of mutational processes. *Methods:* Sporadic, mismatch repair proficient YOCRCs and YOAds from the ANGELS study (n = 85) and the Colon Cancer Family Registry (n = 110) underwent tumor and matched germline whole exome sequencing. Single base substitution (SBS) and indel (ID) TMS were calculated with COSMIC v3.2 definitions, with individual signatures considered present when observed at ≥10% within a tumor. *Results:* Of the 173 YOCRCs (mean age at diagnosis 37.8±7.8 years, 56.6% females), 17.3% were diagnosed between 18-30 yrs, 40.5% between 31-40yrs and 42.2% between 41-50 yrs with 31.8% located in the right colon, 38.7% left-sided and 28.9% rectal. The most prevalent TMS with associated known aetiologies were SBS1 (84.4%), SBS87 (53.2%), ID1 (63.6%) and ID2 (45.7%). For TMS without an associated or known aetiology, SBS89 (16.2%), SBS39 (5.2%), ID5 (31.2%) and ID4 (27.7%) were the most prevalent. SBS89 and ID5 TMS were enriched in YOCRCs between 18-30 yrs (p = .004) and located in the right colon (p = 0.024). SBS88, associated with colibactin DNA damage from *pks*$^{+}$*E.coli* bacteria, was enriched in YOAds compared with YOCRCs (p = 0.03). *Discussion:* A young and right-sided subset of YOCRC is characterised by mutational processes defined by SBS89 and ID5 but of unknown aetiology. YOAds demonstrated evidence of bacteria-related tumourigenesis. TMS profiling can stratify YOCRCs for further aetiological investigation.

Identification of Genetic Variants Causing Paediatric Cataract in Myanmar

Kathryn P. Burdon[1], Johanna L. Jones[1], Daisy Boardman[1], Khine Nweni[2], Franoli Edo[1], Isabelly M. Barros de Lima[1], Pakdhipat Lertsinpakdee[1], Soe Hlaing[2], Robert Casson[3,4], Ashwin Mallipatna[3,4], Ye Win[2], Bennet J. McComish[1], Naing Lin[5], James S. Muecke[3,4], Andy Griffiths[4], Martin Holmes[4] and Than Htun Aung[2]

[1]Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia, [2]Yangon Eye Hospital, Yangon, Myanmar, [3]Department of Ophthalmology, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia, [4]Sight For All, Adelaide, SA, Australia and [5]North Okkalapa General and Teaching Hospital, Myanmar

Background: Paediatric cataract is a rare disease. Known genes account for 50−70% of cases, but as low as 20% in some reports. *Aim:* To determine the genetic causes of paediatric cataract in children from Myanmar. *Methods:* Whole-exome sequencing was performed on DNA from saliva from 22 children with cataract from 20 families. A panel of 180 genes previously linked to cataract were screened for disease-causing variants as classified by the ACMG-AMP guidelines. A minigene splicing assay was performed to test alteration of splicing of a variant in *SLC7A8*. *Results:* Pathogenic or likely pathogenic variants were identified in 45% (9/20) of probands including pathogenic variants in *MIP, COL2A1, SLC7A8* and *PAX6* and likely pathogenic in *NHS, GJA8, GJA3, CRYGC.* Most of these are well-known cataract genes but *COL2A1* and *SLC7A8* are rarely reported. The *COL2A1* variant was present in a child with a phenotype consistent with Stickler Syndrome and the *SLC7A8* variant was co-inherited with a second variant (of uncertain significance), consistent with the reported recessive inheritance pattern. We also identified two variants of uncertain significance in *CRYBB2* and one in *GJA3* that are likely to be important, for a maximum diagnostic rate of 12/20 probands (60%). *Conclusions:* This is the first study to examine the genetic aetiology of paediatric cataract in Myanmar. We report the genetic cause of cataracts in 45−60% of children for a genetic diagnostic rate comparable to reports in other populations and provide additional support for a role for *COL2A1* and *SLC7A8* in paediatric cataract.

Mainstreaming Clinical Cardiovascular Genetics into Primary Care

Karen Birkenhead[1,2], David Sullivan[1,3], Madeline Calder[4], Catherine Spinks[4], Cameron Hemmert[1] and Mitchell Sarkies[1,2]

[1]University of Sydney, Sydney, NSW, Australia, [2]Sydney Health Partners, Sydney, NSW Australia, [3]NSW Health Pathology, Sydney, NSW, Australia and [4]Institute of Precision Medicine and Bioinformatics, Sydney, NSW, Australia

Background: Advances in clinical cardiovascular genetics emphasise the importance of integrating genetic medicine across healthcare systems, including general practice. Primary care presents an ideal environment to offer equitable and efficient access to genetic services. Familial hypercholesterolaemia (FH) is a Tier 1 genomic application supported by strong evidence-based guidelines and represents a health condition that can be successfully diagnosed and managed in general practice. *Aim:* To describe a process for tailoring a primary-tertiary shared model of care for FH so that it works locally.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Methods: Data were collected through semi structured interviews (n = 10) with local stakeholders in New South Wales. Interviews gathered feedback on how to tailor a national shared-care model for FH to local needs. Reflexive thematic analysis was used to analyse interview transcripts. *Results:* Feedback from interviews identified challenges to, and key components needed, to implement the model. Challenges included insufficient knowledge of genetic testing, complex family dynamics, and time constraints. Enablers included providing detailed guidelines for conducting genetic testing, resources for GPs and patients, and access to lipid specialist support when needed. Overall, participants felt the model was acceptable and could be successfully implemented provided key supports were in place to assist GPs. Based on these results a generic blueprint for integrating genetic testing for other conditions into primary care was developed, using FH as an exemplar condition. *Conclusions:* This study describes a process for tailoring a primary-tertiary shared model of care for FH to local context, applicable across a range of genetic conditions.

Views of Reproductive Genetic Carrier Screening Participants Regarding Screening for Stargardt Disease in Australia

Ana Cano-Gomez[1], Lucinda Freeman[1,2], Kris Rogers[1], Lisa Dive[1], Martin Delatycki[3,4] and Edwin Kirk[2,5]

[1]University of Technology Sydney, Graduate School of Health, Sydney, NSW, Australia, [2]UNSW Sydney, School of Women's and Children's Health, Faculty of Medicine, Sydney, NSW, Australia, [3]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [4]Murdoch Children's Research Institute, Melbourne, VIC, Australia and [5]Sydney Children's Hospital, Randwick, Centre for Clinical Genetics, Sydney, NSW, Australia

Background: Stargardt disease is a genetic condition that causes progressive and irreversible vision loss in children, adolescents and young adults. Due to its genetic complexity, uncertain genotype-phenotype relationship in many cases, and variable onset and severity of the condition, the inclusion of Stargardt disease is challenging for reproductive genetic carrier screening (RGCS). There is also a lack of research on how people perceive vision loss caused by Stargardt disease within the context of RGCS. *Aim:* As part of the Mackenzie's Mission program, this study explored the views of RGCS participants regarding the inclusion of the gene associated with Stargardt disease in RGCS. *Methods:* Online surveys consisting of 13 attitudinal questions about Stargardt disease were sent to 1826 individuals who received a low-chance RGCS result. A total of 1116 questionnaires were received and analysed (participation rate 61%). *Results:* Most participants (80%) considered Stargardt disease a serious health condition with significant impact on quality of life. The majority (91%) would want to be screened for Stargardt disease, and 75% would consider using reproductive options to avoid having a child with this condition. Most participants (90%) believe Stargardt disease should be included in RGCS, and 83% agreed that couples at increased risk should have access to reproductive options. *Conclusions:* Most participants considered that vision loss due to Stargardt disease is a serious health condition and it should be included in the screening panels. Moreover, the results suggest that most participants would take steps to prevent the birth of a child with this condition.

Patient/Parent and Donor Concerns About Participating in IVF or Other ART Services

Will Carr[1,2], Eloise Uebergang[1], David Thorburn[1,3,4] and John Christodoulou[1,3,4]

[1]Brain and Mitochondrial Research Group, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Australian Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia and [4]Victorian Clinical Genetics Services, Melbourne, VIC, Australia

Background: In vitro fertilisation (IVF) and other assisted reproductive technologies (ART) are procedures used to help people with fertility challenges to conceive. In recent years, uptake of these technologies has increased. The concerns and priorities of individuals undergoing treatments have mostly been recorded discretely by specific cohort, rather than broadly across populations. *Aim:* To identify the key concerns of patients/parents and donors participating in IVF or other ART services, as captured in the literature. *Methods:* The Medline database was searched for any eligible papers published between 2018-2023. Identified papers were screened for duplicates and relevance. Included papers were read in full and any identified parent/patient/donor concerns were tabulated and categorised. *Results:* 26 papers were included in the final review. Key concerns identified included Psychosocial Needs, Ethical Concerns, Relationship Impacts, Functional and Theoretical Concerns during Treatment, Financial Concerns, and Concerns about Care for Specific Cohorts (LGBTQIA+, Religious, Rural/Regional, Male Partner, and Disease-Specific). There were strong messages that participants want clear, comprehensive, and timely information about the treatment process, as well as easy access to psychosocial support. Some prominent concerns pertained to worries participants had about the way they would be viewed by their communities; friends and family, religious communities, colleagues, or the wider society. *Conclusions:* This informal review indicated that patient/parent and donor concerns are varied, but that there are some strong themes present in the literature (e.g., psychosocial needs). Based on the findings of this review, a formal scoping review is being conducted on the same topic.

Assessing the Unmet Needs of Genomic Testing in Australia: A Geospatial Analysis

Sarah Casauria[1,2], Felicity Collins[3,4], Susan M. White[1,5,6], Paul Konings[7], Mathew Wallis[8], Nicholas Pachter[9,10,11], Julie McGaughran[12,13], Christopher Barnett[14] and Stephanie Best[1,2,5,15,16]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Australian Genomics, Parkville, VIC, Australia, [3]University of Sydney, Sydney, NSW, Australia, [4]Royal Prince Alfred Hospital, Sydney, NSW, Australia, [5]University of Melbourne, Melbourne, VIC, Australia, [6]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [7]Australian National University, Canberra, ACT, Australia, [8]Tasmanian Clinical Genetics Service, Hobart, TAS, Australia, [9]King Edward Memorial Hospital, Perth, WA, Australia, [10]University of Western Australia, Perth, WA, Australia, [11]Curtin University, Perth, WA, Australia, [12]Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia, [13]The University of Queensland, Brisbane, QLD, Australia, [14]South Australian Clinical Genetics Service, Adelaide, SA, Australia, [15]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia and [16]Victorian Comprehensive Cancer Centre, Melbourne, VIC, Australia

Background: The role of genomic testing in rare disease clinical management is growing. However, inequitable uptake of testing exists

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

due to geographical socioeconomic factors. Despite this, a geographical evaluation of genomic testing access across Australia has not been undertaken. *Aim:* To visualise the geospatial distribution of genomic testing nationally and compare testing distribution across varying remoteness and socioeconomic areas. *Methods:* We requested patient postcodes, age, and test type from genomic testing records from seven NATA-accredited laboratories for a 6-month period between August 2019 and June 2022. Number of tests per postcode were aggregated to Local Government Areas (LGAs) and visualised geospatially. Data were further aggregated to Remoteness Areas and Socio-Economic Index for Areas (SEIFA) quintiles for exploratory analysis. *Results:* 11,708 genomic testing records were collected and aggregated to 547 LGAs for analysis. The median age at testing was 7.0 years (IQR 3.0−25.0). Most tests were microarray-based (n = 8186, 69.9%). The median number of tests per LGA was 5.4 (IQR 1.0−21.0). The number of tests showed a negative correlation with remoteness (r = -0.516, p = 0.005), and a positive correlation with SEIFA quintiles (r = 0.288, p = 0.020). The highest rate of testing per 100,000 populations was observed in Remote areas (58.8) and lowest in Very Remote areas (31.3). Additionally, the rate was highest in the 40−59% SEIFA quintile (58.7) and lowest in the 80−100% quintile (38.3). *Conclusions:* Our findings establish a foundation for ongoing assessment of genomic testing accessibility, and highlight the necessity for outreach strategies to improve access for patients in remote or low socioeconomic areas.

Determining the Optimal Number of Genes for Equitable, Pan-Ancestry Opportunistic Genomic Screening

Alison Chen[1,2,*], Mia J. Gruzin[1,2,*] and Leslie Burnett[1,2,3]

[1]Garvan Institute of Medical Research, Sydney, NSW, Australia, [2]School of Clinical Medicine, UNSW Medicine and Health, St Vincent's Clinical Healthcare Campus, Sydney, NSW, Australia and [3]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

*These authors contributed equally to this work.

Background: Opportunistic genomic screening (OGS) involves screening for secondary findings (in addition to, or without need for, a primary indication for genetic testing). OGS informs individuals of their risk of developing specific actionable inherited conditions, enabling informed decision-making to avoid, monitor, or prepare for this risk. The US Centers for Disease Control and Prevention (CDC) recommend inclusion of three conditions (10 genes) for population-scale OGS. However, restricting panels to only three conditions may not equally benefit different ancestry groups. *Aim:* We developed a list of prioritised genes and conditions for OGS that considers disease incidence and variant prevalence in genetic ancestry groups, to ensure screening is effective across diverse populations. *Methods:* Using the ACMG v3.2 Secondary Findings list (n = 81 genes), we modeled the impact of secondary finding screening across ancestry groups. We calculated variant and gene allele frequencies for ClinVar pathogenic (P/LP) variants using gnomAD v4.1, constructing and modeling the performance of synthetic OGS panels. *Results:* While the CDC-recommended conditions provide utility in many ancestry groups, adjusting OGS to account for differences between genetic ancestry groups modifies efficacy and equity. Panels were constructed by ranking genes across pan-ancestry groups correcting for targeted ancestry panels drawn from standard databases, which overrepresent European genomes. We defined OGS panel compositions achieving 90%, 95% and 99.7% yield. *Conclusions:* OGS test design requires considering performance across pan-ancestry populations, to ensure relevance and equity. Our approach defines optimal OGS composition, providing a framework to develop OGS programs.

Ataxia-Telangiectasia: Treating Mitochondrial Dysfunction With a Novel Form of Anaplerosis (A-T C7)

Sophie Manoy[1], Matthew Lynch[1,3,7], Peter Sly[3], Claire Wainwright[3,4], Ernst Wolvetang[6], John Feenstra[4,8], Jason Dowling[9], Robert Ware[10], Adam Vogel[11], Kahn Preece[12], Tania Zappala[13], Shaun Dai[3,14], Ann Webber[14], Sara Jose[16], Magtouf Gatei[16], Goutham Subramanian[16], Abrey Yeo[16], Bowen Xin[9], Maharshi Patel[10], Nicoletta Sandona[2], Peter Lewindon[3,15], Martin Lavin[6,16] and David Coman[1,4]

[1]Department of Metabolic Medicine, Queensland Children's Hospital, Brisbane, QLD, Australia, [2]Department of Paediatrics, Wesley Medical Research, Brisbane, QLD, Australia, [3]Child Health Research Centre, Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia, [4]School of Medicine, Griffith University, Gold Coast, QLD, Australia, [5]Department of Respiratory and Sleep Medicine, Queensland Children's Hospital, Brisbane, QLD, Australia, [6]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, Brisbane, QLD Australia, [7]Neurosciences Department, Queensland Children's Hospital, Brisbane, QLD, Australia, [8]Department of Adult Respiratory and Sleep Medicine, Wesley Medical Research, Brisbane, QLD, Australia, [9]Australian E-health Research Center, CSIRO, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia, [10]Biostatistics, Bioinformatics and Epidemiology, Menzies Health Institute Queensland, School of Medicine and Dentistry, Griffith University, Brisbane, QLD, Australia, [11]Speech Pathology and Audiology, The University of Melbourne, Melbourne, VIC, Australia, [12]Department of Immunology and Allergy, John Hunter Children's Hospital, Newcastle, NSW, Australia, [13]Department of Paediatrics and Dermatology, Queensland Children's Hospital, Brisbane, QLD, Australia, [14]Department of Ophthalmology, Queensland Children's Hospital, Brisbane, QLD, Australia, [15]Department of Gastroenterology and Hepatology, Queensland Children's Hospital, Brisbane, QLD, Australia and [16]University of Queensland Centre for Clinical Research, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia

Background: Ataxia-telangiectasia (AT) is marked by neurodegenerative cerebellar ataxia, lung disease, immune deficiency, and cancer. AT cells have mitochondrial dysfunction, via defective endoplasmic reticulum-mitochondrial connectivity through IP3R1-GRP75-VDAC1 (Ca^{2+} homeostasis), and mitochondrial fusion, that are corrected by heptanoate. *Aim:* To investigate association between triheptanoin dose and mitochondrial dysfunction in respiratory epithelial cells. *Methods:* We performed a randomised placebo-controlled dose-escalation Phase 2A/B treatment trial of triheptanoin (C7, Ultragenyx) (NCT04513002). Participants were assessed bi-monthly for 12-months. Doses investigated were 0%, 10%, 20%, 35% of calculated caloric intake. The placebo was medium chain triglycerides. The primary outcome was percentage cell death. Secondary outcomes were neurofilament light chain (Nfl) and ataxia severity, measured using the SARA and ICARS rating scales. *Results:* 31 participants were assessed on 188 occasions (87% of expected). Mean (*SD*) percent cell death dropped from 57.0 (13.3) at baseline to 14.7 (8.9) at 12 months. After adjusting for study month, 10%, 20% and 35% C7, compared to placebo, decreased mean percent cell death by 7.7% (95% CI [3.4, 12.0]), 12.4 (95% CI [7.1, 17.7]) and 9.7 (95% CI [4.6, 16.0]) respectively. Clinical ataxia ratings decreased from 22.6(8.4) (SARA) and 57.4(21.7) (ICARS) at baseline to 20.0 (8.3) and 48.2 (23.2) at 12 months (mean difference: 95% CI –1.2 [-2.3, -0.1] and -5.7 [-8.3, -3.1]). 10%, 20% and 35% C7 doses, compared to placebo, led to Nfl differences of -21.5 (95% CI [-34.9, -8.1]), -27.4 (95% CI [-44.4, -10.5]) and -29.8 (95% CI [-49.9, -9.8]) respectively. *Conclusions:* We have previously demonstrated mitochondrial dysfunction in AT cells that were corrected in vitro and have now demonstrated improvements in vivo. Further Phase 3 studies are required to assess efficacy.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Cell and Gene Therapy: Supporting Patients and Carers in informed decision making and consent

Nicholette A. Conway[1,2] and Emma Bonser[2]

[1]Pavilion Consulting Pty Ltd and [2]Genetic Alliance Australia

Background: The decision to undergo cell or gene therapy or participate in a clinical trial for such therapies is a complex and deeply personal one for patients/ parents of children with chronic or life-threatening conditions. *Aim:* This presentation aims to discuss the guidance and support that patients need from their clinicians and caregivers as they navigate the complex landscape of cell and gene therapies and clinical trial participation. *Method:* This presentation explores key considerations for patients facing this difficult decision-making process. From gaining an understanding of the therapy being offered including potential benefits, and associated risks and uncertainties involved, considering themselves or their child/ren treatment goals and quality of life priorities. Additionally, patients need understand the design and objectives of clinical trials and the impact of their health outcomes, and in some cases consider the broader family, community and societal impacts. In many cases, the financial implications of accessing care and ongoing support is just as complex as the therapy decision. *Result:* A structured approach to consultation with healthcare providers, which includes: education on the therapy, translation into current clinical practice and care, governance and regulatory requirements, professional practice and support from their network essential in navigating this decision-making process. *Conclusion:* Ultimately, patients should feel empowered to make informed decisions that align with their individual circumstances, values, and preferences.

Utility of Genomic Testing in Children, Adolescents, and Young Adults: A Scoping Review

Emily DeBortoli[1], Ella McGahan[1], Tatiane Yanes[1], Jennifer Berkman[1], Noemi Fuentes-Bolanos[2,3,4], Vivienne Milch[5,6], Julia Steinberg[7] and Aideen McInerney-Leo[1]

[1]The University of Queensland, Frazer Institute, Dermatology Research Centre, Brisbane, QLD, Australia, [2]School of Clinical Medicine, University of New South Wales Sydney, Sydney, NSW, Australia, [3]Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia, [4]Children's Cancer Institute, University of New South Wales Sydney, Sydney, NSW, Australia, [5]Cancer Australia, Sydney, NSW, Australia, [6]Caring Futures Institute, Flinders University, Adelaide, SA, Australia and [7]The Daffodil Centre, The University of Sydney, a joint venture with Cancer Council New South Wales, Sydney, NSW, Australia

Background: Genomic testing can inform the diagnosis and personalise management of cancers in children, adolescents, and young adults (CAYA). Few studies have comprehensively evaluated the diagnostic and clinical impact of genomic testing in CAYA cancers. *Methods:* This scoping review explored international evidence on the clinical utility and impact of genomic testing in CAYA cancers. Relevant records published between 2017–2024 were identified by searching PubMed. *Results:* Forty-eight studies (30 original articles; 18 reviews) were identified, most of which focused on advanced cancers. Approximately 16–18% of CAYAs with cancer carry a pathogenic germline variant, where 40% are de-novo. Such variants can guide treatment selection, especially those in DNA repair genes. Somatic pathogenic variants, predominantly copy number alterations or structural rearrangements, inform diagnosis in up to 85% of CAYA primary cancers. Between 22–69% of patients have a somatic variant with a matched therapy, but only one-third receive the genomic-guided recommendation, predominantly due to declining patient condition. Results of limited studies to date suggest better response and survival rates in individuals receiving matched therapies as compared to standard-of-care or those receiving unmatched therapies. Circulating tumor DNA analysis was also sensitive and specific in most CAYA cancers and found to have high concordance with tumor profiling. *Conclusions:* Genomic testing of CAYA cancers is feasible and identifies germline and somatic variants capable of informing diagnosis, prognosis, treatment selection, and risk management strategies. Further research is needed on response rates to genomic-guided treatments and to translate the multiple applications of CAYA cancer genomic testing into routine practice.

Leveraging a Genetic Counselling Community of Practice to Support Mainstreaming in Medical Specialties

Trang Do[1,2,3], Melissa Martyn[1,2,3], Belinda McClaren[1,2,3], Alison McEwen[4] and Clara Gaff[1,2,3]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia, [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia and [4]Graduate School of Health, University of Technology Sydney, NSW, Australia

Background: As genetic counsellors (GC) increasingly embrace the opportunity to work in medical specialties, they are often met with distinct challenges when positioned outside of clinical genetics departments. *Aim:* We established a Community of Practice (CoP) for mainstream GCs in metropolitan Melbourne with meetings held fortnightly with an experienced facilitator and evaluated its impacts on participants. *Methods:* As the second phase of a larger study exploring the views and experiences of mainstream GCs, this study was guided by socio-cultural learning theories and the Promoting Action on Research Implementation in Health Services (PARIHS) framework. We conducted qualitative interviews with all 13 GCs eligible for the study due to their funded mainstream role and participation in the CoP and maintained discussion logs of over 20 CoP sessions. Using thematic analysis, we identify four overarching themes that encapsulate the diverse impacts of participating in the CoP. *Results:* CoP members felt supported and empowered, as they could connect with other GCs working in similar roles, received emotional and practical support, and developed a sense of a community. The CoP enabled continuous learning and professional development. In addition, participants acknowledged that the CoP contributed to improving their mainstream practice, from solving complex problems to facilitating their collaboration with nongenetic specialists. The CoP served as a safe space for critical reflective practice, helping participants find validation in their current role and shape their vision for future genetic counselling profession. *Conclusions:* Our evaluation demonstrates the benefits of a CoP for healthcare professionals transitioning to new working areas.

Cultivating Interprofessional Collaboration to Drive Genomic Change

Trang Do[1,2,3], Melissa Martyn[1,2,3], Belinda McClaren[1,2,3], Alison McEwen[4] and Clara Gaff[1,2,3]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia, [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia and [4]Graduate School of Health, University of Technology Sydney, NSW

Background: The growing demand for genomic healthcare has created opportunities for collaboration between genetic and nongenetic

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

healthcare professionals (HCPs) to mainstream genomics in patient care. *Aim:* In this study we examined the nature and relational strategies inherent in the interactions between genetic counsellors (GCs) and nongenetic HCPs when working together in medical specialties. *Methods:* This ongoing qualitative study deployed interviews with 13 GCs and 5 nongenetic HCPs involved in the delivery of innovative models of providing genomics in Australia. Data analysis was guided by Relational Theory and the Promoting Action on Research Implementation in Health Services (PARIHS) framework. *Results:* Exchanges between GCs and non-genetic HCPs occurred in a range of formal and informal settings, including multidisciplinary clinic meetings, patient co-counselling appointments, education sessions, daily in-person conversations, or virtual communication via emails or a phone support line. GC support in the specialist clinics was well received among nongenetic HCPs, because it improved their understanding of the value of genomics for patient care and facilitated their management of genomic testing results. GCs reported facing multiple challenges, notably, tension arising from differentiated views and practice, and the feeling that their expertise was 'under-utilised' in the specialties. To cope with challenging situations, GC participants adopted diverse relational strategies, for instance, increasing their physical presence in the clinics, being creative with informal engagement activities, negotiating professional boundaries, and tailoring their work to align with local needs and contexts. *Conclusions:* Implementing healthcare innovations increasingly requires the involvement of multidisciplinary groups, hence understanding interprofessional can enhance successful implementation.

Genetic Counselling Challenges in Precision Oncology

Bridget Douglas[1,3,4], Skye MacKay[1,3], Meg Pointon[1], Shuang Liang[1,3], Frank Lin[1,2,3], David Goldstein[1,2], Natalie Taylor[1,3], Mandy Ballinger[1,2,3], Kathy Tucker[1,3,4], Rachel Williams[3,4] and Milita Zaheed[1,2,3,4]

[1]Precision Care Clinic, Prince of Wales Hospital, Sydney, NSW, Australia, [2]Omico, Sydney, NSW, Australia, [3]Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia and [4]Hereditary Cancer Clinic, Prince of Wales Hospital, Sydney, NSW, Australia

Background: Tumor molecular profiling is increasingly sought to guide therapy in patients with advanced cancer. This may identify clinically actionable potential germline variants (PGV), with implications for family members. This 'genome first' approach in the newly launched national Precision Care Clinic (PCC) is an alternate pathway to conventional clinical criteria-based genetic testing, leading to unique challenges for patients and clinicians. *Aim:* Discuss genetic counselling challenges in germline validations in an advanced cancer setting. *Methods:* Advanced cancer patients with PGV identified on tumor profiling are referred to the PCC for assessment. Genetic counselling is provided pre and post NATA accredited germline testing with follow-up to facilitate cascade testing. *Results:* Australia-wide, 21 patients have been seen for PGV in 12 high-utility genes. These patients were seen long after initial diagnosis, with expected poor prognosis. Rapport and relationship building at this stage of care were challenging. As a national clinic, without established connections with the referring oncologists, it was difficult to be updated on changes in clinical status to active palliation. Variants were confirmed as germline in five patients (*BRCA1, BRCA2, PALB2, BRIP1*) and somatic in four (*TP53, BRCA2, MLH1, MSH2, PMS2, PTCH1*). Patient response varied from gratitude to distress, searching for meaning and implications for offspring as they faced their mortality. The time taken from sample collection to results further exacerbated distress and delayed closure. *Conclusions:* Tumor profiling is a valuable service for families of patients with advanced cancer; however, the possibility of PGV in this context presents challenges to genetic counselling.

Molybdenum Cofactor Deficiency: A Case Report Highlighting Rapid Diagnosis Using Urine Metabolic Screen By Tandem Mass Spectrometry

Mary Eggington[1], Joy Lee[1], Abisha Srikumar[1], Kai Mun Hong[1], Isabelle Adant[2], Sophie Newman[3], Oliver Heath[2] and James Pitt[1]

[1]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Department of Metabolic Medicine, The Royal Children's Hospital, Melbourne, VIC, Australia and [3]Neonatal Intensive Care Unit, The Royal Children's Hospital, Melbourne, VIC, Australia

Background: Molybdenum cofactor (Moco) deficiency (MoCD) is rare with its severe form presenting in neonatal/early infancy with refractory seizures, hypotonia, apnea and feeding difficulties. Biallelic pathogenic variants in one of four genes involved in molybdenum synthesis (*MOCS1*, *MOCS2, MOCS3* and *GPHN*) result in the loss of sulphite oxidase, one of the molybdenum dependent enzymes, causing accumulation of toxic metabolites. MoCD has three types (A, B or C) with type A being the commonest form and amenable to treatment if diagnosed expeditiously. *Aim:* We report a case of MoCD type A in a neonate who developed apnea and refractory seizures on Day 4 of life. We highlight the importance of routine urine metabolic screening by tandem mass spectrometry (UMSMS) in the workup of patients with severe but non-specific neurological symptoms. *Method*: Targeted UMSMS was carried out via flow injection cell analysis in negative and positive ion mode with multiple reaction monitoring. *Results:* UMSMS showed decreased uric acid, increased S-sulphocysteine, xanthine and piperidine-6-carboxylic acid. Plasma cystine was undetectable with low plasma uric acid <0.03 mmol/. (RR 0.13-0.39) These results are diagnostic of a molybdenum cofactor deficiency. Trio whole genome sequencing identified a homozygous pathogenic variant in the *MOCS1* gene confirming MoCD type A. *Conclusion:* Routine UMSMS provided a robust and rapid result in the diagnosis of MoCD. It also facilitated the genomic variant prioritisation process that helped in MoCD subtyping. More importantly, the rapid availability of UMSMS results was instrumental in initial family counselling about prognosis and potential available treatment options.

Case Management in Molecular Genetics Pathology Lab Using a Database Application

Rahul Krishnaraj[1], Gladys Ho[1,2] and Bruce Bennetts[1,2]

[1]Sydney Genome Diagnostics, Western Sydney Genetics Program, The Children's Hospital at Westmead, Sydney, Australia and [2]Specialty of Genomic Medicine, Faculty of Medicine and Health, University of Sydney, Sydney, Australia

Background: Pathology genetic tests have multiple data workflows for each test, including benchwork and analytical pipelines spanning across different locations. Tracking and managing cases have become more complex and exhaustive than ever. Existing electronic medical record software for genetic labs are designed to be a clunky data storage solution rather than a lean workflow management tool. Prioritising work, managing case turnaround times, and preventing case mishandling is laborious without a dedicated application. Considering these requirements, an in-house case management tool that allows staff to manage cases concurrently is beneficial. *Aim:* To review the use of a customised scalable web database application that

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

tracks case workflow and allows for role-based data analysis. *Methods:* An application developed using MySQL, PHP, JavaScript stack and implemented in lab for case management. *Results:* Implemented since 2017, the database application has led to better case management, automated workflow, and low case transcription errors. 90% of the cases in the lab are managed through the application and includes massively parallel sequencing, Sanger sequencing and prenatal case management. The application has also contributed to data extraction of testing information for clinicians, researchers and in automating variant submission to Shariant and Clinvar. *Discussion:* The database application has led to automating key process in workflow management, reporting and has enhanced efficiency, data integrity, quality control, security, and data sharing capabilities for the laboratory. In addition, useful workload reports have helped to dynamically make business decisions and resource allocation that impacted positively to the operations of the lab.

Clinicians' Perceived Acceptability, Appropriateness, and Feasibility of Providing Additional Findings as Part of Routine Practice

Stephanie Best[1,2,3], Zoe Fehlberg[1,2], Marlena Klaic[3,4] and Zornitza Stark[1,5]

[1]Australian Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]The University of Melbourne, School of Health Sciences, Melbourne, VIC, Australia, [3]Department of Health Services Research, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [4]The Royal Melbourne Hospital, Allied Health Department, Melbourne, VIC, Australia and [5]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: Providing additional findings analysis from existing genomic data is not routine clinical practice in Australia. An understanding of implementation outcomes relating to clinician acceptability, appropriateness, and feasibility may be essential to realising adoption of practice. *Aim:* To explore clinicians' perceptions of acceptability, appropriateness, and feasibility of providing additional findings. *Methods:* A sequential exploratory mixed-methods approach was employed with datasets integrated during interpretation. We surveyed genetic counsellors and clinical geneticists pre and post implementation of an additional findings programme using validated measures for acceptability, appropriateness, and feasibility. Follow-up interviews explored influences on clinicians' perspectives of the three implementation outcomes. Quantitative data were analysed descriptively, and qualitative data followed deductive and thematic analysis approaches to categorise themes. *Results:* Overall, the survey results (pre $n = 53$ and post $n = 40$), showed borderline mean scores with variable range for each outcome and little post implementation change observed. When integrated with the interview data ($n = 14$), our findings suggest that the necessary prerequisites for implementation are challenged by interrelating factors of acceptability, appropriateness, and feasibility. Five themes were identified: 'possible utility versus resourcing and clinical practice impacts', 'equity in service provision versus resourcing', 'integration into workflows versus resourcing and consumer centeredness', 'acceptability in relation to prior experience', and 'organisational boundaries and resourcing'. *Conclusions:* Insights on clinicians' perceptions of acceptability, appropriateness, and feasibility of providing additional findings can inform future implementation efforts. Implementation strategies that focus on these implementation outcomes may improve the adoption of additional findings into routine practice.

The Science Within Us: A School-Based Program to Build Genetic Literacy in Students and Teachers

Hollie Feller[1], Simone Darling[2,3], Sarthak Ghandi[2], Rachel Smith[2], Katy Anderson[2], Monica Ferrie[1], Arena Nillson[1], Taylen Furness[1] and Carter Hissam[3]

[1]Genetic Support Network Victoria, Melbourne, VIC, Australia, [2]Genetic Support Network Victoria, Melbourne, VIC, Australia, [3]Genetic Support Network Victoria, Melbourne, VIC Australia and [4]Centre for Community Child Health, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: Genomic medicine requires public-expert knowledge transfer to facilitate the uptake of genomics in clinical care. Knowledge transfer to children/adolescents is of interest given they will be faced with genomics medicine throughout life. Schools as universal platforms provide an opportunity to shape genetic literacy for youth while achieving significant reach in a cost-effective way. *Aim:* To increase youth and teacher genetic literacy, generate empathy, and promote social inclusion for young people with genetic health variation through a school-based program. *Methods:* Needs analysis: A literature review was conducted to understand the benefit of genomics teaching resources and best method of delivery. Co-design and consultation: Stakeholders were consulted throughout the development of this school-based program to ensure the needs of teachers and youth were met. Development: Findings from needs analysis and codesign, directed science educators to create year-level specific genetics content, aligned with the national curriculum. Storytelling was used to convey genetic human experiences. Evaluation of feasibility and impact: A mixed methods pilot in 2024 will evaluate classroom use and impact in a sample of Victorian schools. *Results:* Genetic Support Network Victoria developed the Science within Us (SWU), a curriculum-aligned genetic literacy program for 10–18-year-olds that leverages experiential learning through interactive modules and case studies. *Conclusions:* SWU was developed in partnership with people with lived experience and their carers. It is intended to provide relevant evidence-based content in an accessible and engaging format. The evaluation will be critical for demonstrating feasibility, usability, and impact to support national scaling of the program.

Bravo Automation of Agilent Avida Targeted Enrichment for High-Throughput Detection of Genomic Alteration and DNA Methylation

Ashraf Wahba[2], Daniele Belluoccio[1], Tony Ho[2], Sarah Johns[2], Aswati Aravind[2], Heng Wang[2], Neelima Mehendale[2], Gilbert Amparo[2], Khine Win[2], Manuel Gomez[2], Margherita Corioni[2], Michael Ruvolo[2], Kyeong-Soo Jeong[2], Grace Zhao[2] and Douglas Roberts[2]

[1]Diagnostics and Genomics Group, Agilent Technologies Australia Pty Ltd., VIC, Australia and [2]Diagnostics and Genomics Group, Agilent Technologies Inc., CA, USA

Background: Current genomic and epigenomic profiling of cancer tissue DNA or cfDNA (cell-free DNA) in liquid biopsy relies upon separate, time- and sample-consuming technologies for somatic variant detection or methylation analysis. Here we describe workflow

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

and performance of the Agilent Bravo automated liquid handling platform with the Agilent Avida targeted enrichment solution for somatic variant and methylation profiling. This solution can effectively analyse low-input tumor DNA or cfDNA samples. The 'Avida-Duo' workflow enables highly sensitive detection of single nucleotide variant (SNV), insertions and deletion (INDEL), copy number variation (CNV) and DNA methylation profiles from a single sample, without any sample splitting. *Methods:* Panels, reagents, and automated workflows for Avida-DNA, Avida-Methyl, and Avida Duo-Methyl (combined DNA and methylation) kits were developed to accommodate up to 96 samples on the Bravo NGS workstation. *Results:* Leveraging a focused cancer hotspot panel, we demonstrate excellent reproducibility and low allele frequency (SNV at sub 1%) variant detection in cfDNA samples and reference standards with as little as 10ng DNA input. We exhibit similar performance with a larger ~300 kb target region tumor profiling panel. Finally, we demonstrate DNA methylation detection in the standalone or combined ('Duo') workflows across differentially methylated regions (DMRs) with a panel of ~3,400 targets. *Conclusions:* Automation of the Avida targeted enrichment solution with the Bravo NGS workstation enables a sensitive, high-throughput, end-to-end single-day library preparation solution for detecting genomic alterations and DNA methylation changes from a single low-input cfDNA or tumor DNA samples.

Embedding a Genetic Counsellor into a Paediatric Neurology Clinic: The Experiences and the Learnings

Anita Gorrie[1,3], Laura Barth[1], Jessica Planner[1,2], Helen Curd[1,3] and Michael Fahey[1,3]

[1]Monash Genetics, Monash Health, Melbourne, VIC, Australia, [2]Newlife IVF, Melbourne, VIC, Australia and [3]Monash University, Melbourne, VIC, Australia

Background: Demand for genetics and paediatric neurology services at Monash Health continues to grow, resulting in prolonged patient wait times and staff pressures. Increased genomic testing and Medicare item numbers have led to genomic testing being provided by non-genomics specialists. Without appropriate training and adequate time, this can result in sub-optimal patient care. *Aim:* To trial embedding a genetic counsellor (GC) in the paediatric neurology service to assist with genomic testing consent, results disclosure and lab liaison. *Methods:* GCs, in close partnership with neurologists, designed and implemented a trial model of care, which we refined as our understanding of the needs of the clinic and patients deepened. Training in genomics consent was provided. Neurologists were surveyed prior to the trial and three months later. A record of patients was kept. *Results:* Our understanding of one model of mainstreaming genetics has enhanced. The trial led to a marked increase in neurologists' understanding of genetics and the role of GCs. Patients benefited from more informed consent and the ability to receive all genetic information within their neurology appointments. The patients needing referral to genetics reduced. *Conclusions:* This model of care improves patient care and wait times, and presents a solution to the growing demand for clinical genetics and paediatric neurology services. It is a mutually beneficial approach and provides a template model of care that can be extended across the hospital. We are excited to share our experiences, challenges and opportunities of this newly established model of care in a clinical setting.

Determining the Optimal Number of Genes to Include for Equitable, Pan-Ancestry Carrier Screening: The 'Goldilocks' Approach

Mia J. Gruzin[1,2], Matthew Hobbs[1], Sarah Poll[3], Jaysen Knezovich[4], Swaroop Aradhya[3,5] and Leslie Burnett[1,2,6]

[1]Garvan Institute of Medical Research, Sydney, NSW, Australia, [2]School of Clinical Medicine, UNSW Medicine and Health, St Vincent's Clinical Healthcare Campus, Sydney, NSW, Australia, [3]Invitae Corporation, San Francisco, CA, USA, [4]Blue Jay Consulting Services, Brisbane, QLD, Australia, [5]Stanford University School of Medicine, Department of Pathology, Stanford, CA, USA and [6]Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Background: Reproductive genetic carrier screening enables patients and families to make informed reproductive decisions. Expanding carrier screening to hundreds of genes improves carrier yield, but may be associated with increased costs and workforce burden; conversely, restricting testing to fewer genes might be inequitable to populations of admixed and diverse ancestry groups. We previously presented methods for constructing an optimally sised ('Goldilocks') carrier panel, using gnomAD v3.1.2 and v4.0 genome data. *Aim:* We investigated the composition of a 'Goldilocks' pan-ancestry carrier panel that maximises carrier yield across diverse ancestry groups at lowest possible cost, using the most recent gnomAD v4.1 exome and genome dataset. *Methods:* Using gnomAD v4.1 and ClinVar data for ~1,300 genes associated with serious, childhood-onset AR and XL conditions, we developed screening panels and ranked their relative performance in silico and with real-world data from >380,000 individuals. *Results:* Smaller panels provided inequitable benefit to groups with diverse ancestry. Carrier yield increased logarithmically with increasingly sised synthetic panels, and 'Goldilocks' points could be identified at 90%, 95%, 99% and 99.7% carrier yields. Constructing gene panels from gene lists ranked by pan-ancestry allele frequency ensured carrier tests were equitable across pan-ancestry groups. In bottleneck/endogamous groups, achieving 99% carrier yield required fewer genes (~200-250). Real-world data from >75 countries (including Australia) validated our model's carrier yield predictions. *Conclusions:* Our approach can define parameters for the 'future of genomics' in carrier screening, by designing equitable tests that remain clinically effective regardless of ancestry.

Diagnostic Screening Using a 15-Gene NGS Panel Improves the Rate of Detection for Cerebral Small Vessel Disease Mutations

Solomon Guyler, Heidi G. Sutherland, Neven Maksemous, Robert A. Smith and Lyn R. Griffiths

Genomics Research Centre, Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a hereditary cerebral small vessel disease (CSVD) which is a key contributor to familial inherited stroke. CADASIL causes migraine, recurrent strokes, mood disturbance, cognitive decline, and leads to vascular dementia and eventual premature death. There is currently one main causal gene for

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

CADASIL, *NOTCH3*, which encodes a transmembrane receptor essential to vascular smooth muscle cell development. However, genetic testing for CADASIL is currently inefficacious with approximately 80% of suspected cases negative for pathogenic variants in *NOTCH3*. The current study utilised a 15-gene Next Generation Sequencing (NGS) panel containing genes implicated in CADASIL, hemiplegic migraine, and other CSVDs to investigate the presence of pathogenic variants in genes which cause diseases displaying a phenotypic overlap with CADASIL. 104 patient samples, which were initially referred to the Genomics Research Centre Diagnostics Service for *NOTCH3* genetic testing and found to be negative for pathogenic variants, were screened using a targeted NGS panel that includes 15 migraine or CSVD genes. Patient DNA was sequenced using the IonTorrent GeneStudio S5 Plus platform and analysis performed using IonReporter software. Variants were filtered and curated based upon minor allele frequency, location, amino-acid changing effect, and prediction of pathogenicity by in-silico tools. Potentially pathogenic variants were identified across 8 genes related to CSVDs and migraine disorders other than *NOTCH3*, including *HTRA1* and *COL4A1/2*. The increased diagnostic yield we obtained using an extended NGS panel, show that it is an effective mechanism of testing for CADASIL and related CSVDs.

The Australian Undiagnosed Diseases Network (UDN-Aus): An Internationally Networked National Approach for Transforming Diagnosis for Individuals Living With Rare Diseases

Madeleine Harris[1], Ellenore M. Martin[1], Julia Broadbent[1], Susan White[2], Elizabeth E. Palmer[3,4], Azure Hermes[5,6], Julie McGaughran[7], Timo Lassmann[8,9], Suzanne Sallevelt[10], Tiong Yang Tan[1,2,16], Mathew Wallis[11], Daniel MacArthur[21,22], Michael Field[14], Tristan Hardy[15], Cas Simons[21,22], Chloe Cunningham[2], David Stroud[1,2,16], Simon Sadedin[1,2,16], Tracy Dudding-Byth[14], Sandra Cooper[3,12,17], Janine Smith[3,17], Ilias Goranitis[1,16], Ira Deveson[13], Tiffany Boughtwood[1,18], Christopher Richmond[7,19], Shannon LeBlanc[10], Sarah Jelenich[1,18], Sarah Casauria[1,18], Evanthia O. Madelli[1,18], Rachel Austin[7], Ryan Pysar[3], Tegan Stait[1,2], Louise Cilento[10], Lauren Dreyer[20], Ella Jane Wilkins[1,2,16], Elly Lynch[2], Denisse Garza[11], Rocio Rius[21,22], Daniz Kooshavar[1], Xinyu Zhang[1,16], Laura Wedd[21,22], Tian Zhao[1,2,16], Christopher Richards[21,22], Francisco Santos Gonzalez[16]The Undiagnosed Disease Network Australia[1], Gareth Baynam[20] and John Christodoulou[1,2,16]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Victorian Clinical Genetics Service, Melbourne, VIC, Australia, [3]Sydney Children's Hospital Network, Sydney, NSW, Australia, [4]University of New South Wales, Sydney, NSW, Australia, [5]National Centre for Indigenous Genomics, Canberra, ACT, Australia, [6]Australian National University, Canberra, ACT, Australia, [7]Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia, [8]Telethon Kids' Institute, Perth, WA, Australia, [9]University of Western Australia, Perth, WA, Australia, [10]Women's and Children's Hospital, Adelaide, SA, Australia, [11]Tasmanian Clinical Genetics Service, Hobart, TAS, Australia, [12]The Children's Medical Research Institute, Sydney, NSW, Australia, [13]The Garvan Institute of Medical Research, Sydney, NSW, Australia, [14]Genetics of Learning Disability Service, Newcastle, NSW, Australia, [15]SA Pathology, Adelaide, SA, Australia, [16]The University of Melbourne, Melbourne, VIC, Australia, [17]The University of Sydney, Sydney, NSW, Australia, [18]Australian Genomics, Melbourne, VIC, Australia, [19]School of Medicine, Griffith University, Gold Coast, QLD, Australia, [20]Undiagnosed Diseases Program, Genetic Health WA and Rare Care Centre, Perth Children's Hospital, Perth, WA, Australia, [21]Centre for Population Genomics, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, NSW, Australia and [22]Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: Genomic sequencing has transformed diagnosis for individuals with rare genetic disorders. However, half of individuals with a rare presumed monogenic disorder remain undiagnosed after clinically available genomic testing. For these individuals, no national multi-omics testing pathway was available. *Methods:* The MRFF funded Australian Undiagnosed Disease Network (UDN-Aus) was established in 2021, combining a national collaborative network of clinical geneticists (n = 30), genetic counsellors (n = 16) and researchers (n = 23). UDN-Aus facilitates standardised recruitment of genetically unsolved individuals into robust re-evaluation pipelines, including clinician-led genomic reanalysis and flow through to frontier functional genomic technologies. *Results:* Since July 2022, 145 probands have been referred from 10 recruitment sites across five Australian states. 104 probands (72%) and 162 additional family members have been approved and recruited. As of April 2024, sequencing data is available for 50 families in the Centre for Population Genomics' variant filtration and analysis platform, *Seqr*. Reanalysis has been completed for 40 families; pathogenic variants have been identified in five families, promising variants are undergoing further testing in 12 families (including novel candidate disease genes, *EFTUD2, ZDHHC8, ZNF827*), and trio whole genome sequencing and analysis is in progress for in 23 families. Cases have been referred to Australian and international collaborators, and other MRFF funded studies. *Conclusions:* The UDN-Aus study demonstrates the value of a national networked undiagnosed disease approach to facilitate equitable access for patients and their families to additional data reanalysis, genomic, transcriptomic, proteomic and/or functional testing. Together, we hope to improve outcomes for participants and their families.

A Case of Turner Syndrome or Something More Complex?

Sarah Harvey[1], Jennifer Phan[2], Samuel Curtis[1], Jillian Nicholl[1], Nicole Scholefield[1], Ellie Wu[2], Kathryn Friend[2], Jinghua Feng[3] and Karin Kassahn[3]

[1]SA Pathology – Cytogenomics Unit, Adelaide, SA, Australia, [2]SA Pathology – Molecular Genetics, Adelaide, SA, Australia and [3]SA Pathology – Technology Advancement Unit, Adelaide, SA, Australia

An 11-month-old female with focal epilepsy, extensive right hemispheric polymicrogyria, left hemiplegia and developmental delay was referred for SNP microarray testing on blood. Microarray detected monosomy X, however manual examination of the B-allele Frequency indicated possible mosaicism for an additional X chromosome with a terminal Xq deletion. Follow up testing with a G-banded karyotype on blood confirmed low level mosaicism (10%) for a cell 46,X cell line with a derivative X resulting from a translocation between chromosome X and 5 (mos 45,X[47]/46,X,der(X)t(X;5)(q22.3;q15)[5]). This cell line is trisomic for 5q15-qter and monosomic for Xq22.5-Xqter. Additional NGS sequencing performed on blood showed no evidence of this derivative X as the mosaicism level was below the bioinformatic pipeline's level of detection. However, previous NGS sequencing performed on buccal cells by Invitae did report deletions of multiple genes on the X chromosome and duplications of multiple genes on chromosome 5, which is concordant with the karyotype results. This divergence in NGS results may be due to the differing levels of mosaicism present in the different tissue types. The microarray finding of monosomy X did not explain the severity of the patient's phenotype however did provide a clue to something more complicated being present. A karyotype was the key assay which united the genetic data in this patient and provided the likely cause for the patient's presentation due to mosaic monosomy Xq and trisomy 5q.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Resources for People From Priority Populations Living With a Rare Disease — Lessons Learned

Louise Healy, Nicole Millis and Jess Brooklyn

Rare Voices Australia

Background: The National Strategic Action Plan for Rare Diseases (the Action Plan) identified several priority populations that have additional barriers in accessing rare disease information, care and support and research opportunities. To progress the implementation of the Action Plan, education and information resource collections were curated for Aboriginal and Torres Strait Islander (ATSI), Culturally and Linguistically Diverse (CALD) and regional, rural and remote Australians living with a rare disease. Key learnings about developing resources, as well as key gaps for these populations were uncovered during the development process. *Aim:* To progress implementation of the National Strategic Action Plan for Rare Diseases, the resources were developed in collaboration with key peak bodies with relationships with the identified communities. *Methods:* Interviews, iterative reviews of project plans, resources and resource presentation informed the development of resource collections for target priority populations. *Results:* The development of these resource collections highlighted important learnings and key gaps in resources for each of the target populations. Considerations around accessibility, health literacy, presentation of resources and key partners informed the development of the resources. Collaboration and iterative review processes were essential.

The Diagnostic Journey in a Case of Complex Lipid Processing.

Cathie Hilditch[1], Suzanne Sallevelt[1], Arjan Bouman[2], Kathryn Friend[3], Andrew Dubowsky[3], Rishi Agrawal[4], Clair Pridmore[5], Kathryn Billing[6] and Sarah Donoghue[7]

[1]Paediatric & Reproductive Genetics Unit, Women's and Children's Hospital, Adelaide, SA, Australia, [2]Department of Clinical Genetics, Erasmus MC University Medical Center, Rotterdam, the Netherlands, [3]Genetics and Molecular Pathology, SA Pathology, Adelaide, SA, Australia, [4]Department of General Medicine, Women's and Children's Hospital, Adelaide, SA, Australia, [5]Department of Neurology, Women's and Children's Hospital, Adelaide, SA, Australia, [6]Department of Ophthalmology, Women's and Children's Hospital, Adelaide, SA, Australia and [7]Metabolic Unit, Women's and Children's Hospital, Adelaide, SA, Australia

Background: Developmental regression in infants is devastating for parents seeking a diagnosis and the opportunity to access optimal care and quality of life measures for their child. The aetiology of developmental regression requires subspecialty collaboration with involvement of Neurology, Metabolic and Genetic teams to phenotype patients and decide upon appropriate diagnostics. *Case Study:* We describe the journey of a female infant presenting for multidisciplinary diagnostic work-up at 13 months with a constellation of features including neuroregression when unwell, retinal dystrophy, microcephaly, failure to thrive and abnormal neurological signs such as axial hypotonia, dystonia and choreiform movements. She had a normal MRI at 4 months and two previous nondiagnostic clinical exome analyses. *Results:* At 13 months of age, reanalysis of exome data identified compound heterozygous variants in *WDR73,* classified as likely pathogenic and a variant of uncertain significance (VUS*)*. Pathogenic variants (bi-allelic) in *WDR73* cause Galloway-Mowat syndrome (OMIM251300). Also identified were two compound heterozygous VUS in *PI4KA*. These results required further workup as the disorders associated with these genes have overlapping clinical features. Genome analysis of the *WDR73* VUS was able to upgrade this variant to pathogenic. There was no evidence of abnormal splicing on mRNA studies for the *PI4KA* variant. *Conclusions:* Children with developmental regression benefit from multidisciplinary evaluation to improve diagnostic yield. The diagnosis is important for optimising care of the child, and for reproductive counselling for future children. Here, we present a case of a young child with a diagnosis of Galloway-Mowat syndrome, which was established after extensive collaboration between different medical subspecialties.

Unambiguous Genotyping of AGG Interrupts for Fragile X Premutation Carriers is Important to Best Inform the Risk of Expansion

Gladys Ho[1,2], Katrina Fisk[1,2], Lauren Patterson McDonald[1] and Bruce Bennetts[1,2]

[1]Molecular Genetics, Western Sydney Genetics Program, Children's Hospital Westmead, Sydney, NSW, Australia and [2]Specialty of Genomic and Precision Medicine, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia

Background: Determining the number of CGG repeats within the 5' untranslated region of *FMR1* is a vital part of reproductive carrier screening (RCS) to identify premutation (PM) carriers, who are at risk of having child(ren) with fragile X syndrome. Further testing to identify the number of AGG interrupts within the repeat expansion region can better inform the risk of expansion to a full mutation (FM) for female PM carriers. However, this additional testing is not always part of routine RCS. *Methods:* The polymorphic (CGG)n triplet repeat was amplified by a modified Amplidex™ (Asuragen) PCR, in conjunction with an AGG-specific primer assay, to unambiguously determine the genotype of the expansion region in female PM carriers, providing information on the number of AGG interrupts and their position within each allele. *Results:* Since offering this test from 2020, we have tested over 300 individuals, with repeat numbers ranging between 51 and 84. Approximately 80% of individuals were considered to have a low chance of expansion to a FM after AGG testing. Referral numbers were highest (over 50%) for PM between 55 and 59 repeats, with 93% of these individuals deemed to be low risk. *Conclusions:* Precise AGG interrupt genotyping can better inform the risks for PM carriers, reducing unnecessary parental anxiety, counselling time and the need for invasive prenatal testing. We recommend that AGG interrupt testing be incorporated as a reflex second-tier test for low range premutations (55-74 repeats) in RCS.

Identification of Novel Rare Variants in Concussion Genetics

Joseph Holmes[1], Neven Maksemous[2], Robert Smith[2], Heidi Sutherland[1] and Lyn Griffiths[1]

[1]Queensland University of Technology, Faculty of Health, School of Biomedical Sciences, Brisbane, QLD, Australia and [2]Queensland University of Technology, Faculty of Sciences, Research Infrastructure, Brisbane, QLD, Australia

Concussion is a complex neurological disorder, that remains incompletely understood. Current methods of genetic investigation have proven inadequate, producing only a small set of associated genes, with studies often being plagued by underpowered results and conflicting findings. Notably, only one published study has thought to explore novel rare variants, despite these being more likely to be deleterious, in complex neurological conditions. This present study aims to reassess and expand upon a preliminary study exploring rare

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

gene variants that can be potentially implicated in concussion. A cohort of consenting adults ($N = 100$) with chronic concussion complications and/or multiple concussive injuries, underwent whole exome sequencing. Variants were filtered by a minor allele frequency below 0.01 and subsequently filtered in a stepwise approach to identify potential candidate variants. These variants were then subjected to gene-based burden testing against a control group of neurologically heathy individuals ($n = 1000$) derived from the UK Biobank. Preliminary analysis of a subset of this cohort ($n = 33$) revealed several candidate variants in genes linked to various neurological conditions such as ataxia, migraine and epilepsy. While many of these variants were initially classified as benign or likely benign, they still exhibited predicted deleterious effect, suggesting potential functional implications in neuronal impairment and recovery. By expanding the cohort size and employing burden testing, this study aims to promote the use of rare variant studies to enhance the discovery of genes in complex concussion-related disorders.

Translating Clinical Discoveries Into Mouse Models of Hereditary Hematological Malignancies

Claire C. Homan[1], Parvathy Venugopal[1], Jiarna Zerella[1], Peter Brautigan[1], Amelia Lau[1], Nur Hezrin Shahrin[2], Michael W. Drazer[3], Kai Yu[4], David M. Lawrence[5], Jinghua Feng[5], Luis Arriola-Martinez[1], Belinda Phipson[6], Kerry Phillips[7], Nicola K. Poplawski[7], Paul Liu[4], Lucy A. Godley[8], Devendra Hiwase[7]RUNX[1]International Data-Sharing Consortium[9], Christopher N. Hahn[1,2], Hamish S. Scott[1,2] and Anna L. Brown[1,2]

[1]Centre for Cancer Biology, University of South Australia, Adelaide, SA, Australia, [2]SA Pathology, Adelaide, SA, Australia, [3]University of Chicago, Chicago, IL, USA, [4]National Institutes of Health, Bethesda, MD, USA, [5]ACRF Genomics Facility, Centre for Cancer Biology, Adelaide, SA, Australia, [6]Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia, [7]Royal Adelaide Hospital, Adelaide, SA, Australia, [8]Northwestern University, Chicago, IL, USA and [9]RUNX1 International Data-Sharing Consortium

Germline pathogenic variants in *RUNX1, GATA2*, or *DDX41*, collectively represent the most common causes of Autosomal Dominant Hereditary Haematopoietic Malignancies (HHM), albeit with a highly variable risk for leukemogenesis. Currently it is challenging for clinicians to provide tailored risk-assessment to patients as the natural history of carriers is not well understood and there has been no approach to identify HHM individuals at highest risk for leukemogenesis. To address this knowledge gap, we have leveraged our HHM international collaborative network, assembling and characterising the most extensive cross-sectional comparative cohort of patient data from carriers-without HM and carriers-with HM with germline *RUNX1, GATA2*, or *DDX41* variants ($n = 191$, 102 probands). We have demonstrated that *RUNX1, GATA2*, and *DDX41* germline variant carriers experience highly variable risk for clonal haematopoiesis, with unique somatic drivers. Translating these discoveries to further understand the molecular mechanisms of leukemogenesis, we have developed HHM mouse models, using CRIPSR technology, to introduce germline pathogenic variants observed in HHM patients ($GATA2^{T354M/+}$ and $DDX41^{M1I/+}$). Our $DDX41^{M1I/M1I}$ mice are embryonic lethal, while our GATA2 HHM mice, partially recapitulate the human phenotype including haematopoietic and urogenital defects and defective bacterial clearance. To understand disease initiation and progression, we are enlisting a multi-faceted approach, investigating the effect of repeated immune stress (bacterial and viral), and modeling the effect of frequently somatically mutated genes, identified in HHM patients. This approach will allow us to recapitulate the dynamics of clonal evolution, and ultimately identify molecular biomarkers for the development of targeted therapies.

An Audit of Diagnostic Outcomes for NIPT Results Suggesting XO/XY Sex Chromosome Mosaicism

Clare Hunt[1,2], Nicola Flowers[1,2], Alison Archibald[1,2,3], Katrina Scarff[1,2], Isabelle Danos[1,2], Olivia Giouzeppos[1,2], Martin Delatycki[1,2,3] and Mark Pertile[1,2,3]

[1]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia and [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia

Background: Noninvasive prenatal testing (NIPT) enables sex chromosome aneuploidy screening during pregnancy. A complex type of NIPT result is XO/XY sex chromosome mosaicism. This occurs when there is a decrease in Y chromosome sequencing counts relative to the fetal fraction in cell-free DNA (cfDNA). This suggests placental and possibly fetal involvement and presents a myriad of possible phenotypic and diagnostic outcomes including XO/XY mosaicism, structurally abnormal Y chromosome, monosomy X and normal male karyotypes. *Aim:* An audit was conducted to determine the diagnostic testing outcomes for pregnancies with an increased risk result for XO/XY mosaicism. *Methods:* The cohort included singleton pregnancies tested via percept NIPT between March 2019 and December 2023 who received an increased risk XO/XY NIPT result. Samples were tested using Veriseq NIPT Solution v2 (Illumina Inc.) and supplemented with manual data review. Where possible, diagnostic testing outcomes were collected. *Results:* Of 150,930 women screened, 35 received an increased risk XO/XY NIPT result, producing a call rate of 1 in every 4312 pregnancies. Diagnostic testing outcomes were available for 27/35 (77%) showing: normal male karyotype (12/27); 45,X/46,XY mosaicism (7/27); complex mosaic karyotypes with structurally abnormal Y chromosomes (4/27), monosomy X (3/27) and 45,X/47,XYY mosaicism (1/27). *Conclusions:* Increased risk NIPT results for XO/XY sex chromosome mosaicism generate considerable counselling challenges due to the potential of a wide range of diagnostic outcomes. This audit illustrates the breadth of diagnostic outcomes that can arise to assist in the provision of genetic counselling.

Diagnostic Findings and Yield of Investigations Requested for Children With Developmental Regression

Kirsten Furley[1,2], Katrina Williams[2,3], Michael C. Fahey[4] and Matthew Hunter[5]

[1]Monash University, Paediatrics, Melbourne, VIC, Australia, [2]Monash Children's Hospital, Developmental Paediatrics, Melbourne, VIC, Australia, [3]Monash University, Head of Paediatrics, Melbourne, VIC, Australia, [4]Monash Health, Head of Neurology, Melbourne, Australia and [5]Monash Health, Head of Genetics, Melbourne, VIC, Australia

Background: Childhood conditions that feature developmental regression are diverse and poorly understood. Phenotype-genotype characterisation and diagnostic yield data are needed to advance understanding of causal processes and inform clinical decision making. *Aim:* The aim of this study is to report the childhood conditions that feature developmental regression and assess the diagnostic yields of investigations. *Methods:* A retrospective chart review of ninety-nine children presenting with symptoms including developmental regression to an Australian tertiary paediatric genetic clinic.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Results: Of 99 children, 31% of (n = 31) children had intellectual disability (ID), 19% (n = 19) were autistic, 39% (n = 39) were autistic with ID, and 9% (n = 9) of children did not have an ID or autism diagnosis. Thirty-two percent (n = 32) of children received a new informative diagnosis, including 8 potential phenotypic expansion of genes for developmental regression. Genomic testing provided the highest diagnostic yield (51.1%, n = 24) and was highest, 63.6% (n = 14) for children with an ID. Fifty percent (n = 3) of children without autism or ID, and 50% of autistic children with an ID (n = 6) received an informative genomic result. *Conclusion:* We highlight the heterogeneity of conditions featuring developmental regression and report proposed phenotypic expansions not previously reported. The high diagnostic yield of genomic testing offers opportunities to identify causes and associations with diagnoses not previously reported to include developmental regression.

Future Considerations for Germline Testing in Childhood Cancer: Parents' and Patients' Perspectives, Experiences and Preferences. A Systematic Review

Jacqueline D. Hunter[1,2,3], Kate Hetherington[1,2], Eliza Courtney[1,4,5], Yasmin Christensen[1,2], Noemi Fuentes-Bolanos[1,4,5], Kanika Bhatia[6] and Michelle Peate[3]

[1]School of Women's and Children's Health, Faculty of Medicine, UNSW Sydney, Sydney, NSW, Australia, [2]Behavioural Sciences Unit, Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia, [3]Department of Obstetrics, Gynaecology and Newborn Health, Royal Women's Hospital, University of Melbourne, VIC, Australia, [4]Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia, [5]Children's Cancer Institute, Lowy Cancer Research Centre, UNSW Sydney, Sydney, NSW, Australia and [6]Royal Children's Hospital, Melbourne, VIC, Australia

Background: Paediatric precision medicine is shaping the future of childhood cancer care. These programs offer germline genomic testing, presenting potential opportunities and challenges. Understanding affected families' opinions of germline testing will support optimal integration into routine care. *Aim:* To explore affected families' perspectives, experiences and preferences towards germline testing of children with cancer. *Methods:* Following PRISMA guidelines, we searched four databases for studies exploring perspectives, experiences, and preferences of parents/caregivers and/or patients regarding germline testing of children with cancer. Articles were screened and assessed for quality using the Mixed-Methods Appraisal tool. Qualitative and quantitative data was extracted, analysed using content analysis, and summarised by research question/themes. *Results:* Twenty-four articles (from 2286) were included, primarily from the US. Nine were qualitative, eleven quantitative, and four mixed-methods. Interest in and uptake of testing was high. Families were motivated by altruism and seeking inheritance information. Testing barriers included psychological concerns, the timing of testing if offered at diagnosis or in poor-prognosis settings, and privacy/discrimination. Testing experiences indicated challenges yet also positive impacts, with results providing psychological relief and informing proactive decision-making. Timing preferences varied, however allowing time to adjust to a new diagnosis was a common theme. Most wanted to receive as many germline sequencing-related results as possible. *Conclusions:* Findings highlight the need to integrate future germline analyses into paediatric cancer care with flexibility and support for families facing challenges. Where possible, consent should be provided at a time that suits each family's situation, with access to information aligning with needs and preferences.

USP9X et al: Deubiquitylating Enzymes in Neurodevelopmental Disorders

Lachlan A. Jolly[1], Xiaoying Yu[1], Alison Gardner[1], Raman Kumar[1] and Jozef Gecz[1]

[1]University of Adelaide and Robinson Research Institute, Adelaide, SA, Australia and [2]School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia

Background: Protein ubiquitylation is a widespread post-translational modification relevant to most proteins, typically culminating in protein degradation. There are ~100 deubiquitylating enzymes (DUBs) encoded in the human genome, which function protected proteins from ubiquitin dependent degradation. Mutations in 12 DUBs cause neurodevelopmental disorders (NDDs), including USP9X, for which we identified >90 variants involved (>50 unpublished). *Aim:* Investigate the involvement of DUBs in NDDs and the cell and molecular mechanisms involved. *Methods:* We combined constraint metrics, protein-protein interaction networks and functional data sets to identify additional DUBs relevant to NDDs. We used USP9X to exemplify the genetic and cellular mechanism of pathology. *Results:* We generated evidence that supports the involvement of 26 additional DUBs in NDDs. We identified loss of abundance of key regulatory proteins controlling the mTOR, WNT, NOTCH and TGFβ signaling pathways USP9X patient-derived primary skin fibroblast cell lines displayed. Intriguingly, these substrates are themselves encoded by genes that cause NDDs through haploinsufficiency. An extended interrogation of all USP9X interactors showed its interactome is enriched in proteins encoded by haploinsufficient NDD genes. This phenomenon was observed for the interactomes of other NDD DUBs including *USP7, USP15, USP27X, USP45, OTUD5, OTUD6B, OTUD7A, and ATXN3*. *Conclusion:* These data implicate a convergent mechanism of pathology in DUB related NDDs involving destabilisation of proteins which themselves cause NDDs through loss of abundance. By extension, these data suggest that NDDs caused by haploinsufficiency can be potentially overcome by antagonising the ubiquitin dependent proteolysis of NDD proteins.

How People From Migrant and Refugee Backgrounds Experience Perinatal Genetic Screening: A Scoping Review

Anaita Kanga-Parabia[1,2], Belinda McClaren[1,2], Laura Biggs[1], Sharon Lewis[1,2], Erin Tutty[1,2] and Alison Archibald[1,2,3]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]University of Melbourne, Melbourne, VIC, Australia and [3]Victorian Clinical Genetics Services, Melbourne, VIC, Australia

Background: People from migrant and refugee backgrounds often have poor healthcare experiences and outcomes. Understanding whether and how this manifests in perinatal genetic screening is a crucial step for equitable care. We reviewed international evidence about perinatal genetic screening experiences of people from migrant and refugee backgrounds. *Methods:* A scoping review was conducted using Joanna Briggs Institute framework. Search strategies were applied to Medline, Embase, and CINAHL databases to identify articles about experiences of perinatal genetic screening for people of migrant and refugee backgrounds. Evidence was synthesised using descriptive and content analysis. *Results:* Of 6925 unique articles identified, 25 met inclusion criteria and were included. Most were set in Western countries, and participants were primarily born in Asia, South America, or Africa. Studies indicated varying awareness,

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

knowledge, and uptake of screening and described factors influencing participant experiences and behaviors. For example, several studies highlighted lack of adequate in-language resources, use of concepts that were unrecognised in particular communities, and poor interactions with healthcare providers. Authors suggested strategies such as person-centered counselling, increased time, access to interpreters, and training for relevant providers. Some studies also suggested addressing structural financial and geographical barriers could improve access to screening. *Conclusions:* This scoping review revealed common barriers that people of migrant and refugee backgrounds may encounter in perinatal genetic screening care as well as related strategies to facilitate equitable care. Understanding perspectives of people from migrant and refugee backgrounds is foundational to ensuring equitable perinatal genetic screening services for all.

Safety Evaluation for CRISPR/Cas9-Based BCL11A Gene-Editing Products

Hyunkeun Kim, Bo Seul An, Nari Seo, Yoo Sung Kim, Sunhee Kim and Jae-ok Kim

Advanced Bioconvergence Product Research Division, National Institute of Food and Drug Safety Evaluation, Cheongju, Republic of Korea

Background: BCL11A genetically controls fetal hemoglobin (HbA, $\alpha_2 \gamma_2$) and adult hemoglobin (HbA, $\alpha_2 \beta_2$) levels during human development. Recently, this BCL11A hemoglobin switching system targeted therapeutics have developed using CRISPR/Cas9 system. Despite the remarkable advances in CRISPR/Cas9 system over the past decade, the assessment methods for CRISPR/Cas9-based human gene-editing products remain to be verified from regulatory perspectives. *Aim:* In this study, as a safety concern, we assessed off-target effects in CRISPR/Cas9-based BCL11A gene-editing products using in silico and in vitro off-target methods with comparative analysis. *Methods:* We generated BCL11A-deficient HEK293T cells using CRISPR/Cas9 system, its gene-editing efficiency was validated by targeted deep sequencing. To investigate genome-wide off-target effect, we performed off-target analysis using in silico prediction tool (Cas-OFFinder) and in vitro Cas9-digested whole-genome sequencing (Digenome-seq). *Results:* In BCL11A gene-edited HEK293T cell, insertion and deletion (Indel) were detected in 59%. To perform Digenome-seq, we produced synthetic gRNA and Cas9-RNP complex in vitro followed by an assessment of DNA digestion efficiency using qPCR. The qPCR method was validated for specificity, linearity, accuracy and precision according to ICH guidelines. Among the highly ranked off-target sites obtained by Cas-OFFinder and Digenome-seq analysis, eight potential off-target sites were validated by NGS-based targeted deep sequencing. The NGS results show that the Indel events were induced with near the detection limit, frequencies below 0.1%. *Conclusion:* To increase the predictability of off-target effect, we suggest that integrated analysis would be necessary with orthogonal approaches using currently available and appropriate off-target methods depending on each CRISPR/Cas9-based gene-editing product.

Re-Analysis of Genomic Data in a Cohort of Genetically Undiagnosed Inherited Retinal Disorder Patients

Richard Lin[1,3], Benjamin Nash[2,3,4], Alan Ma[1,3,4], Gladys Ho[2,3], Bruce Bennetts[2,3], Emma Hackett[2,3], Elisa Cornish[5], John Grigg[4,5] and Robyn Jamieson[1,3,4]

[1]Department of Clinical Genetics, Western Sydney Genetics Program, Sydney Children's Hospitals Network, Sydney, NSW, Australia, [2]Sydney Genome Diagnostics, Western Sydney Genetics Program, Sydney Children's Hospitals Network, Sydney, NSW, Australia, [3]Specialty of Genomic Medicine, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [4]Eye Genetics Research Unit, Sydney Children's Hospitals Network, Children's Medical Research Institute, Save Sight Institute, University of Sydney, Sydney, NSW, Australia and [5]Save Sight Institute, University of Sydney, Sydney, NSW, Australia

Background: The clinical utility of genetic testing in inherited retinal disorders (IRD) is well recognised. However, a substantial fraction of suspected IRD cases remain undiagnosed following genetic testing. Our Ocular Genomics Multidisciplinary Team (OcularGen-MDT) approach addresses this. Re-analysis of genomic data is the first step in this approach for unsolved cases. *Aims/Questions:* This project investigated re-analysis of exome sequence data, in a cohort of patients with IRD who remained genetically undiagnosed following previous exome testing. *Methods:* Thirty probands with IRD phenotypes were included for analysis. All cases had previous phenotype-led gene panel testing on an exome backbone initially performed in 2020/2021, and reported as uninformative. Variants in an expanded IRD gene panel were prioritised using an alternative tertiary bioinformatics platform and curated according to updated ACMG variant interpretation recommendations. *Results:* Likely pathogenic variants in IRD genes with zygosity consistent with disease phenotype were identified in 10% (3/30) of cases. In addition, 23% of cases (7/30) had variant(s) of uncertain significance with pathogenicity criterion suggestive of association with disease phenotype. Identification of new causative and potentially causative variants occurred due to inclusion of new disease genes, likely phenotypic expansion of known disease genes and an updated laboratory pipeline. *Conclusions:* We demonstrate the value in reanalysis of previous exome sequence data in IRD patients with previously uninformative testing. Correlation of the significance of these new genetic findings in the context of the clinical ophthalmic phenotypes and further testing in family members will likely add to the improved diagnostic yield in this cohort.

Investigating the Clinical Efficacy of Antenatal Sequencing for Fetal Anomalies

Mandy Lobley, Tenielle Davis, George McGillivray and Susan Fawcett

Objectives: To determine if clinical management or diagnostic yield of an antenatally detected fetal anomaly on a Fetal Anomalies Panel (FAP) differs from those receiving a complete Whole Exome Sequencing (cWES). Furthermore, would a FAP improve clinical efficacy including cost and turn-around time for results. *Method:* A subset of the hospital funded cWES performed at the Royal Women's Hospital (RWH) in Melbourne Australia, which returned a positive result between 31 July 2017 and 30 June 2023 were analysed. Results were compared to understand if all clinically significant variants found in genes on the cWES have been identified on a FAP. If the clinically significant variants were reported on a cWES but were absent on a FAP, it will only be considered a missed variant if it changed clinical management of the pregnancy. *Results:* Preliminary findings suggest that there is no reduction to quality of care or clinical efficacy by ordering a FAP over a cWES. However, there has been improvement in cost efficiency and patient experience. *Conclusions:* Implementing the utilisation of a FAP into standard practice will reduce the financial investment required by the genetics department and improve the quality of patient care. Therefore, this allows prenatal exome testing to be offered to more patients, thus increasing patient access.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Assessing Willingness of Generation Victoria to Participate in Genomics Research

Fiona Lynch[1,2], Alina Stechert[2], Elizabeth K Hughes[2], Melissa Wake[2], Richard Saffrey[2], Daniel MacArthur[3] and Danya F. Vears[1,2]

[1]The University of Melbourne, Melbourne, VIC, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia and [3]Centre for Population Genomics, Australia

Background: Generation Victoria (GenV) is a whole-of-state consented cohort open to all Victorian births over a 2-year period (Oct 2021-23). GenV's participants (117,000 babies and parents to date) closely reflect the diversity of Australian birthing families. Nearly all have provided perinatal biosamples and consented to genetic research. However, the brevity of the recruitment contact precluded exploring the implications of (and thus consenting for) return of individual genetic results for themselves or their child. *Aim:* To assess parents' willingness to participate in different components of a hypothetical future 'GenV Genomes' initiative. *Methods:* Between March 2023 and January 2024 GenV parent participants were contacted via an online platform and a notice in GenV's newsletter. They were invited to complete a brief survey written at Grade 6 level about their preferences should it become possible to offer clinically actionable genomic findings for themselves and/or their child in the future. *Results:* A self-selected sample of 517 GenV parents completed the survey. Of these, the vast majority indicated they would be willing/very willing to sign a new consent form to participate in genomic research (86.4%) and were interested/very interested in receiving genomic information that might be relevant to their (90%) or their child's (89%) health. 84.6% would be willing/very willing to give a blood sample for themselves, but <50% would agree to this for their child. *Conclusions:* While not necessarily reflecting the views of all GenV parents, this convenience sample was very supportive of genomic research that might include clinically actionable findings.

PRECISE – A Protocol for Delivering Genomic Education and Improving Genomic Capabilities in Primary Care

Alan Ma[1,2,*] and The PRECISE Project Team

[1]Specialty of Genomic Medicine, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia and and [2]The Sydney Children's Hospital Network – Westmead Sydney, NSW, Australia

*The PRECISE Project team: Dr Amelia K Smit, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Dr Kate Dunlop, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Prof Meredith Makeham, University of Sydney Assoc Prof Carissa Bonner, University of Sydney Prof Anne E Cust, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Ms Bronwyn Terrill, Australian Genomics Assoc Prof Julia Steinberg, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Prof Kristi J Jones, Sydney Children's Hospitals Network, University of Sydney Prof Robyn Jamieson, Sydney Children's Hospitals Network, University of Sydney, Children's Medical Research Institute Prof Lynn Monrouxe, University of Sydney Prof David Wilkinson, The Royal Australian College of General Practitioners Assoc Prof Nicole Rankin, University of Melbourne Assoc Prof Stephen Barnett, University of Wollongong Assoc Prof Shailendra Sawleshwarkar, University of Sydney Ms Kirsten Boggs, Sydney Children's Hospitals Network Dr April Morrow, Centre for Genetic Education, Health Education and Training, NSW Health Ms Edwina Middleton, Centre for Genetic Education, Health Education and Training, NSW Health Ms Janette Mumford, Genetic Alliance Australia Mr Andrew Coe, Western NSW Primary Health Network Dr Caitlin Forwood, Royal North Shore Hospital Dr Alexandra Williams, Health Pathways, Nepean Blue Mountains Primary Health Network Dr Anthony Brown, Health Consumers NSW Nick Rosser, Health Pathways, Nepean Blue Mountains Primary Health Network Dr Fi Lam Ms Nehal Singh, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia

Background: The growing demand for genomics in all areas of medicine has led to massive challenges in service provision, education and upskilling requirements for non-genetics healthcare professionals, especially in primary care. The PRECISE (Practitioner Readiness, Education and Capabilities, with Implementation Science Evaluation) research program aims to co-design and evaluate genomics resources and develop strategies for successful implementation of genomics in the primary care sector, including in rural, regional and remote settings. *Methods:* This project will utilise implementation science frameworks, as well as principles of education co-design, and program evaluation. The first stage will identify the education needs, capability gaps, and enablers in applying genomics through a scoping review and horizon scan. The second stage will build on our findings from the literature and codesign genomics resources that support primary care practitioners. Lastly, we will evaluate our approach and strategies for successful implementation of genomics into primary healthcare. *Discussion:* The PRECISE project will utilise an implementation science approach to address the clinical need for genomic education in this sector, as well as the health system barriers to uptake beyond an education program. By engaging with stakeholders in primary care, consumers, industry, primary health networks and general practice colleges in metropolitan and rural/remote settings, we seek to identify the systemic issues and enablers to facilitate improved genomic care in the sector. *Conclusions:* The PRECISE project presents a unique approach, bringing a diverse team from clinical genetics, primary care, academia, industry and policy to build genomics capabilities in the Australian primary health sector.

3D Total-Body-Imaging Reveals Genotype-Dermatological Phenotype Correlations in Hereditary Melanoma Genes: *POT1, POLE, BAP1* and *CDKN2A*

Ellie Maas[1], Brigid Betz-Stablein[1], Maura Gillis[2], Clare Primiero[1,3], Miriam Portony[3], Adam Mothershaw[1], Sam Kahler[1,4], Thi Pham[2], Vanessa Weir[2], Nicholas Kurtansky[2], Josep Malvehy[3,5], Susana Puig[3,5], Veronica Rotemberg[2], H. Peter Soyer[1,4] and Aideen McInerney-Leo[1]

[1]Frazer Institute, The University of Queensland, Dermatology Research Centre, Brisbane, QLD, Australia, [2]Memorial Sloan Kettering Cancer Center, Department of Dermatology, New York, NY, USA, [3]Dermatology Department, Melanoma Unit, Hospital Clínic de Barcelona, IDIBAPS, Universitat de Barcelona, Barcelona, Spain, [4]Department of Dermatology, Princess Alexandra Hospital, Brisbane, QLD, Australia and [5]Centro de Investigación Biomédica en Red en Enfermedades Raras (CIBERER), Valencia, Spain

Introduction: CDKN2A is the primary familial melanoma gene, Genotype-phenotype studies show increased atypical nevus counts in *CDKN2A* carriers; but other phenotypic-dermatological variables have been underexplored. There have been no studies exploring correlations between the dermatological phenotype and *POT1/POLE/BAP1* genotypes. *Method:* Fifty-two individuals — Australia (n = 22), Spain (n = 18), and North America (n = 11) — with pathogenic variants — *CDKN2A* (n = 19), *POT1* (n = 16), *BAP1* (n = 10)], *POLE* (n = 6) — and diagnosed with primary melanoma, underwent 3D-total-body-imaging (TBI; VECTRA-WB360). Phenotypic variables investigated included nevus count, size (≥2−5mm diameter and >5mm diameter), location by body site, and severity of UV-damage.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

An unaffected cohort (n = 127 individuals) was used as a comparator. *Results:* TBI revealed that pathogenic variant carriers had significantly greater nevus counts >2mm diameter compared to controls (median n = 102 nevi and n = 39 nevi respectively, p value= <.0001) and most were located on the back and lower limbs. *POLE* carriers had the highest total nevus counts >2mm diameter (median n = 220 nevi), followed by *POT1* (median n = 101 nevi), then *CDKN2A* (median n = 81). *BAP1* nevus counts (median n = 60 nevi) were not significantly increased compared to controls. *CDKN2A* carriers had significantly greater nevus counts on the head and neck (median n = 9 nevi >2mm) compared to controls (n = 0 nevi; p value= <0.0001). Of interest, *POLE* and *POT1* carriers exhibited significantly greater nevus counts >5mm diameter in body sites with absent-mild UV-damage compared to *CDKN2A*, *BAP1* and control groups: lower-back (p value ≤ <0.0001); abdomen (p value ≤ 0.01). *Conclusions:* Carriage of a pathogenic variant in *POLE/POT1/CDKN2A* increased nevus development generally on the back and lower limbs, and nevi >5mm diameter in *POLE* and *POT1* carriers, independently of or with mild UV-exposure in this cohort.

Innovative Exome Sequencing Technologies for Spinocerebellar Ataxia Type 2, 3, 6 and 7 Screening

Neven Maksemous[1], Robert Smith[1] and Lyn Griffiths[2]

[1]Queensland University of Technology, Faculty of Sciences, Research Infrastructure, Genomics Research Centre, Brisbane, QLD, Australia and [2]Queensland University of Technology, Faculty of Health, School of Biomedical Sciences, Genomics Research Centre, Brisbane, QLD, Australia

Spinocerebellar ataxia (SCA) is a type of autosomal dominantly inherited disease characterised by progressive loss of balance and coordination accompanied by slurred speech. More than 40 SCA subtypes have been identified to date, and 12 of them (SCA1-3, 6-8, 10, 12, 17, 31, 36-37) are caused by polynucleotide repeat expansions in the coding or non-coding regions of their associated genes. The current widely used molecular diagnostic methods (exome or targeted gene panels) limit their identification due to the inability of massively parallel sequencing to cope with the large read lengths required to accurately type pathogenic variants. This lack of detection capacity results in missed diagnoses, which is disadvantageous to affected individuals and their families, especially for rare disorders, that have overlapping symptoms with other diseases, such as the spinocerebellar ataxias. This study applied a customised WES to accurately detect the coding and noncoding CAG repeat expansions in the four most common SCA types (SCA2, SCA3, SCA6 and SCA7).

Advancing Disease Modeling of Unresolved Genomic Findings Through the Australian Functional Genomics Network

Ebony Matotek[1,2], Tessa Mattiske[1,2], Robert Bryson-Richardson[3], Ian Smyth[4], Jozef Gecz[5,6], John Christodoulou[1,7,8], Nathan Palpant[9], Kelly Smith[10], Coral Warr[11], Bruce Bennetts[12,13], Paul Thomas[14,15,16], Josephine Bowles[9,17], Massimo Hilliard[18], Gary Hime[10], Livia Hool[19,20], Leonie Quinn[21], Ernst Wolvetang[22], Seth Masters[23], Robyn Jamieson[13,24,25], Gareth Baynam[26,27,28,29], Tracy Dudding-Byth[30,31], Di Milnes[32], Megan Higgins[32,33], Jonathan Rodgers[32], Fallon Noone[32], Mark Cleghorn[34], Sunita Biswas[35], Laura St Clair[36], Annabelle Enriquez[37,38], Lisa Ewans[36,39,40], Mathew Wallis[41,42], Elizabeth Palmer[36,43], Tiong Yang Tan[8,44,45], Chirag Patel[32], Kristi Jones[7,25,46], Hamish Scott[35,47,48,49], Patrick Tam[50,51], Zornitza Stark[2,8,45], Sally Dunwoodie[38,51] and Andrew Sinclair[1,45]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Australian Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]School of Biological Sciences, Monash University, Melbourne, VIC, Australia, [4]Department of Anatomy and Developmental Biology, Development and Stem Cells Program, Monash Biomedicine Discovery Institute, Monash University, Melbourne, VIC, Australia, [5]School of Medicine, Robinson Research Institute, University of Adelaide, Adelaide, Australia, [6]South Australian Health and Medical Research Institute, Adelaide, SA, Australia, [7]Discipline of Child and Adolescent Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia, [8]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [9]Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia, [10]Department of Anatomy and Physiology, The University of Melbourne, Melbourne, VIC, Australia, [11]School of Agriculture, Biomedicine and Environment, La Trobe University, Melbourne, VIC, Australia, [12]Department of Molecular Genetics, The Children's Hospital at Westmead, Sydney, NSW Australia, [13]Specialty of Genomic Medicine, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [14]School of Biomedicine, University of Adelaide, Adelaide, SA, Australia, [15]Genome Editing Program, South Australian Health & Medical Research Institute, Adelaide, SA, Australia, [16]South Australian Genome Editing Facility, University of Adelaide, Adelaide, SA, Australia, [17]School of Biomedical Sciences, The University of Queensland, Brisbane, QLD, Australia, [18]Clem Jones Centre for Ageing Dementia Research, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia, [19]School of Human Sciences, The University of Western Australia, Perth, WA, Australia, [20]Victor Chang Cardiac Research Institute, Sydney, NSW, Australia, [21]Division of Genome Science and Cancer, The John Curtin School of Medical Research, The Australian National University, Canberra, ACT, Australia, [22]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, QLD, Australia, [23]Hudson Institute of Medical Research, Melbourne, VIC, Australia, [24]Eye Genetics Research Unit, The Children's Hospital at Westmead, Save Sight Institute, Children's Medical Research Institute, The University of Sydney, Sydney, NSW, Australia, [25]Department of Clinical Genetics, The Children's Hospital at Westmead, Sydney Children's Hospitals Network, Sydney, NSW, Australia, [26]Undiagnosed Diseases Program, Genetic Services of Western Australia, King Edward Memorial Hospital, Perth, WA, Australia, [27]Division of Paediatrics and Telethon Kids Institute, Faculty of Health and Medical Sciences, Perth, WA, Australia, [28]Rare Care Centre, Perth Children's Hospital, Perth, WA, Australia, [29]Western Australian Register of Developmental Anomalies, King Edward Memorial Hospital, Perth, WA, Australia, [30]Genetics of Learning Disability Service, Newcastle, NSW, Australia, [31]University of Newcastle, Newcastle, NSW, Australia, [32]Genetic Health Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia, [33]The Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia, [34]Royal Melbourne Hospital, Parkville, Melbourne, Australia, [35]Department of Genetics and Molecular Pathology, SA Pathology, Adelaide, SA, Australia, [36]Center for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia, [37]Department of Clinical Genetics, Nepean Hospital, Sydney, NSW, Australia, [38]School of Clinical Medicine, Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [39]Genomics & Inherited Disease Program, Garvan Institute of Medical Research, Sydney, NSW, Australia, [40]School of Paediatrics and Child Health, University of New South Wales Medicine & Health, University of New South Wales, Sydney, NSW, Australia, [41]Tasmanian Clinical Genetics Service, Tasmanian Health Service, Hobart, TAS, Australia, [42]School of Medicine and Menzies Institute for Medical Research, University of Tasmania, Hobart, TAS, Australia, [43]Discipline of Paediatrics and Child Health, Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [44]Rare Disease Discovery group, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [45]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia, [46]Kids Neuroscience Centre, Kids Research, The Children's Hospital at Westmead, Sydney, NSW, Australia, [47]Centre for Cancer Biology, University of South Australia and SA Pathology, Adelaide, SA, Australia, [48]ACRF Cancer Genomics Facility, Centre for Cancer Biology, University of South Australia and SA Pathology, Adelaide, SA, Australia, [49]Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia, [50]Children's Medical Research Institute, University of Sydney, Sydney, NSW, Australia, [51]School of Medical Sciences, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia and [52]Developmental and Regenerative Biology Division, Victor Chang Cardiac Research Institute, Sydney, NSW, Australia

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Background: Clinical genomic analysis is becoming embedded into the Australian healthcare system due to the increased diagnostic rate of human diseases. However, as the pace of discovery slows, the proportion of variants categorised as variants of uncertain significance (VUS) is increasing and novel disease genes remain to be discovered. *Aim:* The Australian Functional Genomics Network (AFGN) is a national collaboration between clinical geneticists and research scientists that aims to improve the diagnostic rate for rare disease patients through the coordination and management of functional genomics research across Australia. *Methods:* The AFGN connects clinicians and researchers through use of the AFGN researcher registry, a database of model systems researchers. Utilising our review panel process, we will prioritise and distribute $5 million over 5 years (2021-2026) to patient-driven functional genomics research initially in two major streams: Stream 1 (S1, single variants) and Stream 2 (S2, multiple VUS). *Results:* As of April 2024, the AFGN has awarded funding to 32 projects following clinical and scientific review. Funding amounts range from $15,000 (S1) to $200,000 (S2), supporting projects involving organoid and animal model generation, in vitro and RNA assays, and higher throughput functional assays. Data from these projects has already provided evidence of disease causality and impacted gene and variant classifications. *Conclusions:* By fostering collaborations between clinicians and researchers, the AFGN will empower clinically relevant research and build lasting research capacity to accelerate the development of more effective diagnoses, interventions, and treatments for patients with genetic disorders.

Short-Term Psychosocial Impact of Glaucoma Risk Assessed by Polygenic Risk Score Analysis

Giorgina Maxwell, Robert Allen, Lucinda Hodge, Simone Kelley, Jamie E. Craig, Sarah Cohen-Woods and Emmanuelle Souzeau

Flinders University, Adelaide, SA, Australia

Background: Polygenic risk scores (PRS) for glaucoma show effective risk stratification and utility, supporting clinical implementation. However, assessment of potential adverse psychological outcomes of results is needed. *Aim:* Explore the short-term psychosocial impact of PRS results for glaucoma. *Method:* Participants were recruited from the GRADE Study, which provides glaucoma PRS testing to individuals from the general population (over 50 years). Participants received a report indicating their risk of developing glaucoma based on whether their PRS score was in the bottom, middle, or top decile. Prior to receiving results, participants completed questionnaires assessing general anxiety and depression levels and glaucoma-focused anxiety. Two-weeks after receiving results participants repeated these questionnaires and additional questionnaires assessing test-related distress and decisional regret. Linear and nonparametric regression models were used for data analysis. *Results:* Participants (N = 113) completed the questionnaires, receiving a low, moderate, or high-risk result. Participants reported lower levels of anxiety, depression, and glaucoma anxiety ($ps < .05$) after having received results. PRS scores did not have a main or interaction effect on these results ($ps > .05$). Decisional regret was not predicted by PRS score (p = .76). Measures of test-related distress identified differences between PRS groups ($ps < .05$). Higher levels of negative emotions, uncertainty, and privacy concerns ($ps < .015$) were reported in the high-risk compared to the moderate-risk group. The low-risk group reported higher levels of positive experience ($p < .001$) than the high-risk group. *Conclusions:* This was the first study to assess for psychosocial impact of PRS for glaucoma. The outcomes will inform adequate delivery strategies and support for this novel service model.

followME Fabry Pathfinders Registry: Renal Effectiveness In A Cohort Of Patients On Migalastat Treatment For At Least 3 Years

Michael West[1], Derralynn Hughes[2], Gere Sunder-Plassmann[3], Ana Jovanovic[4], Eva Brand[5], Daniel G. Bichet[6], Antonio Pisani[7], Albina Nowak[8], Roser Torra[9], Aneal Khan[10], Olga Azevedo[11], Anna Lehman[12], Aleš Linhart[13], Simon McErlane[14], Jasmine Rutecki[15], Joseph D. Giuliano[15], Eva Krusinska[15,a] and Peter Nordbeck[16]

[1]Department of Medicine, Dalhousie University, Halifax, NS, Canada, [2]Lysosomal Storage Disorders Unit, Royal Free London NHS Foundation Trust and University College London, London, UK, [3]Division of Nephrology and Dialysis, Department of Medicine III, Medical University of Vienna, Vienna, Austria, [4]Northern Care Alliance NHS Foundation Trust, Salford, UK, [5]Internal Medicine D, Department of Nephrology, Hypertension and Rheumatology, Interdisciplinary Fabry Center Münster, University Hospital Münster, Münster, Germany, [6]Department of Medicine, Hôpital du Sacré-Coeur, University of Montréal, Montréal, QC, Canada, [7]Department of Public Health, Nephrology Unit, Federico II University Hospital, Naples, Italy, [8]Department of Endocrinology and Clinical Nutrition, University Hospital Zurich and University of Zurich, Zurich, Switzerland, [9]Inherited Kidney Diseases, Nephrology Department, Fundació Puigvert, Universitat Autònoma de Barcelona, Barcelona, Spain, [10]M.A.G.I.C (Metabolics and Genetics in Canada) Clinic Ltd., Department of Paediatrics, University of Calgary, Cumming School of Medicine, Calgary, AB, Canada, [11]Cardiology Department, Reference Center on Lysosomal Storage Disorders, Hospital Senhora da Oliveira, Guimarães, Portugal, [12]Department of Medical Genetics, University of British Columbia, Vancouver, BC, Canada, [13]Second Department of Internal Cardiovascular Medicine, First Faculty of Medicine, Charles University and General University Hospital, Prague, Czech Republic, [14]Amicus Therapeutics, Sydney, NSW, Australia, [15]Amicus Therapeutics Inc., Princeton, NJ, USA and [16]University Hospital Würzburg, Würzburg, Germany

[a]Author working as a consultant under the contract of Pharmaland Consulting Group

Background: The followME Fabry Pathfinders registry (EUPAS20599) is evaluating real-world safety, effectiveness, and patient-reported outcomes for patients with Fabry disease (FD). *Aim:* We present effectiveness data across categories of kidney function at enrollment in patients who had received ≥3 years of migalastat treatment. *Methods:* Patients were enrolled into one of three groups: migalastat-amenable *GLA* variants receiving migalastat (reported here), any *GLA* variant receiving enzyme replacement therapy, and migalastat-amenable *GLA* variants not receiving FD-specific therapy (untreated). Patients were ≥16 years old with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. *Results:* As of August 2022, 125 patients (60.0% males; median age, 58.0 years) had a mean migalastat exposure of 3.9 years. At enrollment, mean ± *SD* eGFR was 83.7±22.5 mL/min/1.73 m^2 and, overall, 17 patients (13.9%) had an eGFR <60 mL/min/1.73 m^2. Median urine albumin-creatinine ratio was 19.0 mg/g (range 0–1124, n = 40). Mean ± *SD* eGFR annualised rate of change (mL/min/1.73 m^2/year) in the overall cohort was −0.9 ± 4.9. When analysed by eGFR category at enrollment, mean ± *SD* annualised change was −1.0 ± 3.9 in patients with eGFR ≥90 (33.6%), −1.0±5.9 in patients with eGFR ≥60–<90 (43.2%), and −0.4 ± 3.5 in patients with eGFR ≥30–<60 (12.8%). Overall, 99.2% of patients did not experience a renal Fabry-associated clinical event.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Excluding patients with the predominantly cardiac variant p.N215S (30.4%, $n = 38$), median eGFR rate of change was −1.5 (Q1 −3.7 to Q3 0.8) mL/min/1.73 m^2/year, $n = 81$. *Conclusions:* These data support sustained effectiveness with migalastat, regardless of kidney function at enrollment, in an amenable real-world cohort of patients with FD.

An Integrated Approach to Ethics Education in Genetics

Lisa Dive and Alison McEwen

University of Technology Sydney, Sydney, NSW, Australia

Background: Medical education incorporates ethics teaching to equip clinicians for ethical dilemmas they encounter in their practice. Genetic counselling is an area of practice with a high degree of ethical complexity. *Aim:* We describe an approach to integrating ethics content throughout a postgraduate genetic counselling program to equip students for a range of ethically complex scenarios. Our approach is based on two key clinical ethics competencies. First, students need access to a basic array of ethical concepts to articulate and map ethical complexity. Second, they need reasoning skills to evaluate potential courses of action and critically assess different approaches. *Method:* Early in our postgraduate program students complete an introductory module in health ethics. This module introduces a range of ethical concepts and prominent ethical theories, and teaches students to distinguish between normative and descriptive propositions. We introduce basics of philosophical reasoning, and students apply this knowledge to simple clinical scenarios. Throughout the two-year course of study, students apply ethical concepts to increasingly complex scenarios such as research and public health genomics. Ongoing ethics education also includes supported reflection on ethically complex cases in small supervision groups. *Results:* In the first six years of teaching there has been little change to our approach. Most students report enjoying the ethics content and engage robustly with practical exercises. Based on student feedback we now explain our model for ethics education more explicitly. *Conclusions: Our* approach demonstrates the value of equipping students with conceptual and practical tools for grappling with ethically complex situations.

Empowering Human Research Ethics Committees (HREC) Members to Review Genomics Ethics Applications: Qualitative Evaluation of a Pilot Version of a Custom Online, Educational Resource

Ella McGahan[1], Jennifer Berkman[1], David Milne, Amy Nisselle[3,4], Bronwyn Terrill[5], Russell Gear[6], Susan Gardiner[2], Lisa Eckstein[7], Natalie Taylor[8], Ingrid Winship[4,6], Rebekah McWhirter[9], Jason Lodge[10] and Aideen McInerney-Leo

[1]Frazer Institute, University of Queensland, Brisbane, QLD, Australia, [2]Metro South Human Research Ethics Committee, Brisbane, QLD, Australia, [3]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [4]The University of Melbourne, Melbourne, VIC, Australia, [5]Garvan Institute of Medical Research, University of New South Wales, Sydney, NSW, Australia, [6]Royal Melbourne Hospital, Melbourne, VIC, Australia, [7]Faculty of Law, University of Tasmania, Hobart, TAS, Australia, [8]Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [9]School of Medicine, Deakin University, Melbourne, VIC, Australia and [10]School of Education, University of Queensland, Brisbane, QLD, Australia

Background: There has been an exponential expansion in the complexity and utilisation of genomic technologies in research. However, HREC members have reportedly low confidence in reviewing genomics applications. *Aim:* Develop and evaluate an online educational resource comprehensible by nonscientific HREC members, capturing education on genomics and the ethical, social, and legal implications of genomic research. *Methods:* A resource was developed referencing the Program Logic Model for Genomics Education Interventions and guided by adult/online learning principles. This pilot-test is the first step of a multi-staged evaluation. Qualitative semi-structured interviews with HREC members/experts elicited feedback regarding utility, impact on confidence, and suggestions for refinement. Transcribed interviews were analysed using deductive content analysis. *Results:* 12 participants (10 HREC members and 2 genomics experts) reported that the resource was easy to access and intuitive to navigate. Most found the content comprehensive, appropriately pitched, with a manageable/optimal quantity of information. Recommendations included a progress bar, active learning elements, hints for reviewing applications, and more detail regarding data storage. HREC members perceived improved genomic confidence and reported intentions to re-access the resource in the future. Participants would recommend this resource to other HREC members, and genomic researchers developing an ethically defensible plan. *Conclusions:* This is the first study to develop and evaluate a genomic education resource tailored to Australian HREC members. Pilot testing will inform refinement of the resource prior to quantitative evaluation by HRECs nationally. Ultimately, this resource will increase HREC member confidence in reviewing genomics ethics applications and empower researchers to prepare quality HREC applications.

Implementing a Precision Care Clinic Into Routine Healthcare — Phase 1 Learnings

Skye McKay[1,2], Shuang Liang[1,2], Jeffery Chan[2], Arya Shinde[2], Bridget Douglas[1,2], Helen Ke[1], Mandy Ballinger[1,2,3,4], David M Thomas[1,2,3,4], Frank Lin[1,2], Milita Zaheed[1,2], Kathy Tucker[1,2], David Goldstein[1,2] and Natalie Taylor[1,2]

[1]Precision Care Clinic, Prince of Wales Hospital, Sydney, NSW, Australia, [2]Faculty of Medicine and Health, University of New South Wales, Sydney, NSW, Australia, [3]Genomic Cancer Medicine Program, Garvan Institute of Medical Research, Sydney, NSW, Australia and [4]Omico, Sydney, NSW, Australia

Background: Despite significant advances in precision medicine, gaps persist in the real-world provision of genomics-care, resulting in fragmented implementation and missed opportunities for patients. The Precision Care Clinic (PCC) has been established to facilitate the integration of genomic data into routine cancer care, with the support of implementation science to promote successful integration and inform scale-up. *Aim:* Phase 1 aims to co-design the PCC, an implementation platform, and a suite of outcome measures to concurrently assess the implementation and effectiveness of the clinic. *Methods:* Clinic co-design took place from April–Dec 2023. A mixed methods approach was applied to data from stakeholder interviews, a patient pilot cohort, meeting minutes, and clinical observations to identify underlying factors influencing the implementation of the PCC. Implementation strategies and outcome measures linked to determinants at each level (i.e., implementation, service, patient) were refined using co-design approaches. *Results:* Determinants influencing PCC implementation include; access to materials and equipment, existing workstreams, and relative priority (Inner Setting); PCC inclusion in clinical communication, and awareness of the PCC rationale and access process (Outer Setting). The rapidly changing landscape of precision medicine has influenced PCC co-design, and subsequent outcomes (Implementation Process). From the patient perspective, constructs of accessibility, timeliness, shared understanding, and satisfaction hold value. *Conclusions:* Implementation of the PCC requires

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

built-in flexibility to allow for optimal fit within evolving precision medicine practices. Defining "success" on multiple levels within the broad context of precision medicine requires a shared understanding of stakeholder values and co-design to develop meaningful outcome measures.

A Case of KARS-Related Disease — A Diagnostic Odyssey Highlighting the Benefit of Local Research Collaborations and Expertise

Fiona McKenzie[1,2], Maina P. Kava[2,3,4], Tara R. Richman[5,6,7,8], Jonathon Silberstein[2,3], Preeti Raghwani and Aleksandra Filipovska[5,6]

[1]Genetic Health WA, Perth, WA, Australia, [2]School of Paediatrics and Child Health, UWA Medical School, University of Western Australia, Perth, WA, Australia, [3]Department of Neurology, Perth Children's Hospital, Perth, WA, Australia, [4]Department of Metabolic Medicine, Perth Children's Hospital, Perth, WA, Australia, [5]ARC Centre of Excellence in Synthetic Biology, University of Western Australia Centre for Medical Research, Perth, WA, Australia, [6]Telethon Kids Institute, Perth Children's Hospital, Perth, WA, Australia, [7]Harry Perkins Institute of Medical Research, QEII Medical Centre, Perth, WA, Australia and [8]Centre for Medical Research, The University of Western Australia, QEII Medical Centre, Perth, WA, Australia

Background: A female child of non-consanguineous birth with a complex regressive neurodevelopmental disorder, including significant global developmental delay, refractory epilepsy, dyskinesia, dysautonomia, bulbar dysfunction, bilateral profound sensorineural hearing loss and chronic microcytic anemia, died at 20 months. A provisional diagnosis of KARS-related disease was made based on identifying a homozygous variant of uncertain significance in the nuclear-encoded lysyl-transfer RNA synthetase (LysRS) — KARS (c.1043G>A, p.(Arg348His)). Functional studies confirming pathogenicity were awaited. *Results:* Muscle biopsy showed mitochondrial cytopathy, with normal respiratory chain analysis on muscle and skin fibroblasts. Immunoblotting using patient fibroblast cells was unremarkable, limiting the scope for additional functional validation. Four years after our patient's loss functional analyses of mitochondrial protein synthesis showed a significantly reduced rate of translation, typical of variants in tRNA synthetases, including LysRS. The follow up functional analyses benefited from proximity of local specialists to experts in mitochondrial biology within our state. *Conclusions:* We present a case of KARS-related disease, a rare mitochondrial condition. Perseverance for a diagnosis after the patient's death helped to finally confirm the diagnosis. This study illustrates the complexity associated with rare diseases, including the diagnostic odyssey for families, compounded by uncertainty of molecular results in the absence of clinically available functional studies to validate the suspected cause. It also highlights the need for better and early functional testing to enable timely reproductive planning. We hope this will improve knowledge of mitochondrial conditions and highlight the importance of research collaborations and available local expertise in providing definitive answers for families.

How Has Genetic Counselling Practice Responded to Direct-To-Consumer Genetic Testing?

Cushla McKinney[1], Giselle Newton[2], Vaishnavi Nathan[2] and Aiden McInerney-Leo[2]

[1]University of Technology Sydney, NSW, Australia and [2]University of Queensland, Brisbane, QLD, Australia

Background: Direct to consumer genetic testing (DTC-GT) has expanded exponentially in the past decade. Genetic counselling professionals (GCPs) are in a unique position to help people understand and contextualise DTC-GT, with their psychoeducational expertise. Little is known, however, about GCPs' experience with, attitudes towards, and capacity to meet the needs of DTC-GT consumers. *Aims:* To consolidate what is known about how GCPs currently support DTC-GT customers, understand counsellor and consumer needs, and identify research gaps. *Methods:* A scoping review was conducted in PubMed, Medline, EMBASE, Scopus, CINAHL, PsychInfo, and ProQuest Theses and Dissertations, capturing empirical research on DTC-GT and counselling from 2007-2024. *Results:* Of the thirty-seven relevant articles identified, the majority assessed the views of GCPs working in clinical settings. GCPs felt that consumers should be offered counselling to facilitate informed consent and result interpretation but had mixed views on whether this was within the purview of clinical practice. Many felt it was the responsibility of companies to provide counselling but were concerned about conflicts of interest. Greater input by the profession was called for, as well as resources and practice guidelines around counselling consumers. *Conclusions:* Despite the consensus that genetic counselling should accompany DCT-GT, little is known about DTC-GT companies' provision of counselling. GCPs also questioned the quality of industry-provided consumer support. Further research is needed to understand the nature and efficacy of company-provided counselling to DTC-GT consumers. To our knowledge, this is the first review to evaluate attitudes towards and impact of DTC-GT specifically on genetic counselling professionals.

Interrogation of Open Reading Frame 15 (ORF15) of *RPGR* for Increasing Diagnostic Yield in Patients With X-Linked Retinitis Pigmentosa (XLRP)

Zachary E. McPherson[1,2], Benjamin M. Nash[2,3], Emma Hackett[2,3], Katherine Holman[2,3], Bruce Bennetts[2,3], Elisa E. Cornish[5], John R. Grigg[4,5] and Robyn V. Jamieson[1,2,4]

[1]Department of Clinical Genetics, Western Sydney Genetics Program, Sydney Children's Hospitals Network, Sydney, NSW, Australia, [2]Specialty of Genomic Medicine, Faculty of Medicine and Health, University of Sydney, Sydney, NSW, Australia, [3]Sydney Genome Diagnostics, Western Sydney Genetics Program, Sydney Children's Hospitals Network, Sydney, NSW, Australia, [4]Eye Genetics Research Unit, Sydney Children's Hospitals Network, Children's Medical Research Institute, Save Sight Institute, University of Sydney, Sydney, NSW, Australia and [5]Save Sight Institute, University of Sydney, Sydney, NSW, Australia

Background: Previous literature suggests that half of X-Linked Retinitis Pigmentosa (XLRP) can be attributed to variants found in open reading frame 15 (ORF15) of the *RPGR* gene. This region of the gene is difficult to sequence, especially on standard whole exome sequencing (WES) technologies, leading to diagnostic uncertainty for patients with clinical diagnoses of XLRP. *Aim:* To describe and quantify the diagnostic yield of Sanger sequencing for ORF15 of *RPGR* and sequencing of long-range PCR products by next generation sequencing methodology in patients who have previously had uninformative results based on WES technologies. *Methods:* 31 patients with a clinical diagnosis of XLRP with a previous uninformative WES were included. 15 participants had *RPGR* ORF15 assessed by an optimised focussed Sanger sequencing assay. 20 participants had *RPGR* ORF15 assessed by next generation sequencing (NGS) of long-read PCR products. Four were investigated with both methods. *Results:* Of the 15 participants who had *RPGR* ORF15 interrogated with a focused ORF15 Sanger sequencing based assay, four variants in *RPGR* were identified. Of the 20 participants who had *RPGR* ORF15 interrogated with long-read NGS, further analysis is

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

underway. *Discussion:* In the advent of rapidly progressing gene therapeutics for patients with XLRP, providing a genetic diagnosis is of significant clinical importance. *Conclusion:* Specific testing by a focussed *RPGR* ORF15 sanger sequencing based assay or Long Read next generation sequencing has significant diagnostic yield for suspected XLRP patients with previous uninformative exome testing. These results will be correlated with clinical phenotypic features for confirmation of the new genetic diagnoses for these patients.

Identification and Analysis of Stroke-Linked Gene Variants in Familial Migraine Populations

Zizi Molaee

Queensland University of Technology – Genomics Research Centre, QLD

Background: Migraine is recognised for its widespread prevalence and complex symptomatology, which poses significant management challenges. This study delves into the shared genetic foundations between migraines and vascular disorders, aiming to bridge the diagnostic gaps commonly faced in migraine assessments. *Method:* Our investigation into the genetic predisposition for stroke within familial migraine cohorts involved Whole Exome Sequencing (WES) on index cases from 20 migraine pedigrees. WES data was then subject to assessment for the presence of rare Single Nucleotide Variants (SNVs) with potential effects on gene function in genes commonly associated with stroke. *Results:* Candidate SNVs underwent segregation analysis, conducted via Sanger sequencing on the available family members. Candidate variants showing promising segregation were genotyped in a vast, unrelated migraine case-control cohort of around 1500 individuals. *Conclusion:* Our research offers valuable insights into the genetic complexity of migraine and its association with stroke, potentially transforming future diagnostic and therapeutic strategies for migraine management.

MEN2B Syndrome, the Impossible Clinical Challenge and How Genomic Newborn Screening Will Improve Morbidity and Mortality

Tashunka Taylor-Miller[1], Katherine Tucker[2,3], Ella Sugo[4], Antoinette Anazodo[3,5] and David Mowat[1,3]

[1]Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia, [2]Hereditary Cancer Centre, Prince of Wales Hospital Randwick, Sydney, NSW, Australia, [3]Discipline of Paediatrics, School of Clinical Medicine, UNSW Medicine & Health, UNSW, Sydney, NSW, Australia, [4]Department of Anatomical Histopathology, John Hunter Hospital, Newcastle, NSW, Australia and [5]Kids Cancer Centre, Sydney Children's Hospital, Sydney, NSW, Australia

Background: MEN2B syndrome, due to pathogenic M918T variant in the *RET* proto-oncogene, carries very high morbidity and mortality with >20% of patients deceased by 25 years of age. Larger cohort studies have demonstrated that thyroidectomy performed <1 year of age drastically changes morbidity and likely mortality. However, identifying these children is clinically extremely difficult due to the constellation of non-specific gastrointestinal, musculoskeletal and endocrine symptoms, which results in the mean age of diagnosis ~13 years of age by which time medullary thyroid carcinoma has metastasised. *Aims:* We advocate that including the M918T variant in *RET* gene in universal newborn screening programs and careful exclusion of intestinal ganglioneuromatosis on histopathology is the only way to enable earlier identification of affected children, which will improve clinical outcomes and provide an opportunity for thyroidectomy within the first year of life. *Results:* We present a 5-patient case series with excellent clinical photography and histopathology images, including subglottic mucosal ganglioneuromatosis which has not previously been described. *Conclusion:* We highlight that there are unique clinical features identifiable in the first 12 months of life of severe, persistent chronic constipation and alacrima (tearless crying) but often their significance is not recognised. There are also identifiable histopathological features of intestinal ganglioneuromatosis on gastrointestinal biopsies with adequate submucosa when the reviewing pathologist maintains a broad differential diagnosis mindset and is not blinkered by only excluding Hirschsprung disease.

Identity, Gratitude, and Responsibility: Importance of Reflexivity for Research Genetic Counsellors

Vaishnavi Nathan[1]

Frazer Institute, University of QLD, Translational Research Institute, Brisbane, QLD, Australia

Recent years have seen an increase in nontraditional genetic counselling roles such as the Research Genetic Counsellor. Genomic research projects recruiting patients and the public need personnel with genetic expertise and interpersonal skills for information provision, obtaining informed consent, and interpretation and return of results. The pressing need for a good cultural fit in research teams has also become apparent. The South Asian Genes and Health in Australia (SAGHA) study aims to increase South Asian involvement in health and genetic research to improve equity in healthcare. My role in the SAGHA study has been to lead Focus Groups with the Queensland South Asian community, engage and build relationships with community members and leaders, recruit participants, and return positive genetic results for Familial Hypercholesterolemia. As a research genetic counsellor who understands the cultural nuances and intersectionality of being a South Indian female, my role as Clinical Research Coordinator in this project has been immensely fulfilling, but has prompted deep reflection on identity, and appreciation and gratitude for culture, religion, and community. Unexpected outcomes of my involvement have been the weight of responsibility I have felt to succeed in this project, and the privilege of being entrusted with this work. Being a qualitative researcher with a personal connection to the work, highlights the importance for reflexivity, and acknowledging my role in the research process. Insights into the complexities and rewards of working with community to undertake genetic counselling research and the potential for personal impacts will be shared.

MN1 Haploinsufficiency: A Case Report and Review of an Ultra-Rare Syndrome

Fahaz Yusuf Nazer[1,2] and Andrew Paul Fennell[1,2]

[1]Monash Genetics, Monash Health, Melbourne, VIC, Australia and [2]Department of Paediatrics, Monash University, Melbourne, VIC, Australia

Background: MN1 is a tumor suppressor gene initially identified as having a role in meningioma and myeloproliferative disorders. MN1 C-terminal truncation (MCTT) syndrome was first described in 2020

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

associated with global developmental delay and craniofacial and brain abnormalities. Transcript analysis of MCTT patients supported a gain-of-function mechanism for C-terminal truncated *MN1* variants. Recently, a syndrome associated with *MN1* N-terminal truncations has been reported in a small number of individuals. N-terminal truncations are presumed to undergo nonsense-mediated decay (NMD) and limited data suggests they lead to a different, milder phenotype than MCTT syndrome. *Case:* We present a 14-year-old boy of Indian ethnicity with postnatal short stature, microcephaly, conductive hearing loss, facial dysmorphism, mitral valve regurgitation, delayed dentition, and features consistent with immunodysregulation. *Results:* Trio exome sequencing revealed a *de novo* heterozygous pathogenic variant in *MN1* c.1306C>T,p.(Gln436*), which is predicted to result in NMD. *Discussion:* Literature review identified seven individuals with N-terminal truncating variants in *MN1*. MN1 Haploinsufficiency syndrome is associated with a phenotype of conductive hearing impairment, postnatal short stature, microcephaly, cleft palate, craniosynostosis, and variable facial dysmorphism. As expected, our patient has several matching phenotypic features together with some novel features. However, this molecular diagnosis does not appear to account for his immunodysregulation phenotype, which may have a separate aetiology. *Conclusion:* This case adds to the current, limited understanding of MN1 Haploinsufficiency syndrome due to N-terminal truncating variants in *MN1*. Further cases are needed to comprehensively understand the phenotypic spectrum in this rarely reported syndrome.

Development and Optimisation of High-Throughput Laboratory and Bioinformatics Processes for Population DNA Screening in Australia

Tú Nguyen-Dumont[1,2], Jason A. Steen[1], Adam Brotchie[3], Bryony Thompson[4], Ari Horton[4,5,6], Paul A. James[4,7], Ingrid Winship[4,8], Jane Tiller[3], Melissa C. Southey[2,9,10], Paul Lacaze[3] and on behalf of the DNA Screen Investigator Group

[1]School of Translational Medicine, Monash University, Melbourne, VIC, Australia, [2]Department of Clinical Pathology, The University of Melbourne, VIC, Australia, [3]School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC,Australia, [4]Royal Melbourne Hospital, Melbourne, VIC, Australia, [5]Paediatric Cardiology and Cardiovascular Genomics, Monash Health, Melbourne, VIC Australia, [6]Victorian Heart Institute, Monash University, Melbourne, VIC, Australia, [7]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [8]Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia, [9]Precision Medicine, Monash University, Melbourne, VIC, Australia and [10]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC, Australia

Background: DNA Screen is a national pilot study of population genomic screening for Hereditary Breast and Ovarian Cancer (HBOC), Lynch Syndrome (LS) and Familial Hypercholesterolemia (FH). *Method:* The DNA Screen study recruited >10,000 participants, aged 18-40 years, who consented to germline DNA screening for HBOC (*BRCA1, BRCA2, PALB2, ATM*:c.7271T>G), LS (*MLH1, MSH2, MSH6)* and FH (*APOB, LDLR, PCSK9*). We developed and optimised high-throughput laboratory and bioinformatics processes for i) targeted sequencing using a multi-gene panel, ii) identification of high-confidence genetic variants, iii) prioritisation and curation of medically actionable variants and iv) reporting to the study participants. *Results:* Libraries were enriched using a custom SureSelect XTHS2 panel (Agilent) and sequencing was performed on a NextSeq550 (Illumina). The bioinformatics pipeline was written in Nextflow and used BWA for mapping and VarDict for variant calling. Variant annotation was performed using VS-Clinical (VarSeq, Golden Helix). Variant prioritisation was performed by a variant curator. The genomic and sample metadata were stored on a PostgreSQL database, with in-house scripts developed for variant filtering and reporting. *Conclusion:* We will present the challenges and lessons learnt from piloting a screening program at this scale, with a focus on the technical aspects of the genetic test/variant curation, from a laboratory and bioinformatics point of view.

A Multi-Omic Approach to Precision T-Cell Receptor Therapy Against HLA-Presented Cancer Antigens in an Immunologically Cold Cancer

Gwo Yaw Ho[1,2], Peter Eggenhuisen[2], Anh Doan[2], Anusha Yellapragada[2], Ting Tian[2], Qi Xiong[2], Tracy Putoczki[3], Belinda Lee[3,4], Janet Chang[2], Jessica Wu[2], Holly Barker[3], Jason Steen[5], Justin Bedo[3,6], Sophia Frentzas[1,2], Cassandra Vandenberg[3], Hanim Abd Halim[2], Kylie Loh[2], Paul Hertzog[7], Sean Grimmond[4,8], Tony Papenfuss[3], Clare Scott[3,4], Eva Segelov[2,9], Pouya Faridi[2], Joshua Ooi[2] and Tu Nguyen-Dumont[5,8]

[1]Monash Health, Melbourne, VIC, Australia, [2]School of Clinical Sciences, Monash University, Melbourne, VIC, Australia, [3]Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia, [4]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [5]Central Clinical School, Monash University, Melbourne, VIC, Australia, [6]Department of Computing and Information Systems, University of Melbourne, Melbourne, VIC, Australia, [7]Hudson Institute of Medical Research, Melbourne, VIC, Australia, [8]Department of Clinical Pathology, University of Melbourne, Melbourne, VIC, Australia and [9]Faculty of Medicine University of Bern and Department of Radiation Oncology, Bern University Hospital, University of Bern, Switzerland

Background/Aim: T-cell receptor therapy (TCR-T) is a cell-based immunotherapy targeting human leukocyte antigen (HLA)-presented tumor neoantigens (TNA) using naturally occurring TCRs, enabling targeted immune-activation at very low-antigen density. TCR-T requires identification of cancer-specific HLA-presented TNAs and corresponding high-affinity TCRs against these TNAs. *Methods/Results:* We developed an integrated multi-omics TNA discovery platform, combining immunopeptidomics, genomics, and immunologic techniques. We successfully identified an immunogenic mutant HLA-presented TNA in aggressive immunologically 'cold' ovarian cancer with low tumor mutational burden: neuropeptide W E100Q (NPW_E100Q), restricted to HLA-A*33:03. Using single-cell RNA sequencing (scRNAseq), we discovered three high-affinity TCRs against NPW_E100Q in context of HLA-A*33:03. First, we optimised the antigen presenting cell (dendritic cell; DC) and CD8+ T-cell co-culture conditions (14-day culture with IL-7/IL-15/IL-21) to selectively expand NPW_E100Q-specific CD8+ T-cells, utilising HLA-matched healthy donor blood. We demonstrated that CD8+ T-cells expanded *in vitro* with DC pulsed with NPW_E100Q peptide showed increased NPW_E100Q-specific CD8+ T-cell proliferation. Subsequent scRNAseq revealed 1,023 paired α/β-TCR clonotypes in CD8+ T-cells co-cultured with NPW_E100Q peptide-pulsed DC. High-affinity TCRs were the α/β-TCR pairs of the most abundant clonotypes. Lastly, we engineered these high-affinity TCRs into HLA-match CD8 T cells and demonstrated in vivo efficacy by improving median time to harvest (TTH) of tumor bearing mice (42 vs. 21 days, p = .015). *Conclusion:* We successfully generated proof-of-concept evidence for precision TCR-T. We will expand this study into a cohort of well-curated pancreatic biospecimens with matched genomic and clinical data. This work

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

has the potential to revolutionise solid tumor treatment landscape with precision immunotherapy.

Insights From the 2022–23 Census of the Australasian Genetics Workforce

Amy Nisselle[1,2], Jaitika Duggal[1,3], Amy Pearn[3], Lauren Hunt[3], Anaita Kanga-Parabia[4], Ben Lundie[5,6,7], Claire Wong[8], Helen Mountain[9], Jason Pinner[10], Lyndon Gallacher[4], Rachel Williams[4], Sebastian Lunke[5], Yemima Berman[10] and Clara Gaff[1,2]

[1]Genomics in Society, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Australian Genomics, Melbourne, VIC, Australia, [3]Human Genetics Society of Australasia, Sydney, NSW, Australia, [4]Australasian Society of Genetic Counsellors Diversity, Inclusion, Cultural Competency and Equity Committee, Sydney, NSW, Australia, [5]Australasian Society for Diagnostic Genomics, Sydney, NSW, Australia, [6]Pathology Queensland, Brisbane, QLD, Australia, [7]University of Queensland, Brisbane, QLD, Australia, [8]NSW Health, Sydney, NSW, Australia, [9]Australasian Society of Genetic Counsellors, Sydney, NSW, Australia and [10]Australasian Association of Clinical Geneticists, Sydney, NSW, Australi

Background: As genetics services are evolving, a census of the genetics workforce was urgently needed to inform workforce modeling. *Aim:* To assess current Australasian genetic workforce practice and perceptions of meeting demand. *Methods:* Individuals working/studying in human genetics in Australasia completed an online survey deployed by HGSA with Australian Genomics (Nov'22–Mar'23). Data included demographics, practice and work conditions, and were analysed using descriptive statistics, z-tests and c^2 tests, plus content analysis of open-text responses. *Results:* Surveys were completed by 541 individuals: 252 (47%) genetic counsellors, 167 (31%) laboratory scientists or genetic pathologists, 75 (14%) clinical geneticists, and 47 (9%) other (administrators, ethicists, educators, etc.). Respondents primarily identified as female (82%); 63% resided in VIC/NSW. 42% had <10 y experience. 65% were employed by a public clinical/pathology service; 68% were in a permanent role. 44% felt their current workload was not appropriate and 53% worked overtime (up to 5 h/wk). Respondents spent an average 50% of work hours on clinical or laboratory tasks, and 14% on administrative tasks. 16% planned to retire within 10 y. Over 90% of respondents indicated shortages in meeting service demand across all professions, now and in the future. *Conclusions:* This census is the first to include all professions working in human genetics across Australasia and is contributing to workforce modeling calculations. Shortages were seen across both clinical and laboratory professions; more administrative support may increase capacity to meet demand. Census data are being used to inform state and federal policy, research programs, and international comparisons.

Antenatally Detected Copy Number Variants and Their Impact on Pregnancy Termination Rates Following Counselling at a Public Clinical Genetics Unit

Fallon Noon[1] and Christopher M. Richmond[1,2]

[1]Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia and [2]School of Medicine, Griffith University, Gold Coast, QLD, Australia

Background: Chromosome microarray (CMA) is routinely incorporated in prenatal invasive testing paradigms. Detection of copy number variants (CNV) on CMA has been shown to influence termination of pregnancy (TOP) decision-making. *Aim:* To identify the number of women proceeding to TOP following genetic counselling for CNVs identified in their current pregnancy and whether rates differ based on the woman's demographic details and CNV characteristics. *Methods:* Retrospective clinical audit evaluated pregnant women who received counselling at Genetic Health Queensland between 1 January 2020 and 31 December 2023 following antenatal CNV detection. *Results:* The clinical audit identified 109 women; 90 (82.6%) electing to continue their pregnancy (COP) and 19 (17.4%) proceeding to TOP. Women selecting TOP were more likely to be nulliparous, have experienced a previous miscarriage or TOP and live in a metropolitan or regional area. A greater proportion of culturally and linguistically diverse women who did not require an interpreter were present in the TOP cohort whilst there were no women who identified as First Nations. Detected CNVs in the TOP cohort were more likely de novo, > 1Mb in sise, classified (likely) pathogenic and detected in the setting of fetal structural anomalies ($p < 0.05$). *Conclusions:* This audit suggests access to CNV parental segregation results and detailed fetal structural ultrasounds are important factors influencing TOP decision-making. Demographic information suggested women from more advantageous social and education backgrounds and women who had experienced previous pregnancy loss are more likely to pursue TOP.

Can Saliva-Derived DNA Be Used as a Template for the Detection of Clonal Hematopoiesis of Indeterminate Potential?

Robert O'Reilly[1], Jared Burke[1], Philip Harraka[1], Paul Yeh[2,3], Kerryn Howlett[1,3], Kiarash Behrouzfar[3], Amanda Rewse[1], Helen Tsimiklis[1]The Archimedes Investigators, The ABC Study Investigators, Kristen Bubb[6,9], Stephen J. Nicholls[6,7], Roger L. Milne[1,4,5] and Melissa C. Southey[1,4,8]

[1]Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Melbourne, VIC, Australia, [2]Monash Haematology, Melbourne, VIC, Australia, [3]Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia, [4]Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, VIC, Australia, [5]Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [6]Victorian Heart Institute, Monash University, Melbourne, VIC, Australia, [7]Victorian Heart Hospital, Melbourne, VIC, Australia, [8]Department of Clinical Pathology, The University of Melbourne, Melbourne, VIC, Australia and [9]Biomedicine Discovery Institute, Monash University, Melbourne, VIC, Australia

Background: Clonal haematopoiesis of indeterminate potential (CHIP) has been associated with many adverse health outcomes. Recent analyses of large human datasets identified CHIP associated subtypes, stratified by somatic mutations. Further research is required to understand the critical genes and pathways relevant to each CHIP subtype, evaluate how CHIP clones evolve over time, and to further advance functional and therapeutic studies. Mature, large epidemiological studies are well placed to address these questions, but those studies often collect saliva rather than blood from participants. *Aim:* To assess saliva-derived DNA as a template for the detection of CHIP. *Methods:* We used a custom targeted CHIP-gene panel (Agilent SureSelect XT HS2) and paired saliva- and blood-derived DNA samples from 94 participants of the Australian Breakthrough Cancer study. Data from the ten genes most frequently identified to carry CHIP-associated variants were included in this analysis. *Results:* Fourteen variants (*DNMT3A*=10, *TP53*=2, *TET2*=2), associated with CHIP were identified in the 188 test DNA samples with a Variant Allele Fraction (VAF) of 0.02 - 0.2 and variant depth >5 reads. Eleven (79%) of these CHIP-associated variants were detected in both the blood- and saliva-derived DNA sample after applying these thresholds. Three variants (21%) fell below VAF 0.02 in the paired saliva-derived DNA sample. *Conclusion:* Saliva-derived DNA is a suitable template

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

for detecting CHIP-associated variants. Saliva offers a non-invasive, cost-effective, practical alternative biospecimen that could be utilised to both advance CHIP research and be a companion to clinical translation into settings such as risk prediction, precision prevention, and treatment monitoring.

Expanding Upon *CTU2*-Related Microcephaly, Facial Dysmorphism, Renal Agenesis and Ambiguous Genitalia (MFRG) Syndrome

Sinead O'Sullivan and Julie McGaughran

Genetic Health Queensland, Brisbane, QLD, Australia

Background: Microcephaly, facial dysmorphism, renal agenesis and ambiguous genitalia (MFRG) syndrome is due to pathogenic variants in the *CTU2* gene. The *CTU2* gene encodes a thiouridylase protein involved in post-transcriptional tRNA modifications required for accurate protein synthesis. MFRG syndrome was first identified in 2016 and is also known as DREAM-PL syndrome. 11 cases have been reported to date. Cardinal features include global developmental delay (GDD), microcephaly, dysmorphism and genital anomalies. Congenital anomalies of the heart, brain, kidney and eye, seizures and hearing loss can also feature. *Aim:* We present three further cases to broaden the knowledge base about this rare paediatric condition. *Methods:* Parental consent was obtained for publication. Retrospective chart review was undertaken to document congenital malformations, growth parameters and development. A results table was created in Excel to capture the relevant data. *Results:* Patients A and B are sisters, aged 7 and 8 years. They both have two likely pathogenic (LP), in trans, *CTU2* variants (c.1691+1G>A, c.199C>T). Patient C is a 3-year-old male. He is homozygous for a LP *CTU2* variant *(*c.188T>C). All couples were nonconsanguineous. All patients had microcephaly, brachycephaly, dysmorphism, GDD, seizures and structural brain anomalies. Patient A had renal agenesis and Patient C had ambiguous genitalia. Patients A and C have hearing loss. Patient C additionally has significant colobomatous microphthalmia bilaterally. *Conclusion:* Widespread congenital malformations are associated with MFRG syndrome, in keeping with the underlying molecular pathophysiology. Ambiguous genitalia and renal agenesis may or may not feature. Colobomatous microphthalmia is an additional discriminating feature.

Health and Genetic Health Literacy Education for Students With Intellectual Disabilities: Teachers' and Students' Perspectives

Iva Strnadová[1,2], Karen-Maia Jackaman[1], Jennifer Hansen[1], Julie Loblinzk[1,2], Manjekah Dunn[1,3], Skie Sarfaraz[2], Sam Hurd[1], Joanne Danker[1], Michelle Tso[1], Sierra Angelina Willow[1], Chloe Molnar[1], Jackie Boyle[4], Jackie Leach Scully[1], Elizabeth Emma Palmer[1,3] and Bronwyn Terrill[1,5,6]

[1]University of New South Wales, Sydney, NSW, Australia, [2]Self-Advocacy Sydney, Sydney, NSW, Australia, [3]Sydney Children's Hospitals Network, Sydney, NSW, Australia, [4]Genetics of Learning Disability Service, Waratah, NSW, Australia, [5]Australian Genomics, Melbourne, VIC, Australia and [6]Garvan Institute of Medical Research, Sydney, NSW, Australia

Background: People with intellectual disability want to learn more about genetics, genomic testing and genetic conditions, but need to be empowered with the knowledge and skills to make informed health choices. Key to building this genetic health literacy is ensuring students with intellectual disability can access and participate in foundational science education at school. *Aim:* To explore whether teachers are adequately prepared or resourced to improve the genetic health literacy of students with intellectual disability, and to understand how students perceive their educational experience. *Methods:* Semistructured interviews and focus groups were conducted with 15 teachers in mainstream and special schools who teach genetics, genomics and health to students with intellectual disability, and 15 students and young people with intellectual disability. The interviews and focus groups were analysed using inductive content analysis. *Results:* Teachers said they lacked confidence, training, and resources to support students' genetic health literacy through the curriculum and expressed concerns about the potential sensitivity of the topics. Students and young people with intellectual disability reported they were not taught about genetics or genomics, how to make informed health choices, or how to make related life decisions. They were concerned that this lack of accessible knowledge would disadvantage them in becoming informed health consumers. *Conclusions:* Design and implementation of professional development opportunities and accessible, multimodal, resources to establish foundational genetic health literacy in schools is urgently needed. It is essential to upskill teachers so they can teach students with intellectual disabilities in a respectful, supportive, and trauma-informed manner.

Economic Evaluation of Genetic Exome Sequencing in an Australian Adult Genetic Department

Sumudu Perera Kimmantudawage[1], Seema Vyas[2], Leo Meekins-Doherty[1], Kirsty West[1], Paul James[1] and Maie Walsh[1]

[1]The Royal Melbourne Hospital, Melbourne, VIC, Australia and [2]London School of Hygiene and Tropical Medicine, London, England

Background: While the robust diagnostic yield of exome sequencing in adult patients across a variety of ages and phenotypes has previously been demonstrated, no economic analysis has been completed in an Australian context for adult exome data. *Aim:* To assess the relative cost-effectiveness of exome sequencing (ES) testing in adult patients in an Australian adult genetics medical department, compared to standard-care investigations and surveillance. *Methods:* Data on patients who underwent ES through an adult genetic department between 2016 and 2024 were analysed. A decision-analytic model which combines a Markov model and a decision tree, is to used to determine lifetime costs and quality-adjusted life years (QALYs) for the two strategies. Deterministic and probabilistic sensitivity analyses are to be undertaken to assess the robustness of findings and to explore decision uncertainty. *Results:* The incremental cost per additional QALY of ES testing compared with standard care investigations will be calculated. Cost-effectiveness will be measured against established thresholds of cost-effectiveness. *Conclusions:* If cost-effectiveness of adult-exome genetic testing is demonstrated, this may lead to wider scale implementation, thus leading to more accurate and timely diagnoses across Australia for genetic conditions, leading to a possible shorter time to accurate treatment and thus overall reduced government health-expenditure. If pathogenic variant detection rate rises and new evidence for personalised

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

treatment of at-risk individuals becomes available, the cost-effectiveness of cascade testing will further increase.

Efficacy and Safety of Oral Sepiapterin in Participants With Phenylketonuria on Sapropterin Dihydrochloride at Time of Phase 3 APHENITY Study Entry

Roberto Zori[1], Melissa Lah[2], Stephanie Offord[3], Allan Lund[4], Thomas Opladen[5], Heidi Peters[6], Laura Guilder[7], Fatih Ezgü[8], Margo Sheck Breilyn[9], Filippo Manti[10], Ixiu del Carmen Cabrales Guerra[11], Philip Jenkins[12], Kimberly Ingalls[13], Zhenming Zhao[13], Alexandra Larkin[13], Catalina Hughes[13], Kathleen Somera-Molina[13], Neil Smith[13] and Nicola Longo[14]

[1]Department of Paediatrics, University of Florida College of Medicine, Gainsville, FL, USA, [2]Department of Medical and Molecular Genetics, Indiana University School of Medicine Indianapolis, IN, USA, [3]Department of Paediatrics, Medical College of Wisconsin, Milwaukee, WI, USA, [4]Department of Paediatrics and Clinical Genetics, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark, [5]Heidelberg University, Medical Faculty Heidelberg, Center for Paediatric and Adolescent Medicine, Division of Paediatric Neurology and Metabolic Medicine, Heidelberg, Germany, [6]Department of Metabolic Medicine, Royal Children's Hospital, Melbourne, VIC, Australia, [7]The Hospital for Sick Children, Toronto, ON, Canada, [8]Faculty of Medicine, Gazi University, Ankara, Turkey, [9]Department of Genetics and Genomics, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [10]Department of Human Neuroscience, Unit of Child Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy, [11]PanAmerican Clinical Research, Guadalajara, Jalisco, Mexico, [12]PTC Therapeutics Pty Ltd, Melbourne, VIC, Australia, [13]PTC Therapeutics Inc., South Plainfield, NJ, USA and [14]Division of Medical Genetics, University of Utah, Salt Lake City, UT, USA

Background: The Phase 3 APHENITY trial (NCT05099640) was a global, two-part, registration-directed study evaluating the efficacy and safety of sepiapterin in a broad PKU population. APHENITY met its primary endpoint demonstrating significant reductions in blood Phe with sepiapterin. We assessed the efficacy and safety of sepiapterin versus placebo in a subset of participants receiving sapropterin dihydrochloride at study entry. *Methods:* Participants receiving sapropterin dihydrochloride at study entry completed a 7-day washout period prior to sepiapterin dosing. Part 1 was a 14-day sepiapterin-responsiveness test. Participants ≥2 years with ≥15% reduction in blood Phe progressed to Part 2 (6-week, randomised, placebo-controlled, double-blind). Safety was also evaluated. *Results:* Of the 157 participants in APHENITY, 27 (17.2%) (median age 14.0 years; [min, max; 2, 42]) were receiving sapropterin dihydrochloride at study entry (mean blood Phe of 581.8µmol/L). Following a 7-day washout, mean blood Phe increased to 680.9µmol/L. After 14 days of sepiapterin treatment (60 mg/kg), mean blood Phe was reduced by 48% from 581.8µmol/L to 304.6µmol/L. Most participants (23/27, 85.2%) responded to sepiapterin with a blood Phe reduction of ≥30% from baseline (Part 1). At Weeks 5 and 6 of Part 2, a significant reduction in mean blood Phe from baseline was observed with sepiapterin (n = 14; least-square mean change [*SE*], −467.5 [44.5]µmol/L) compared to an increase with placebo (n = 7; 123.6 [62.3]µmol/L; $p < 0.0001$). Overall, sepiapterin was well tolerated. *Conclusions:* Treatment with sepiapterin resulted in a clinically meaningful and significant reduction in blood Phe in children and adults with PKU receiving sapropterin dihydrochloride at study entry.

Benefits and Challenges Associated With the New MBS Item Numbers for Reproductive Genetic Carrier Screening

Nathan Petricevic, Michelle Challis, Sree Koilkandadai, Trent Anderson, Cara Roux, Amelia Stott, Charlotte Bulbrook, Lisa Ward, Lisa Bickley and Melanie Smith

Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: In November 2023, two new item numbers for Reproductive Genetic Carrier Screening (RGCS) were introduced to the Medicare Benefits Schedule (MBS). The item numbers 73451 and 73452 cover RGCS for cystic fibrosis, spinal muscular atrophy and fragile X syndrome. Victorian Clinical Genetics Services (VCGS) has been offering fee-for service RGCS under the name *prepair*™ since 2012 and have adapted our workflow to include the new MBS item numbers. *Aim:* Evaluate the benefits and challenges associated with the RGCS MBS item numbers. *Methods:* Review the accessibility to MBS funded RGCS and the benefits and challenges VCGS has observed with the new MBS item numbers. *Results:* The new MBS item numbers have enabled greater access to RGCS with no out of pocket cost for individuals, resulting in a 500% increase in tests being received on a weekly basis at VCGS. Of these RGCS requests 98% of individuals were eligible for the Medicare rebate. Challenges encountered included: increased sample volumes, high throughput wet lab processes, additional staffing resources, impact on turnaround times, Laboratory Information Management System integration, Medicare consent, lack of awareness and understanding of individuals and health practitioners regarding screening and arranging partner screening. *Conclusions:* Medicare funded RGCS has increased accessibility to *prepair*™ screening with a noted increase in the uptake in genetic carrier screening. Ongoing challenges include finding the balance between not compromising on our service, educating new referrers, streamlining processes, and using our resources efficiently. VCGS experience in adapting to MBS funded RGCS may prove valuable to other organisations.

Mitochondrial DNA Maintenance Defects — Clinical Review of Two Cases of Optic Atrophy Type 1 (OPA-1)

Sally Smith[1,3], Liza Phillips[1,3], Anita Inwood[1,3], Dave Coman[2,3], Jim McGill[4], Michelle Lipke[1,2] and Janelle Nisbet[1,3]

[1]Queensland Lifespan Metabolic Service, Mater Hospital, Brisbane, QLD, Australia, [2]Queensland Lifespan Metabolic Service, Queensland Children's Hospital, Brisbane, QLD, Australia, [3]University of Queensland, Brisbane, QLD, Australia and [4]Mater Research Institute-University of Queensland, Brisbane, QLD, Australia

Background: The Optic atrophy type 1 (*OPA-1*) gene encodes a protein that localises to the inner mitochondrial membrane and is integral to a number of cellular processes. OPA1 (OMIM#125250) is one of the most common causes of autosomal dominant optic atrophy (OA), however up to 20% of patients develop a more complex neurodegenerative disorder, including deafness, chronic progressive extraocular ophthalmoplegia (CPEO), ptosis, ataxia, peripheral neuropathy and myopathy. Although this condition is reportedly

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

characterised by significant intra- and inter-family phenotype variability, we present two unrelated cases from our centre who exhibit similar features and clinical challenges. *Aim:* To highlight the potential phenotypes and clinical challenges associated with this condition. *Methods:* Chart review of patients with *OPA-1* at our centre. *Results:* Case-1 (C1), 24 years and Case-2 (C2), 28 years, had normal early development and presented with OA in their teens. Both developed sensorineural deafness. Dysfunctional voiding has been a feature with C1 undergoing appendicovesicotomy and C2 has planned suprapubic catheter insertion. The clinical course of both has been characterised by chronic fatigue, weakness, obesity (BMI > 35 kg/2) and intermittent, fluctuating neurological symptoms with no clear aetiology defined. The pathogenic variants identified are: c.2708_2711del/p.(V903Gfs*3) and c.1391G>A respectively. *Conclusions:* OPA-1 presents with predictable features including OA and sensorineural deafness. Obesity has not been reported as a feature in the literature. Dysfunctional voiding is a feature in both our patients. Neurological manifestations may result from both organic and non-organic pathology and these symptoms in addition to chronic pain present a challenge for ongoing management, which is largely supportive.

XQ21.33Q22.1 Deletion Involving *PCDH19* in a Female Patient With Epilepsy, Intellectual Disability and Behavioral Abnormalities

Claire Pitts, Lex Smallhorne, Jasen Anderson, Minh La and James Harraway

Sullivan Nicolaides Pathology, Brisbane, QLD, Australia

Background: Traditionally, X-linked inheritance is characterised by affected males with unaffected or variably affected female carriers. However, a unique X-linked inheritance pattern has been described in association with epilepsy and mental retardation, whereby females are affected, and carrier males are spared. *Case presentation:* A 32 year-old female with epilepsy, intellectual disability and behavioral abnormalities was referred for microarray testing. SNP array of DNA from peripheral blood was performed and showed a female pattern with two copy number variants, including a pathogenic 3.2Mb deletion on the X chromosome, within bands q21.33-q22.1, wholly deleting *PCDH19*. Loss of function mutations and deletions in *PCDH19* are associated with epilepsy and mental retardation limited to females (EFMR). The disorder is characterised by infantile-onset seizures with variable intellectual impairment, autistic features and neuropsychiatric disease. EFMR is unique in that heterozygous females are affected with males largely spared, except in cases of mosaicism and Klinefelter syndrome (XXY). The underlying molecular mechanisms are yet to be fully elucidated, though hypotheses include cellular interference, blood-brain barrier disruption, and impaired function of gamma-aminobutyric acid (GABA) type A receptors. Genetic counselling and clinical correlation with features of EFMR was recommended, as was follow-up testing of the patient's parents to determine recurrence risk. *Conclusions:* SNP microarray successfully identified a pathogenic Xq21.33q22.1 deletion involving *PCDH19* in a patient with clinical features consistent with EFMR. This case highlights the importance of genetic testing of *PCDH19* in patients with epilepsy, intellectual disability and behavioral abnormalities. EFMR challenges the traditional understanding of X-linked inheritance patterns.

How Does Genetic Screening Impact Gamete Donation: A Scoping Review

Diya Porwal[1], Giselle Newton[2], Julia Mansour[3] and Lisa Dive[1]

[1]University of Technology, Sydney, NSW, Australia, [2]University of Queensland, Brisbane, QLD, Australia and [3]Clear Genetics, Hobart, TAS, Australia

Background: As genetic screening becomes more common in assisted reproduction, its clinical, social and ethical impacts remain unclear. Specifically, little is known about the experiences and perspectives of stakeholders affected by genetic screening in gamete donation. *Aim:* This study aims to understand what is known about the impact of genetic screening on gamete donation and identify any knowledge gaps. by summarising and synthesising the existing literature on the experiences and perspectives of various stakeholders. *Methods:* A scoping review was conducted using Medline, Embase, CINAHL and Scopus to identify original research, position statements, conference abstracts and posters. *Results:* Of the 474 articles identified, 25 papers from 20 studies were included in the review. Thematic analysis identified how genetic screening of gamete donors impacted: (1) donor selection, (2) donor recruitment and availability of donor samples, (3) relationships between clinics, donors and recipients, and (4) the responsibilities of healthcare professionals in fertility medicine. Donors expressed hesitation about their participation in expanded carrier screening. Genetic screening was a primary factor in recipient donor selection, yet other factors contributed to their application of genetic screening results. Health professionals working in fertility medicine felt they do not have sufficient expertise with genetic carrier screening to support donors and recipients. *Conclusions:* To our knowledge, this is the first review to consider the impact of genetic screening of gamete donors. Results suggest that all stakeholders feel uncertainty and discomfort around the implications of genetic screening. Further research is required to understand its impact on accessibility of gamete donation and explore how to support stakeholders.

Prenatal Diagnosis Following Preimplantation Genetic Testing for Monogenic Conditions (PGT-M)

Alice Poulton[1,2,3], Melody Menezes[1,2], Tristan Hardy[1,2], Sharon Lewis[2,3] and Lisa Hui[2,3,4,5]

[1]Monash IVF Group LTD, Melbourne, VIC, Australia, [2]University of Melbourne, Melbourne, VIC, Australia, [3]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [4]Mercy Hospital for Women, Melbourne, VIC, Australia and [5]The Northern Hospital, Melbourne, VIC, Australia

Background: Professional bodies currently advise all pregnant individuals to undertake confirmatory prenatal diagnostic testing following preimplantation genetic testing for monogenic conditions (PGT-M). *Aim:* We aimed to ascertain uptake of prenatal diagnostic testing following PGT-M in a large single centre population. *Methods:* This observational linkage study was undertaken using routinely collected outcome data from PGT-M cycles performed at one of Australia's largest PGT-M providers, and of prenatal

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

samples cytogenetically analysed in Victoria, Australia, between 2015-2022. Outcomes of all PGT-M clinical pregnancies were collected in compliance with the Reproductive Technology Accreditation Committee code of practice, which mandates reporting of pregnancy outcomes for clinical quality monitoring. *Results:* During the study period, there were 176 clinical pregnancies following the transfer of a PGT-M tested embryo in 132 patients. Eleven patients undertook confirmatory prenatal diagnostic testing in 12 pregnancies, representing a confirmatory testing rate of 8.3% (95% CI [4.7, 14.3]) per patient and 6.8% (95% CI [3.9, 11.5]) per pregnancy. The 176 clinical pregnancies resulted in 152 live births and pregnancies ongoing at the time of reporting, 21 losses ≤20 weeks gestation and 1 stillbirth. *Conclusions:* Most patients who conceive following the transfer of a PGT-M tested embryo do not undertake confirmatory prenatal diagnostic testing. The low uptake of confirmatory testing raises important considerations for genetic counselling for PGT-M and the acceptability of current clinical practice recommendations.

Multinational survey study Assessing GENetic Testing and counselling among patients (pts) with breAst cancer (MAGENTA): Results of the Genetic Counselling Experience

Sarah Powell[1,*], Marta Artigas[†], Irina Borovova[‡2], Poorva Gadiya[§3], Alice Hsu[‖], Ranjit Kaur[¶4,5,6], Lisa Kidd[7,*], Denise Rosenfeld[#], Mai Mohamed Saeed[**], Evelin Scarelli[††8] and Magdy Waheeb Youssef[9]

[1]Pink Hope, Sydney, NSW, Australia, [2]Russian Association of Oncology Patients 'ZDRAVSTVUY!', Russia, [3]Nag Foundation, Pune, India, [4]Consultant, Breast Cancer Welfare Association Malaysia, Selangor, Malaysia, [5]Board Member, Reach to Recovery International, Towson, MD, USA, [6]Board Member, Advanced Breast Cancer Global Alliance, Lisbon, Portugal, [7]Victorian Department of Education, Beaconsfield Primary School, Beaconsfield, VIC, Australia, [8]OncoGuia Institute, São Paulo, Brazil and [9]Medical Affairs, AstraZeneca International, Egypt

*Patient author, Australia, [†]Patient author, Argentina, [‡]Patient author, Russia, [§]Patient author, India, [‖]Patient author, Taiwan, [¶]Patient author, Malaysia, [#]Patient author, Mexico, [**]Patient author, Egypt, [††]Patient author, Brazil

Background: Despite genetic testing (GT) and counselling (GC) being key in breast cancer (BC) risk assessment, GC uptake rates are low even among pts undergoing GT. A global survey was conducted among pts with BC to identify gaps in the GC experience and to propose strategies to fill them. *Methods:* A steering committee comprising of pts and pt advocates co-developed a 38-question survey, which was offered to pts in Argentina, Australia, Brazil, Egypt, India, Malaysia, Mexico, Russia and Taiwan in local languages, through social media. The questions pathway was dependent on response to prior questions. Chi-square test was used to assess significance between responses, if applicable. *Results:* The final analysis set (FAS) included responses from 1176 respondents with a >90% completion rate of survey questions. In the FAS, 737 (63%) respondents reported having undergone GT. Most respondents in the FAS (768/1061; 71%) rated their awareness level of GT/GC (before BC diagnosis) as between 'very low' to 'moderate'. Among pts undergoing GT, 616 respondents responded to the question enquiring on the resources available to them to guide their GT experience, beyond their oncologist. These were the genetic counsellor (295/616; 48%), pt support groups (232/616; 38%) and websites (217/616; 35%). *Conclusions:* Most pts with BC are not offered GC, which significantly correlates with GT uptake. Since poor awareness of GC is a critical gap, improving GC services and pt education through pt advocates and online tools may increase GT rates, offering a more impactful GT experience for pts and their families.

Multinational Survey Study Assessing GENetic Testing and Counselling Among Patients with BreAst Cancer (MAGENTA): Results of Perceptions on Testing

Sarah Powell[1,*], Marta Artigas[†], Irina Borovova[‡2], Poorva Gadiya[§3], Alice Hsu[‖], Ranjit Kaur[¶4,5,6], Lisa Kidd[7,*], Denise Rosenfeld[#], Mai Mohamed Saeed[**], Evelin Scarelli[††8] and Magdy Waheeb Youssef[9]

[1]Pink Hope, Narrabeen, NSW, Australia, [2]Russian Association of Oncology Patients 'ZDRAVSTVUY!', Russia, [3]Nag Foundation, Pune, India, [4]Consultant, Breast Cancer Welfare Association Malaysia, Selangor, Malaysia, [5]Board Member, Reach to Recovery International, Towson, Maryland, USA, [6]Board Member, Advanced Breast Cancer Global Alliance, Lisbon, Portugal, [7]Victorian Department of Education, Beaconsfield Primary School, Beaconsfield, VIC, Australia, [8]OncoGuia Institute, São Paulo, Brazil and [9]Medical Affairs, AstraZeneca International, Egypt

*Patient author, Australia, [†]Patient author, Argentina, [‡]Patient author, Russia, [§]Patient author, India, [‖]Patient author, Taiwan, [¶]Patient author, Malaysia, [#]Patient author, Mexico, [**]Patient author, Egypt, [††]Patient author, Brazil

Background: Genetic testing (GT) is vital in the risk assessment of breast cancer (BC) and along with genetic counselling (GC), may inform treatment decisions. However, fewer than one-third of patients (pts) with BC undergo GT. A multinational survey was conducted for a deeper understanding of the barriers in the uptake of GT and GC. Results from this survey, focusing on awareness and patients' perceptions towards GT and GC have been reported here. *Methods:* A steering committee comprising of patients and patient advocates co-developed a 38-question online survey, which was launched in local languages for pts in Argentina, Australia, Brazil, Egypt, India, Malaysia, Mexico, Russia and Taiwan, through different social media platforms. The questions pathway was determined based on response to certain questions on GT & GC uptake. Percentage responses to a response option was calculated against the number of respondents for that question. *Results:* The final analysis set (FAS) included responses from 1176 participants with more than 90% completion rate of survey questions. Median age among respondents in the FAS was 42 years (IQR: 35, 49) at the time of BC diagnosis. Among survey respondents, 63% (737/1176) had undergone GT, and 37% (439/1176) did not undergo GT. *Conclusions:* There are critical gaps in the awareness of GT among pts and the public, along with gaps in perceived value and access to GT, with notable variance between the tested and the non-tested populations. Strategic action is needed to overcome the barriers to GT and to improve the pt experience.

Barriers and Facilitators of Pharmacogenomic Informed Antidepressant Prescribing in General Practice: Patient and General Practitioner Perspectives

Georgia Ramsay[1], Philip Ly[1], Sibel Saya[1], Chad Bousman[2], Jennifer Bibb[1], Victoria J Palmer[1] and Jon Emery[1]

[1]The University of Melbourne, Melbourne, VIC, Australia and [2]University of Calgary, Calgary, AB, Canada

Background: The successful implementation of pharmacogenomic (PGx) informed antidepressant medication prescribing in general

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

practice settings relies on a range of clinician and patient factors including patient-General Practitioner (GP) rapport, perceived evidence supporting PGx and integration into existing workflows. *Aim:* To explore patient and GP participant perspectives on the use of PGx informed prescribing in the context of the PRESIDE Trial (a randomised controlled trial of PGx informed antidepressant prescribing in general practice). *Methods:* Semistructured interviews are being conducted with patients and GPs (data collection ongoing, 20 participant and 11 GP interviews completed). Interviews are recorded and transcribed prior to thematic analysis being conducted using a mixed inductive and deductive approach. Themes are mapped to the Consolidated Framework for Implementation Research domains. *Findings:* While patients reported good understanding and enthusiasm about PGx, this often did not translate to discussions with their GP about the PGx informed antidepressant recommendations provided. Potential barriers to the implementation of PGx include a mismatch in timing of the PGx report with timing of prescribing decisions and the perception that GPs would initiate discussions about the PGx report. A strong patient-GP relationship facilitated PGx informed decision making. GPs had mixed perceptions on the value of PGx in antidepressant prescribing. Barriers identified included cost, stigma around antidepressant medication and PGx guidance being available at the most appropriate time during a patient's treatment. *Implications:* These insights are important for understanding how PGx informed prescribing, particularly in relation to antidepressant medications, can be implemented in the Australian context.

General Practitioner Perspectives on Genomics in Primary Care: A Qualitative Exploration of Using Polygenic Risk Scores for Evaluating Cancer Risk

Georgia Ramsay[1], Rachel Brooks[1], Christina Wade[1], Jamie Jie Mei Liew[1], Pavithran Alphonse[1], Jennifer McIntosh[1], Laura Forrest[2], Jon Emery[1], Sibel Saya[1] and the CRISP Trial, SCRIPT Trial and MAGPIE Study Investigators

[1]University of Melbourne, Melbourne, VIC, Australia and [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia

Background: Polygenic risk scores (PRS) can predict an individual's risk of developing a range of chronic conditions, including colorectal, melanoma, breast and prostate cancers. Primary Care is suggested as being best placed to provide PRS assessment in the Australian context. *Aim/Research Question:* What are General Practitioners' (GPs') opinions on the acceptability and utility of PRS-based approaches in primary care? Does exposure to PRS information through clinical trials influence GPs' perspectives of PRS? *Methods:* GPs were recruited in association with four, sequential research projects, 3 of which were bigger trials of PRS in primary care. Semi-structured interviews were completed, recorded and transcribed. Thematic analysis, with a mixed inductive and deductive approach was conducted. Co-coding was performed on a proportion of transcripts. *Results:* Thirty-one GPs participated (90% metropolitan based, 52% female). Themes identified across participants from all substudies included primary care being the appropriate setting for the implantation of PRSs for cancer risk evaluation and provide an avenue for encouraging patients to make cancer-risk modifying lifestyle changes within existing preventative health approaches. There was consensus on the need for education and endorsed clinical guidelines to underpin the responsible use of PRS. Common concerns raised by GPs included the short duration of standard consultations, implications on referral pathways for individuals identified as being at increased risk of specific cancer types and psychosocial impacts of receiving risk information. *Discussion/Conclusions:* While the integration of PRS into existing approaches to risk assessment in primary are settings is promising, several barriers must be addressed prior to implementation.

Genetics and Genomics Competencies in Master of Genetic Counselling: A Mapping Exercise

Gabrielle Reid and Jan Hodgson

Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia

Background: In 2022 the Human Genetics Society of Australasia IHGSA) developed 'Core Capabilities in Genetics & Genomics for Medical Graduates' to guide medical school curricula and inform credentialing of postgraduate education bodies. This included knowledge sets pertaining to science, public health, communication, and ethical, legal, and social issues in genomics. By comparison, the Australasian Society of Genetic Counsellors Board of Censors requires Master of Genetic Counselling (MGC) programs to meet competencies across domains, including genetics/genomics, counselling, ethics, and research. The genetic/genomic competencies are less detailed compared to topics included in HGSA competencies for medical graduates. *Aim:* To compare the two guidelines in terms of genetics/genomics content to identify whether the University of Melbourne (UoM) MGC curricula could complement and enhance the UoM Doctor of Medicine (MD). *Methods:* All domains of the HGSA core competencies document were systematically mapped against content and learning outcomes of current UoM MGC genetics/genomics curriculum. *Results:* The UoM MGC curricula provides more comprehensive coverage of the genetic and genomic competencies than the UoM MD and generally exceeds all 112 of the suggested MD Core Capabilities. *Conclusions:* The UoM MD enables students to customise their degree through 'MD Discovery' subjects. The MGC genetics/genomics curricula could contribute to this, ensuring that students with an interest in genomics are able to achieve the suggested Core Capabilities.

Genetics Immersion Program: Building Clinician Confidence, Workforce Capability and Inter-Specialty Collaboration

Chris Richmond[1,2]

[1]Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia and [2]School of Medicine, Griffith University, Gold Coast, QLD, Australia

Background: Genomics has important applications across all medical specialties and targeted genetic education/training is core to incorporation of accessible, safe and effective genomics in routine healthcare. Opportunities for meaningful genetics training for nongenetic medical trainees are, however, limited. *Aim:* The Genetics

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Immersion Program aimed to deliver dedicated clinical genetics training ('immersion') terms for clinicians training in non-genetic specialities in Queensland, Australia. Medical trainees completed a 3-month program placed within in a statewide public clinical genetics service, gaining clinical exposure and targeted education relevant to their home specialty. Trainees completed supervised projects, focused on improving clinical workflow, genetic testing or referral pathways within their specialty. Trainee perspectives on genomics, satisfaction and confidence were measured by pre- and post-term survey. *Results:* Five trainees from multiple adult and paediatric medical training pathways completed immersion terms with universally positive feedback. The program resulted in improved confidence in concepts, interpretation and application of genomics across all metrics surveyed. All trainees indicated the term was worthwhile, would change practice and was relevant to their home specialty. Trainees additionally completed thirteen separate genetics-focused projects, guidelines or work instructions, illustrating a value multiplier effect. Less tangible outcomes have included improved interspecialty collaboration, networking and enactment of the embedded genetics champion in health systems. *Conclusions:* Integrated genetic 'immersion' placements improve knowledge, confidence and ability of non-genetic clinician trainees to deliver effective genomic healthcare. Hospitals and Health Systems investment in genetics immersion initiatives has the potential to expand workforce capability, collaboration and interdisciplinary education across medical teams.

A Basic Physician Trainee's Genetic Immersion Experience in Cardiac Genetics

Sjors V Plugge[1], Christopher M Richmond[1,2], Julie McGaughran[1,3] and Jason Davis[3,4]

[1]Genetic Health Queensland, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia, [2]School of Medicine, Griffith University, Gold Coast, QLD, Australia, [3]School of Medicine, University of Queensland, Brisbane, QLD, Australia and [4]Cardiology Department, Royal Brisbane & Women's Hospital, Brisbane, QLD, Australia

Background: The rapidly expanding field of cardiovascular genomic medicine has required an increased knowledge of genetic testing and counselling. Targeted genomics education of nongenetic clinicians is essential to implement cardiac genomics in routine healthcare. *Aim:* The Genetics Immersion Program is a research-funded position for nongenetic clinicians to undertake a 3-month training program embedded within the Queensland statewide clinical genetics service. This poster details qualitative experiential outcomes of a basic physician trainee in cardiology completing the program. *Results:* In 2023, I undertook a 12-week placement with Genetic Health Queensland with a focus on cardiac genetics. Targeted orientation, education, weekly cardiac clinics and a genetics focused project was developed with clinical geneticist and cardiologist co-supervision. Over a 12-week period I consulted patients in outpatient cardiac genetic clinics with supervision of clinical geneticists. This included exposure to all aspects of inpatient and outpatient genomic healthcare; including phenotyping, consent, genetic testing and results interpretation. Completion of the immersion program increased my confidence in delivering informed genomic healthcare. *Conclusion:* The cardiac genetic immersion program has provided me with a skillset and resources to become a 'genetic champion' within my home cardiology department. This term has provided me with genomic literacy, an appreciation of the role of genetic testing in the cardiac clinic, an understanding of how to interpret genetic testing and the limitations of genetic testing. Increased training of non-genetic registrars in genetic clinics will improve appropriate referral and utilisation of genetic testing results in patients and relatives with genetic cardiac diseases.

The PERSYST Study: Pathogenic Evaluation of Recalcitrant Variants By Systematic Transactivation

Tarin Ritchie[1,2], Emmylou C. Nicolas-Martinez[1,3], Alison Gardner[1,2], Jamie Voueleng Zhang[1,2]The PERSYST Investigator Team, Lachlan A. Jolly[1,3] and Jozef Gecz[1,2,4]

[1]The Robinson Research Institute, University of Adelaide, Adelaide, SA, Australia, [2]Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia, [3]School of Biomedicine, University of Adelaide, Adelaide, SA, Australia and [4]South Australian Health and Medical Research Institute, Adelaide, SA, Australia

Background: Elucidating the mechanisms of splicing variants for diagnostic research often requires RNA-based functional investigations. Current diagnostic practices utilise patient clinically accessible tissues (CATs) to analyse variant impacts on Mendelian gene mRNA. However, >1500 Mendelian genes are not expressed in CATs, which we term 'silent Mendelian genes (SMGs)'. Functional investigations of splicing variants in SMGs, therefore, cannot be assessed by diagnostic research pipelines. The PERSYST study introduces novel application of CRISPR/dCas9 gene transactivation technology to induce SMG expression within CATs to functionally assess splicing variants. *Aim:* To resolve the functional mechanism of splicing variants of uncertain significance (VUS) for variant reclassification. *Methods:* Variant submissions via REDCap enquiry are reviewed against recruitment criteria: likely genetic condition, predicted splicing VUS, main phenotype, and availability of a patient CAT; skin fibroblast cell line. Fibroblast cell lines from recruited patients are subject to gene transactivation, and isolated mRNA is assessed by unbiased RNA sequencing. Project success is measured by resolving VUS impact on mRNA splicing and, ultimately, VUS reclassification. *Results:* As of April 2024, PERSYST has established a national equitable recruitment network of hospitals ($n = 4$), diagnostic laboratories ($n = 3$), and research collaborators ($n = 2$). We successfully transactivated 25 SMGs, opening opportunities for patient recruitment. Currently, 25 variants are approved for study, 15 cell lines are under investigation, and 1 variant has been submitted for reclassification. *Conclusions:* PERSYST is a revolutionary technology providing evidence for splicing VUS functional assessment to support reclassification. PERSYST is potentially relevant to >1500 OMIM genes and >280,000 ClinVar VUS splicing variants.

Curating RettBASE: Systematic Classification of *MECP2* Variants

Rocio Rius[1,2,3], Laura Wedd[1,2], Samantha J Bryen[1,2], Daniel G MacArthur[1,2], Cas Simons[1,2] and John Christodoulou[3,4,5]

[1]Centre for Population Genomics, Garvan Institute of Medical Research, and UNSW Sydney, Sydney, NSW, Australia, [2]Centre for Population Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia, [4]Murdoch Children's Research Institute, Melbourne, VIC, Australia and [5]Victorian Clinical Genetics Services, Melbourne, VIC, Australia

Background: RettBASE (http://mecp2.chw.edu.au/), established over two decades ago, is a publicly accessible database documenting *MECP2, CDKL5 and FOXG1* variants in 5150 individuals with

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Rett syndrome and related conditions. Prior to the availability of ACMG criteria, variant pathogenicity was classified based on inputs from the literature and direct submissions. With advances in variant classification, updating legacy databases like RettBASE to align with the current ACMG standards has become crucial for ensuring accurate diagnoses. *Aim*: To update the classifications of *MECP2* variants in RettBASE based on current ACMG curation standards, and submit data to ClinVar. *Methods: MECP2* variants were imported from RettBASE into a custom database and standardised to HGVS nomenclature in accordance with the NM_004992.4 MANE clinical transcript. Variants were classified through the ClinGen Variant Curation Interface (VCI) by applying the Rett and Angelman-like Disorders VCEP recommendations of ACMG/AMP guidelines for *MECP2* variants. The classified variants were then uploaded to ClinVar. *Results:* To date, variants from 94% of the participants in RettBASE with *MECP2* variants (n = 4485 individuals) have been classified and uploaded to ClinVar. 57% of the variants have been classified as pathogenic or likely pathogenic, and 25% as benign or likely benign. Additionally, 33% of these variants were novel or not previously associated with Rett syndrome in ClinVar. *Conclusions:* The systematic classification of RettBASE catalogue demonstrates effective application of current curation standards, with population allele frequency criteria having the largest effect on classifying variants as benign or likely benign. This highlights the utility of population databases in variant classification. Future efforts will focus on expanding curation to additional genes associated with Rett syndrome.

Only Seen in Clumps

Priya Susan Roy[1], Hnin Aung[1], Sarbjit Riyat[1], Antoon Hoekstra[1], Nandini Adayapalam[1], Ghusoon Abdulrasool[1,2] and Chiyan Lau[1,2]

[1]Pathology Queensland, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia and [2]University of Queensland Brisbane, QLD, Australia

Background: 1q chromosomal aberrations are associated with teratomas and tumorigenesis. However, prenatal detection of 1q tetrasomy has only ever been reported in 2 cases without an associated teratoma. *Case Description:* A 41-year-old female at 20 weeks gestation had abnormal ultrasound imaging showing foetal brain malformations. Foetal MRI revealed multiple intracranial anomalies with a dysplastic cerebellum, vermis, large cisterna magna, corpus callosum agenesis and ventricular dilatation. This was investigated further with an amniocentesis, which showed a mosaic (15%) tetrasomy (triplication) for 1q by microarray. FISH using the *CDKN2C* (1p32)/CKS1B (1q21) probe set confirmed the presence of some abnormal cells with tetrasomy for 1q, which appear to aggregate within a clump of cells from direct harvest of the amniotic fluid. *Discussion:* 1q trisomy (mosaic/non-mosaic) have been reported in the literature in association with a wide range of severe fetal abnormalities (including brain abnormalities, craniofacial dysmorphisms and other congenital anomalies) as well as stillbirth or short ex-utero survival. However, 1q tetrasomy has commonly been reported in the context of cases with prenatally detected oral teratoma. The finding of 1q tetrasomy is likely to be causative of the clinical phenotype observed in this fetus. The presence of mosaicism may influence the phenotype. The atypical behavior of the abnormal cells (i.e., clumped together) on direct harvested uncultured amniotic fluid suggests the presence of tumor cell clusters, potentially arising from a fetal tissue that directly shed cells in the amniotic fluid such as the oral cavity or cervical region. Microarray of the fetal skin revealed no abnormality. Autopsy and parental karyotype are underway.

'I've Never Been Asked': Community Perceptions of Involvement in Genomics Research in Australia

Fiona Russo[1], Isabella Sherburn[2], Keri Finlay[3], Jack Nunn[4], John Cannings[5], Monica Ferrie[6], Anne McKenzie[7], Sean Murray[8], Greg Pratt[9] and Tiffany Boughtwood[10]

[1]University of Southern Queensland, QLD, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [3]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [4]La Trobe University, Melbourne, VIC, Australia, [5]Involve Australia, Australian Genomics, VIC, Australia, [6]Involve Australia, Australian Genomics, VIC, Australia, [7]Involve Australia, Australian Genomics, VIC, Australia, [8]Involve Australia, Australian Genomics, VIC, Australia, [9]Involve Australia, Australian Genomics, VIC, Australia and [10]Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: There is increasing global support from governments and other funding bodies for community involvement (CI) in research, alongside a scientific and moral imperative for responsible and ethical research practice. 90% of Australian patient-led organisations in rare diseases have clearly articulated research priorities, indicating a desire among people affected by disease to be involved in research that impacts their communities. Philanthropic research, which is likely to have predominantly community-minded priorities, is worth over AU$1billion annually and increased more than 100% between 2007 and 2017. *Aim:* This research aimed to understand public perspectives on CI in health-related research activities, and to inform the development of guidelines for genomic researchers to improve this. *Methods:* A 37-question survey was distributed to 1,206 members of the Australian public by Dynata. The survey was co-designed by the Involve Australia working group of community members within Australian Genomics. *Results:* Key themes emerging from the survey data that impact potential involvement were: low community confidence to contribute, a limited understanding of CI, roles and recognition, trust and governance of data, perceived trustworthiness of research funders, and barriers and enablers related to time and personal resources. A variety of motivations for involvement were also stated. *Conclusions:* Members of the Australian public are interested in research involvement, however the differences between involvement and participation is poorly understood and a variety of barriers still exist. Researchers must actively reach out into community and offer opportunities to engage with research and identify community priorities.

Exploring the Role of the Noncoding Strand: Antisense Transcription and Gene Regulation

Jihoon Ryu[1,2]

[1]Cambridge Centre for International Research, Milton, Cambridge, England and [2]Daegu International School, Daegu, South Korea

The growing research on antisense transcription has revealed the importance of cellular function in the regulation of gene expression. As the prevalent, unappreciative regard of the noncoding strand has

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

shifted, the investigation of the transcript and the process of antisense transcription itself has come upon. Utilising RNA-Seq and NET-Seq datasets, the general trend of sense and antisense transcription was depicted with sense transcription showing a rise near the transcription start site and antisense transcription rates forming a gradual valley throughout the genes. In addition, the MNase-Seq and ChIP-Seq datasets were used to find out that nucleosome levels near the antisense transcription region do not drop significantly in comparison with sense transcription regions. However, as transcription factors and H3K4me3 levels rise when antisense transcription rates are high as well, they show a positive correlation. At last, the stability levels of the transcripts were measured, and it revealed a larger amount of unstable sense transcripts than anti-sense transcripts. This result may have been produced as the sense transcription levels are significantly greater than anti-sense transcription levels. The findings on antisense transcription hold significant promise for diverse applications in the future. In an era where genetic disorders without medical cure appear, antisense oligonucleotides (ASO) and RNA-based therapies may help treat the disorders. Currently, two ASO-mediated therapies are by the US Food and Drug Administration for the treatment of Duchenne muscular dystrophy and spinal muscular atrophy. Taken together, the outcomes underscore the substance of antisense transcription, emphasising that it should not be overlooked.

Evaluation of the Clinical Utility of Genomic Testing Using the Clinician-Reported Genetic Testing Utility InDEx (C-GUIDE) at Sydney Children's Hospitals Network, Australia

Ruvishani Christina Samarasekera[1,2], Penny Xiao[3], Ryan Pysar[1,2], Stephanie Luca[3], Elizabeth Emma Palmer[1,2], Robin Z. Hayeems[3,*] and Lisa Jean Ewans[1,2,4]

[1]Centre for Clinical Genetics, Sydney Children's Hospitals Network Randwick, Sydney, NSW, Australia, [2]School of Women's and Children's, University of New South Wales Sydney, Sydney, NSW, Australia, [3]The Hospital for Sick Children, Toronto, ON, Canada and [4]Genomics and Inherited Disease Program, Garvan Institute of Medical Research, Sydney, NSW, Australia

*Joint senior authors

Background/Objectives: Demonstrating the clinical utility (CU) of genomic testing is crucial but challenging due to the complexity of genetic disease and the breadth of clinical and patient-reported outcomes. The Clinician-reported Genetic testing Utility InDEx (C-GUIDE) is validated tool to assess these outcomes and CU from a clinician's perspective. Using the C-GUIDE, this study aimed to measure the CU of genomic testing performed at a tertiary paediatric centre. *Methods:* Genetic and non-genetic health professionals across the Sydney Children's Hospital Network, Australia, were recruited. Participants completed the C-GUIDE following the disclosure of test results. De-identified rater and case information was captured. Using univariate statistics, mean, and item-specific C-GUIDE scores were analysed for differences between result groups and a regression analysis identified factors predictive of CU. *Results:* Most of the 140 rated cases were paediatric (89%), with an even distribution of multi- and single-system presentations. Clinicians perceived diagnosed cases as having strikingly higher CU than undiagnosed cases (18.2 vs. 2.58; $p < .001$). Diagnostic results scored highly across three domains (i.e., understanding diagnosis/ prognosis, informing medical management and reproductive and health implications). The psychosocial impact on patients/ families was perceived to be moderate across all result types with greater harm and benefit in the diagnosed group. *Conclusions:* Genomic testing has the highest CU for diagnosed individuals, emphasising the importance of robust genomic testing pathways in obtaining a genetic diagnosis. The clinician's perception of uninformative results highlighted the importance of a patient assessment tool for CU. The C-GUIDE presents a standardised approach in research and clinical pathways to demonstrate CU.

MITOMDT — The Mitochondrial Diagnostic Network for Genomics and Omics Contributing to the Future of Genomics

Amanda Samarasinghe[1], John Christodoulou[1,2,3], David Coman[4,5,6], Maina Kava[8], Shanti Balasubramaniam[9,10], Suzanne Sallevelt[11], Drago Bratkovic[11], Mike Ryan[12], David Stroud[1,2,3], Diana Stojanovski[2], Sean Murray[13], Ryan Davis[10,14], Daniel MacArthur[15], Roula Ghaoui[16], Phillipa Lamont[17]MitoMDT Diagnostic Network for Genomics and Omics, Carolyn Sue[20,21], Aleksandra Filipovska[18,19] and David Thorburn[1,2,3]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]University of Melbourne, Melbourne, VIC, Australia, [3]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [4]The University of Queensland, Brisbane, QLD, Australia, [5]Queensland Children's Hospital, Brisbane, QLD, Australia, [6]The Wesley Hospital, Brisbane, QLD, Australia, [7]The Royal Children's Hospital, Melbourne, VIC, Australia, [8]Perth Children's Hospital, Perth, WA, Australia, [9]The Children's Hospital at Westmead, Sydney, NSW, Australia, [10]The University of Sydney, Sydney, NSW, Australia, [11]Women and Children's Hospital, Adelaide, SA, Australia, [12]Monash University, Melbourne, VIC, Australia, [13]Mito Foundation, Sydney, NSW, Australia, [14]Kolling Institute, Sydney, NSW, Australia, [15]Centre for Population Genomics, Melbourne, VIC and Sydney, NSW, Australia, [16]The Royal Adelaide Hospital, Adelaide, SA, Australia, [17]Royal Perth Hospital, Perth, WA, Australia, [18]The University of Western Australia, Perth, WA, Australia, [19]Telethon Kids Institute, Perth, WA, Australia, [20]Neuroscience Research Australia (NeuRA), Sydney, NSW, Australia and [21]University of New South Wales, Sydney, NSW, Australia

Background: Mitochondrial diseases (MD) show extreme clinical and genetic heterogeneity and represent the challenges of genomic diagnosis in other complex groups of rare diseases. At present, half the individuals with suspected MD remain undiagnosed after clinical genomic testing. *Aim:* MitoMDT is recruiting families with a suspected MD to apply genomic or additional 'Omic' technologies seeking to improve diagnostic rates to over 70%. The major inclusion criterion is suspicion of a probable or definite MD diagnosis using Modified Nijmegen Criteria incorporating a curated set of HPO terms. Both genomics-naïve patients and exome/genome-unsolved patients are eligible. The project combines researchers, clinicians and lab experts covering all states and territories with expertise in genomics, transcriptomics, quantitative proteomics, metabolomics, computational biology and targeted functional testing. Following pre-consent, potential MD patients are reviewed at a National MDT Meeting for consistent identification, recruitment and defining the appropriate testing pathway. Where possible, minimally invasive samples are used, e.g., PBMCs from 1ml blood for proteomics. *Results:* MitoMDT received Royal Children's Hospital Ethics and Governance approval in July 2022 and has recruited over 60 probands to date from approved sites nationally. Initial results from proteomics, lipidomics and targeted functional testings have provided evidence being considered to upgrade VUS in multiple genes to Likely Pathogenic or Pathogenic. We are now increasing recruitment rates with the aim of recruiting up to 200 patients prior to completion

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

of the project in September 2025. *Conclusions:* The national MitoMDT network is implementing multi-omic and targeted technologies to boost diagnostic rates to >70%.

Does a Genetic Counsellor Make a Difference for Parents Receiving a Newborn Bloodspot Screening (NBS) Diagnosis?: An Explorative Qualitative Study

Samantha Anne Sandelowsky[1], Alison McEwen[1], Jacqui Russell[2,3], Kirsten Boggs, Carolyn Ellaway[2,3], Michelle Farrar[4] and Kaustuv Bhattacharya[2,3]

[1]Graduate School of Health, University of Technology Sydney, Sydney, NSW, Australia, [2]Department of Clinical Genetics Sydney Children's Hospital, Sydney, NSW, Australia, [3]Genetic Metabolic Disorders Service Sydney Children's Hospital Network, Sydney, NSW, Australia and [4]Department of Paediatric Neurology, Sydney Children's Hospital, Sydney, NSW, Australia

Background: Newborn bloodspot screening (NBS) detects severe treatable genetic health conditions with onset between birth and early childhood. Receiving a positive NBS result can be stressful for parents. More data is needed to determine whether access to genetic counsellors (GC) improves parents' experiences. *Aim:* To explore the similarities and differences for parents who received a positive NBS result for spinal muscular atrophy (SMA), who had subsequent access to a GC (GC cohort), to a cohort of parents that received a diagnosis of an inborn error of metabolism (IEM) and did not have access to a GC (non-GC cohort). *Methods:* Semistructured interviews explored the retrospective experience of receiving the NBS result, including implications and adaptation. Inductive thematic analysis was used for group comparison. *Results:* Seven SMA families and five IEM families were included. Four themes were identified: (1) minimal pretest counselling, (2) lack of perceived health professionalism, (3) enabling factors for adaptation, (4) implications for individuals and families. Both GC and non-GC cohorts reported insufficient counselling in the pretest period and described poor initial communication of results. Families with subsequent GC input described better disease understanding and opportunities for support group connections. The non-GC cohort described poor understanding of the disease due to the frequent use of medicalised terms, minimal understanding of reproductive options, familial communication, and cascade screening. *Conclusions:* Genetic counsellors can support information needs and adaptation following a NBS diagnosis.

Paediatric Precision Oncogenomics — Evaluation of a New Model of Multidisciplinary Care

Lillian Shegog[1], Emma Murdoch[2], Erin Turbitt[1], Rosie O'Shea[3] and Alan Ma[2,3]

[1]Graduate School of Health, University of Technology Sydney, NSW, Australia, [2]Department of Clinical Genetics, Sydney Children's Hospital Network – Westmead, Sydney, NSW, Australia and [3]Specialty of Genomic Medicine, University of Sydney, NSW, Australia

Background: Paediatric cancer genomic testing is increasingly becoming part of standard care in the oncology clinic. It plays a vital role in helping to diagnose patients and informing their treatment/management. The Sydney Childrens Hospital Network – Westmead has established a paediatric oncogenomic multidisciplinary service. It is a collaboration of genomics expertise with clinical genetics and genetic counselling, as well as oncology and research. This collaboration has led to the paediatric precision oncogenomics multidisciplinary clinic and multidisciplinary team (MDT) meeting. *Aims:* (1) Retrospectively evaluate the paediatric oncogenomics model of care at SCHN and its impact on patient care; (2) Identify barriers, gaps and enablers to implementation of the multidisciplinary clinic and team meetings, and how it can be improved to facilitate better care. *Methods:* The retrospective study includes data from June 2021 to October 2023, using hospital medical records and meeting notes. The multidisciplinary clinic and team meetings were evaluated with an implementation evaluative framework (REAIM), identifying the Reach, Effectiveness, Adoption, Implementation and Maintenance of the service. *Results:* A total of 103 patients were referred to the clinic. 72 had genetic testing finding 31 patients with pathogenic variants, identifying 11 cancer predisposition syndromes. The 11 MDT meetings discussed 92 new cases, mostly regarding testing being organised and referrals to genetics being made. *Conclusions:* This new model incorporates multidisciplinary care for children with cancer and haematological malignancies. It is enabling more rapid genetic diagnosis and informing treatment and management. The model also identifies key contributors (genetic counsellors) in facilitating mainstreaming and genomic care.

Disruption Of An Atypical U12-Type Minor Intron in *SCN5A* Causes Conduction Disease and Recurrent Ventricular Fibrillation

Emma S. Singer[1,2,3], Serena Li[2,3], Ginell Ranpura[2,3], Seakcheng Lim[2,3], Stuart T Fraser[2], Jeremy D. K. Parker[4], Christopher Semsarian[2,3,5], Zachary Laksman[4,6] and Richard D. Bagnall[1,2,3]

[1]Bioinformatics and Molecular Genetics Group at Centenary Institute, The University of Sydney, Sydney, NSW, Australia, [2]Agnes Ginges Centre for Molecular Cardiology at Centenary Institute, The University of Sydney, Sydney, NSW, Australia, [3]Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [4]Centre for Heart Lung Innovation, University of British Columbia, Vancouver, BC, Canada, [5]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, NSW, Australia and [6]Heart Rhythm Services, Division of Cardiology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada

Aim: The functional consequence of variants that disrupt U12-type minor intron splicing is largely unknown. This study aims to functionally assess the outcomes of RNA splicing in a person with a c.392+3A>G variant in an atypical U12-type minor intron of *SCN5A*. *Method:* Genetic testing of 184 cardiac disease genes was performed in a woman with conduction disease and recurrent ventricular fibrillation. In silico tools were used to filter and predict the consequences of rare candidate variants. Induced pluripotent stem cell cardiomyocytes (iPSC-CMs) were derived from the proband and two control individuals. Transcriptome sequencing was performed on iPSC-CMs, with and without cycloheximide treatment, and control myectomy tissue. Splicing outcomes were confirmed through Sanger sequencing of RT-PCR and T/A cloning products. *Results:* An *SCN5A* c.392+3A>G minor intron donor splice-site variant of uncertain significance was predicted to disrupt splicing by SpliceAI (donor loss 0.62), but not others, including MaxEntScan. *SCN5A* transcripts from the proband's iPSC-CMs revealed multiple cryptic splice products that were enhanced with cycloheximide

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

treatment. Sanger sequencing of RT-PCR products and T/A cloned products confirmed five alternatively spliced transcripts resulting in a premature termination codon. All alternatively spliced products reverted to major intron-type splicing involving GT-AG or GT-CG dinucleotides. *Conclusion:* Caution is required with in silico prediction of variants affecting U12-type minor introns. A variant in a U12-type minor intron of *SCN5A* reverts splicing to canonical GT-AG splice dinucleotides, leading to a predicted loss of function in a person with conduction disease and recurrent ventricular fibrillation.

Genomic Education Needs, Gaps, and Enablers for Building Capacity in Genomics in Primary Care: A Scoping Review

Nehal Singh[1], Kate Dunlop[1,2], Amelia Smit[1,2], Alan Ma[3,4,*] and The PRECISE Project Team

[1]The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, NSW, Australia, [2]Melanoma Institute Australia, Sydney, NSW, Australia, [3]Specialty of Genomic Medicine, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia and [4]The Sydney Children's Hospital Network — Westmead, Sydney, NSW, Australia

*The PRECISE Project team: Dr Amelia K Smit, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Dr Kate Dunlop, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Prof Meredith Makeham, University of Sydney Assoc Prof Carissa Bonner, University of Sydney Prof Anne E Cust, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Ms Bronwyn Terrill, Australian Genomics Assoc Prof Julia Steinberg, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia Prof Kristi J Jones, Sydney Children's Hospitals Network, University of Sydney Prof Robyn Jamieson, Sydney Children's Hospitals Network, University of Sydney, Children's Medical Research Institute Prof Lynn Monrouxe, University of Sydney Prof David Wilkinson, The Royal Australian College of General Practitioners Assoc Prof Nicole Rankin, University of Melbourne Assoc Prof Stephen Barnett, University of Wollongong Assoc Prof Shailendra Sawleshwarkar, University of Sydney Ms Kirsten Boggs, Sydney Children's Hospitals Network Dr April Morrow, Centre for Genetic Education, Health Education and Training, NSW Health Ms Edwina Middleton, Centre for Genetic Education, Health Education and Training, NSW Health Ms Janette Mumford, Genetic Alliance Australia Mr Andrew Coe, Western NSW Primary Health Network Dr Caitlin Forwood, Royal North Shore Hospital Dr Alexandra Williams, Health Pathways, Nepean Blue Mountains Primary Health Network Dr Anthony Brown, Health Consumers NSW Nick Rosser, Health Pathways, Nepean Blue Mountains Primary Health Network Dr Fi Lam Ms Nehal Singh, The Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, Sydney, Australia

Background: Primary care practitioners (PCP) are increasingly at the forefront of genomics. However, despite availability of education resources, the knowledge, skills, and capacity for PCPs to deliver genomics in primary care are lacking. *Aim:* The study aimed to conduct a scoping review of the literature on genomic education needs, gaps, and enablers for building capacity in genomics in primary care for the PRECISE (Practitioner Readiness, Education and Capabilities, with Implementation Science Evaluation) Genomics Research Project. *Methods:* Systematic searches of five databases: Medline, Embase, CINAHL, Scopus, and CENTRAL was completed. Data were extracted according to the Theoretical Domains implementation science Framework (TDF) and synthesised in a narrative format according to genomic education needs, gaps, and enablers. A grey literature search was also completed on current genomic education programs and resources in primary care. *Results:* Our search generated 6961 articles, of which 64 were included for full text data extraction. Education needs, gaps and enablers for building capacity were identified within the TDF domains of knowledge, skills, beliefs about capabilities, reinforcement, and intention. Further analysis will determine themes for the Australian primary care setting. To date, theory-informed resources on genomics include eleven education and training resources (e.g., webinars, factsheets) and two guidelines for PCPs in Australia along with three international education websites. *Conclusion:* Multiple existing resources on genomics were found for PCPs. Findings from this review will inform next steps in the PRECISE project in particular co-design of genomic education resources and the identification of implementation strategies for primary care.

The Clinical Utility of Low Pass Whole Genome Sequencing (WGS) in the Treatment of Renal and Liver Transplant Patients

Sangavi Sivagnanasundram[1], Steven Bentley[2], Lokman Pang[1], Karl Vaz[3], Stephanie Kuo[1], Susan Fisher[1], Gina McLachlan[3], Amy Clarke[4], Jacqui Montgomery[2], Melanie O'Keefe[2], Linda Ciccarelli[3], Christy Atkinson[1], Michael Christie[1], Bryony Thompson[1] and Paul James[1]

[1]The Royal Melbourne Hospital, Melbourne, VIC, Australia, [2]Australian Genome Research Facility, Melbourne, VIC, Australia, [3]Austin Health, Melbourne, VIC, Australia and [4]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia

Background: The assessment of pharmacogenomic genes can play a pivotal role in the detection of any potential drug-gene interactions in high-risk individuals. This project is part of Melbourne Genomics Health Alliance's multi-site clinical change projects (CCP) with the purpose of addressing implementation challenges across various clinical settings. *Aim:* We aim to identify whether the use of low pass WGS in renal and liver transplant patients will help inform pretransplant planning focusing on pharmacogenomics and relevant co-morbidities. We also aim to inform families of any relevant monogenic findings. *Methods:* Low pass (~5x) WGS and Illumina Global Screening Array (GSA) were performed by Australian Genome Research Facility (AGRF) and analysed. Using modified ACMG/AMP guidelines, only LP/P variants were reported in genes relevant to the patient (Transplant Co-morbidities and Kidneyome or Liverome SuperPanels). An in-depth pharmacogenomic analysis was performed using Illumina's DRAGEN and PharmCat and reported according to the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines. *Results:* We have recruited over 100 transplant patients of which 53 have been reported. Of these, 9 patients had a clinically actionable finding. An overview of our findings will be presented. Of note, we identified a germline variant in a renal transplant that has led to a diagnosis of Dent's disease and a normal metaboliser phenotype for tacrolimus in a pretransplant renal patient. *Conclusion:* While this study is still ongoing, we can acknowledge that these results indicate the benefit of low pass WGS in informing transplant planning and post-operative care in transplant patients.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

RE Pathways: A Program to Establish the Value of Genetic Testing for Cerebellar Ataxia

Penny Snell[1], Haloom Rafehi[2,3], Kayli Davies[1,4], Tess Field[1], Greta Gillies[1], Justin Read[1,4], Genevieve Thompson[1,4], Lauren Sanders[5,6], David Szmulewicz[7,8], Martin Delatycki[1,4,9], Melanie Bahlo[2,3] and Paul J Lockhart[1,4]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Population Health and Immunity Division, Walter and Eliza Hall Institute for Medical Research, Melbourne, VIC, Australia, [3]Department of Medical Biology, University of Melbourne, Melbourne, VIC, Australia, [4]Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia, [5]St Vincent's Hospital, Melbourne, VIC, Australia, [6]Department of Medicine, University of Melbourne, Melbourne, VIC, Australia, [7]Royal Victorian Eye and Ear Hospital, Melbourne, VIC, Australia, [8]Bionics Institute, Melbourne, VIC, Australia and [9]Victorian Clinical Genetics Services, Melbourne, VIC, Australia

Background: Recent genetic advances have demonstrated that cerebellar ataxia (CA) often has a monogenic cause. CA affects movement, cognition and affect. Disease modifying treatments are limited, requiring further research. Whole genome sequencing (WGS) can identify different types of variants, including repeat expansions, a frequent cause of CA. Unfortunately, WGS is rarely accessible for individuals with CA. *Aim:* The overarching goal of this research is to better understand genetic causes of CA and improve availability of genomic testing for this condition. RE Pathways aims to: offer genomic testing to individuals with CA, work with a clinical diagnostic laboratory to offer further repeat expansion testing, and support medical specialists by provision of ataxia specific genomic knowledge. *Methods:* A cohort of 800 individuals with CA will be recruited by referral from interested specialists or self-referral, including from the Australian Cerebellar Ataxia Registry (CARe). *Results:* To date, we have successfully recruited 127 adults with CA. Notably, consent rates are over 90%. Individuals with CA and their families are enthusiastic to be part of furthering knowledge in this area. We have identified pathogenic or likely pathogenic variants in 48 individuals (38%), facilitating subsequent cascade testing and informed family planning for participants and their relatives. *Conclusions:* There is considerable utility in genomic testing in adults with CA, including ending the diagnostic odyssey for individuals who otherwise might not have access to appropriate testing. Our participants and their families are very interested in the opportunity of research for both genetic results and potential for future therapeutic developments.

'Y' is it Important to Follow Up?

Ling Sun[1], Christa Whelan[1], Kyle Dennis[1], Essra Bartlett[1], Emma Brown[2], Julie Davies[2], Lovepreet Kaur[2], Lucy Gugasyan[2], Peter Taylor[1], Abhijit Kulkarni[1] and Mark Williams[1]

[1]Genomic Diagnostics, Melbourne, VIC, Australia and [2]Monash Health Pathology, Diagnostic Genomics, Melbourne, VIC, Australia

Background: Noninvasive prenatal test (NIPT) is utilised nationally to screen pregnancies at risk of chromosomal aneuploidies. The most prevalent technology is whole-genome sequencing (WGS), where cell-free DNA present in the maternal blood is sequenced, aligned, counted and normalised. Monosomy X is a common cause for early fetal loss. On NIPT, it has a low positive predictive value of 20-50% due to biological factors such as loss of X chromosome in maternal cells, co-twin demise or confined placental mosaicism. Here we report a limitation of WGS-based NIPT that has led to a high risk monosomy X result. *Case study:* A 34-year-old at 13 weeks gestation was referred for NIPT as part of routine screening. Results indicated high risk for monosomy X with a fetal fraction estimation of 7% and presence of a very low signal of Y chromosome below the calling threshold. This finding was reported with standard recommendations for genetic counselling and invasive testing. Fluorescent in situ hybridisation (FISH), G-banded karyotype and microarray performed on amniotic fluid were consistent with a male fetus harbouring a rare structurally abnormal derivative Y chromosome with duplication of Yp and deletion of the distal Yq region. Fetal ultrasound showed a male fetus. On review of the NIPT sequencing coverage, uneven distribution of target reads across the Y chromosome could explain this result. *Conclusion:* This case highlights the importance of genetic counselling, fetal ultrasound and follow up cytogenetic prenatal testing when a high risk for monosomy X is detected. The presence of a structurally abnormal Y chromosome should be considered when discussing the result with the patient.

Investigation of Orexin/Hypocretin Receptor Variants in Migraine Disorders

Heidi G. Sutherland, Alexis Lam, Charlene Bron, Neven Maksemous, Robert A. Smith, Ngan K. Tran, Rod A. Lea and Lyn R. Griffiths

Genomics Research Centre, Centre for Genomics and Personalised Health, School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia

Background: The orexin/hypocretin system plays important roles in regulation of sleep–wake rhythms, feeding behavior and energy homeostasis, reward systems, cognition, and mood. Orexin A (hypocretin-1) and orexin B (hypocretin-2) are neuropeptides generated by proteolytic processing of prepro-orexin and secreted from neurons in the hypothalamus, which bind the hypocretin-1 and 2 receptors (encoded by *HCRTR1* and *HCRTR2*), to regulate functions of serotonergic neurons. While there is little human variation in the hormonal orexin peptides, both common and rare protein-altering variants may be present in the receptors. Some have been implicated in a range of disorders including narcolepsy, insomnia, and cluster headache, while findings in migraine have been inconsistent. *Aim:* To further investigate potential functional variants in hypocretin receptor genes in both familial and common migraine subtypes. *Methods:* We have screened whole exome sequencing (WES) data of a cohort of 185 hemiplegic migraine patients and 30 migraine families for the presence of common and rare missense or functional variants in *HCRTR1* and *HCRTR2*. These were further genotyped and tested for association in a migraine case-control cohort and the UK Biobank. *Results:* We detected the *HCRTR2* p.Pro10Ser and p.Pro11Thr variants, which are known to affect orexin signalling, as well as other rare missense variants, in hemiplegic migraine and familial migraine samples. Some of these were present at elevated allele frequencies in migraine cases compared with controls, and in the UK Biobank population. *Conclusions:* We suggest a potential role for *HCRTR* variants in migraine susceptibility, although further validation for rare variants is required.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Consider *CUX1* Variants in Children With Variation of Sex Development and Neurodiversity

Lynn Tan[1,2,*], Shelley G. Young[3,*], Andrew H. Sinclair[3,4], Matthew F. Hunter[1,2,+] and Katie L. Ayers[3,4,+]

[1]Monash Genetics, Monash Health, Melbourne, VIC, Australia, [2] Department of Paediatrics, Monash University, Melbourne, VIC, Australia, [3]The Murdoch Children's Research Institute, Melbourne, VIC, Australia and [4]Department of Paediatrics, The University of Melbourne, VIC, Australia

*equal first author, [+]equal senior author

Background: The *Cut Homeobox 1* (*CUX1*) gene is involved in various developmental and cellular processes. It has recently emerged as an important cause of developmental delay and impaired intellectual development. Individuals with *CUX1* variants have been described with a variety of co-morbidities including variations in sex development (VSD). *Aim:* To describe a case of *CUX1*-related VSD and conduct a review of the literature. *Methods:* A case report is presented. A literature review in PubMed and from references of relevant citations was undertaken. *Results:* The proband is a 14-year-old male who presented with congenital complex hypospadias, neurodevelopmental differences, and subtle dysmorphism. A family history of neurodevelopmental differences and VSD was noted. Microarray testing revealed a 46XY karyotype with a large, heterozygous in-frame deletion of exons 4-10 in *CUX1*. This was orthogonally confirmed on trio whole-exome sequencing, which did not identify other variants of interest. There have been two previous publications on the clinical phenotype of individuals with *CUX1* variants. Our case is the first report of familial inheritance of a multi-exon deletion and has been submitted as the third publication worldwide, and the first in Australia. *Conclusions:* Our review of the literature has revealed that variants in *CUX1* are associated with a range of VSDs. *CUX1* should be considered when a VSD is noted at birth, especially where there is a familial history of VSD and/or neurodevelopmental differences. Further work is required to further investigate the role and regulation of CUX1 in sex development, including its contribution to gonadal health and the development of external genitalia.

Clinical Utility of Prenatal SNP Microarray by Clinical Indication

Brian Tan[1], Karen Woodward[1], Sarah Nickerson[1], Tracey Edwards[1], Kathryn Weston[1], Amanda Chionh[1], Hayley Warren[1], Fiona Taylor[1], Kenneth Chitty[1] and Dimitar Azmanov[1]

Department of Diagnostic Genomics, PathWest Nedlands, QEII Medical Centre, Perth, WA, Australia

Background: Chromosome microarray (CMA) is currently recommended first-tier prenatal diagnostic testing. Robust data on CMA diagnostic yields for different clinical indications is important for assessing its ongoing relevance in an era of increasing availability of prenatal whole exome and whole genome sequencing. Variants of uncertain significance (VOUS), neuro-susceptibility loci, and unsolicited findings present significant challenges in CMA reporting and counselling. We present the diagnostic yields and reporting experience from a diagnostic laboratory cohort in Western Australia. *Methods:* 1639 prenatal single nucleotide polymorphism (SNP) CMAs, mostly performed in the last five years, were retrospectively analysed. Diagnostic yields were stratified by indication including the type and number of structural abnormalities and soft markers, as well as if the request met Medicare criteria eligibility. The yield of VOUS, neuro-susceptibility loci, and unsolicited findings was also assessed. *Results:* Overall diagnostic yield for pathogenic/likely pathogenic variants was 8.2%. Diagnostic yield for fetuses with any ultrasound abnormalities was 9.1%, and the combined VOUS/Neuro-susceptibility loci/Unsolicited findings yield was 4.0%. For fetuses with no ultrasound abnormalities, the diagnostic yield was 5.2%, and the combined VOUS/Neuro-susceptibility loci/Unsolicited findings yield was 5.0%. Diagnostic yield for Medicare eligible cases was 10.1%, and 5.0% for Medicare ineligible cases. *Conclusions:* The utility of identifying clinically relevant variants by prenatal CMA outweighs the inadvertent reporting of VOUS, neuro-susceptibility loci, and unsolicited findings. However, this balance must be carefully considered, particularly in fetuses with no ultrasound abnormalities. The increased diagnostic yield of Medicare eligible over ineligible cases supports the cost-effectiveness of the Medicare item.

Genetic Variations in Exercise Training: Comparing a Selectively Bred Rat Model to Human Orthologs

Peter Thomas, Vernon Coffey and Paul Dunn

Bond University, Gold Coast, QLD, Australia

Background: Genetics are the most significant contributor to variation in the adaptation response to exercise, but the exact genomic contributions are unknown. Studies in hereditary traits are naturally limited in humans, so genotyping a heterogenous rat model after many generations using specifically bred high response trainers (HRT) and low response trainers (LRT) to exercise can allow for a greater understanding of genotype-phenotype interactions. *Methods:* RNA sequence data was obtained from prior studies on generation 19 of the HRT/LRT model, producing 36 samples (18 HRT, 18 LRT). The data was mapped to the mRatBN7.2 genome before variant calling and SNP identification. Association analysis was performed using PLINK1.9 at the nominal genome-wide significance of -log10 (1e-5), followed by gene ontology (GO) analysis. Orthologs of the significant genes were aligned to the human genome, and impactful candidate genes were identified through known literature. *Results:* 50 SNPs achieved the nominal genome-wide significance in association with 51 genes. Genes identified have known impact on exercise response in rats and through orthologs in humans, including Abca1 and Lpl. Initial GO analysis identified a molecular function enrichment of actin filament binding (FDR = 0.0153). Further gene ontology analysis is being performed on the significant genes. *Conclusions:* The study investigated the unique HRT/LRT rat exercise model and identified significant variants and associated genes. Several identified genes have direct human orthologs observed within prior human exercise response studies. These results contribute to potentially identifying the cause of human exercise response divergence.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

Diagnosis Day: Evaluation Insights From a Storytelling Project About Rare Genetic Conditions

Rigan Tytherleigh[1,2,3], Chriselle Hickerton[1,3], Amelia Rahardja[1,3,4] and Melissa Martyn[1,2,3]

[1]Genomics in Society, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia, [3]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia and [4]Walter and Eliza Hall Institute, Melbourne, VIC, Australia

Background: Patient stories are a powerful way to convey the value of genomics. Diagnosis Day is a video series about six Australians living with rare genetic conditions; videos were intended to be used for advocacy, education and public engagement. Diagnosis Day is a collaboration between Melbourne Genomics' communication professionals and the Genetic Support Network of Victoria, and was informed by advisors' personal/professional experiences. *Aim:* To conduct a process and reach/impact evaluation of Diagnosis Day. *Methods:* Data were collected from stakeholders using surveys and interviews: domains included experience, perceived effectiveness of the collaboration and use of videos. Web analytics measured impact of an online launch campaign. Quantitative survey data were analysed using descriptive statistics; qualitative data were analysed using content analysis. *Results:* 5/6 families/individuals, 5/5 collaborators, and 5/7 advisors took part in evaluation. Families/individuals hoped sharing their stories would help other families and health professionals by providing insights into daily life and sharing knowledge of supports/resources. All families/individuals reported feeling respected, valued and supported; 4/5 reported having control over how their story was told. Collaborators commented that recruiting diverse participants proved challenging, thus recruitment required alternative strategies. In the first six months, videos received over 79000 views and have been used in education. *Conclusions:* Collaborations can leverage different skills and expertise to amplify patient voices. Involving participants at each stage builds trust and contributes to impactful stories. Evaluation highlighted opportunities for improving future collaborations and storytelling projects. Findings informed development of a collaboration checklist for future storytelling projects.

Spectrum of *RB1* Variants in a South-East Australian Cohort; Impact of Genetic Testing to Management and Counselling

Halianna Van Niel[1], Elly Lynch[2,4], Tiong Yang Tan[1,2,4] and Sandra Staffieri[1,3,4]

[1]University of Melbourne, Melbourne, VIC, Australia, [2]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [3]Department of Ophthalmology, Royal Children's Hospital, Melbourne, VIC, Australia and [4]Murdoch Children's Research Institute, Melbourne, VIC, Australia

Background: Retinoblastoma, a rare paediatric intraocular malignancy, is initiated by biallelic inactivation of the *RB1* gene. Identifying a germline *RB1* variant informs clinical management and surveillance for the patient and their family. We aimed to report the South-East Australian *RB1* variant spectrum and analyse the direct clinical impact of genetic analysis. *Methods:* Over a 30-year period (January 1992 – December 2022) this retrospective clinical audit reviewed variant data for patients with a retinoblastoma diagnosis or germline *RB1* variant. Patient sampling was achieved through the Victorian Retinoblastoma Database and descriptive analyses were conducted. *Results:* From 135 patients analysed, 54 (40%) harboured a germline *RB1* variant. Of these, 9/54 (16.7%) presented with unilateral disease and 35/54 (64.8%) with bilateral disease, 9/54 (16.7%) were unaffected carriers, and 1/54 (1.8%) had retinoma. From 44 unrelated patients, 34/44 (77.3%) single nucleotide variants and 10/44 (22.7%) large genomic alterations in chromosome 13 were identified. We report 12 novel variants, four recurrent variants, and identify six patients with mosaicism in *RB1*. From those diagnosed with non-heritable retinoblastoma, informative genetic analysis resulted in 33/36 (91.6%) probands and 65 additional family members being discharged from invasive ocular surveillance. *Conclusions:* We report a comprehensive *RB1* genotypic spectrum for a South-East Australian cohort. We contribute novel insights to retinoblastoma pathogenicity and contextualise the need for genomic screening in the Australian care pathway. These findings promote best practice genetic counselling and clinical care, including a change in surveillance for probands and family members.

Australian Public Perspectives on Genomic Newborn Screening: Which Conditions Should Be Included?

Fiona Lynch[1,2], Stephanie Best[3,4,5], Clara Gaff[1,6,7], Lilian Downie[1,7,8], Alison D. Archibald[1,7,9,8], Christopher Gyngell[1,7], Ilias Goranitis[4,9], Riccarda Peters[9], Julian Savulescu[1,2,10,11], Sebastian Lunke[8,12], Zornitza Stark[4,7,8] and Danya F. Vears[1,2,7,13]

[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia, [2]Melbourne Law School, The University of Melbourne, Melbourne, VIC, Australia, [3]Sir Peter MacCallum Cancer Centre Dept of Oncology, University of Melbourne, Melbourne, VIC, Australia, [4]Australian Genomics, Melbourne, VIC, Australia, [5]Department of Health Services Research, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [6]Melbourne Genomics, Melbourne, VIC, Australia, [7]Department of Paediatrics, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Melbourne, VIC, Australia, [8]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia, [9]Economics of Genomics and Precision Medicine Unit, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia, [10]Centre for Biomedical Ethics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, [11]Uehiro Chair of Practical Ethics, The Oxford Uehiro Centre for Practical Ethics, Oxford University, Oxford, UK, [12]Department of Pathology, The University of Melbourne, Melbourne, VIC, Australia and [13]Centre for Biomedical Ethics and Law, KU Leuven, Leuven, Belgium

Implementing genomic sequencing into newborn screening programs allows for significant expansion in the number and scope of conditions detected. Yet, decisions about which conditions to include in genomic newborn screening (gNBS) raise significant ethical considerations. As public acceptability of newborn screening programs is integral to their success, we sought to explore public preferences and perspectives on which conditions to include in gNBS. To achieve this, we recruited English-speaking members of the Australian public over 18 years of age, using social media, and invited them to participate in online focus groups. Focus groups were audio-recorded, transcribed, and analysed using inductive content analysis. Seventy-five members of the public aged 23–72 and representing seven states and territories participated in one of fifteen focus groups. Participants agreed that if prioritisation of conditions was necessary, childhood-onset conditions were more important to include than later-onset conditions. Despite the purpose of the focus groups being to elicit public preferences, participants wanted to defer to others, such as health professionals or those with a lived experience of each condition, to make decisions about which conditions to include. Many participants saw benefit in including conditions with no available treatment. Participants agreed that gNBS should be fully publicly funded. How many and which conditions are included in a gNBS program will be a complex decision requiring detailed assessment of benefits and costs alongside public and

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

professional engagement. Our study provides support for implementing gNBS for treatable childhood-onset conditions.

Germline CHEK2 variants – Naughty or Nice?

Parvathy Venugopal[1,2], Stuart Webb[1], Peer Arts[1,2], Sunita De Sousa[2,3], Claire Homan[1,2], Peter Brautigan[1,2], Milena Babic[1,2], Amelia Lau[1,2], Kerry Phillips[4], Nichola Poplawski[4], Andrew Dubowsky[5], Anna L. Brown[1,2], Hamish S. Scott[1,2] and Christopher N. Hahn[1,2]

[1]Department of Genetics and Molecular Pathology, SA Pathology, Adelaide, SA, Australia, [2]Centre for Cancer Biology, an alliance between SA Pathology and the University of South Australia, Adelaide, SA, Australia, [3]Endocrine & Metabolic Unit, Royal Adelaide Hospital, South Australian Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, SA, Australia, [4]Adult Genetics Unit, Royal Adelaide Hospital, Adelaide, SA, Australia and [5]SA Pathology, Flinders Medical Centre, Adelaide, SA, Australia

Through the Australian Familial Haematological Conditions Study (AFHCS), we have identified causal germline variants in several genes causing germline predisposition to haematopoietic malignancies including *GATA2, RUNX1, DDX41, PALB2, MECOM*. CHEK2 (checkpoint kinase 2) is an integral kinase of the DNA damage response pathway wherein the detection of DNA damage leads to activation of ATM which activates CHEK2 via phosphorylation, which subsequently activates several downstream targets including BRCA1 thereby modulating cell cycle, apoptosis and DNA damage repair by homologous recombination. *CHEK2* is a moderate penetrance cancer predisposition gene that is strongly associated with breast cancer, and possibly with other neoplasms such as prostate, thyroid, gastrointestinal and urinary tract. However, there has been significant debate surrounding the degree of risk conferred by *CHEK2* variants given the allele frequency of several common variants in certain populations such as I157T (2.5% allele frequency — European Finnish population gnomAD 4.0). The risk imparted by germline *CHEK2* variants on predisposition to haematopoietic malignancies is an active area of investigation. Here we report on the prevalence of germline *CHEK2* variants in AFHCS and interrogate the complexities associated with expansion of *CHEK2* associated phenotypes in the context of haematological malignancies including myelodysplatic syndrome, acute myeloid leukaemia, acute lymphoblastic leukemia and non-Hodgkin lymphoma. Further, we have conducted functional studies to help characterise intronic variants discovered in our cohort to enable better variant interpretation.

Resolving Uncertainty in Variant Classification By Increasing the Application of Experimental Data in Clinical Diagnostics

Rehan Villani[1], Emma Tudini[1], Michael Parsons[1], Alan Rubin[2,3], Amanda Spurdle[1,4] and the MAVE Education Working Group

[1]Population Health Program, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia, [2]The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia, [3]Department of Medical Biology, University of Melbourne, Melbourne, VIC, Australia and [4]University of Queensland, Brisbane, QLD, Australia

Background: For many patients with a suspected genetic condition, the underlying cause of their condition remains unresolved. Often genetic variants are identified, but there is insufficient evidence to determine pathogenicity. These Variants of Uncertain Significance (VUS) are a growing problem in diagnostic genomics. ClinGen provides generic guidance on the use of evidence in variant classification, but studies show that experimental evidence remains underutilised. *Aim:* To use evidence-based approaches to improve the application of experimental data as functional evidence in diagnostic variant classification. *Methods:* We conducted a survey of applied genetics professionals in Australia to assess their functional evidence assessment and use. In addition, we conducted and collected qualitative data at a workshop at the Australasian Society of Diagnostic Genomics Special Interest Group Meeting in 2023 to describe and apply resources and methods to assist with functional evidence evaluation and application. *Results:* 33 diagnostic and genetic professionals completed the needs survey. Survey results indicated there is variation in the methods used for functional evidence assessment, and professionals' opinions around appropriate evidence application. In the workshop, participant decision making based on an example case study showed functional evidence application varied correlating with participant confidence level. *Conclusions:* We propose that uncertainty in experimental evidence interpretation by applied scientists underpins the relatively lower application of this evidence type in diagnostic genomics practice. We are building additional resources supporting experimental data evaluation according to ClinGen-approved evaluation frameworks, to improve incorporation of experimental evidence into variant classification and enable increased certainty in diagnostic genomics.

Genetic Counsellor Experiences of Implementing Rapid Access to Genetic Counselling and Whole Genome Sequencing for Young Onset Dementia

Kirsty West[1], Nikki Gelfand[2], Adrienne Sexton[1], Ashley Crook[3], Charlotte Webster[1], Alexandra Waxmann[4], Caitriona Monohan[4], Dennis Velakoulis[4], Amy Brodtmann[5,6], Charlotte Webster[1], Amy Clarke[7], Danielle Ariti[7], Maira Kentwell[7], Melissa Martyn[7], Belinda McClaren[7], Trang Do[7], Bryony Thompson[8], Martin Delatycki[2], Michael Fahey[3], Henry Ma[9], Susan Mathers[10], Helene Roberts[9], Michael Woodward[11]Melbourne Genomics Health Alliance, Paul James[1], Ingrid Winship[1] and Aamira Huq[1]

[1]Department of Genomic Medicine, The Royal Melbourne Hospital, Melbourne, VIC, Australia, [2]Genetics Department, Monash Medical Centre, Melbourne, VIC, Australia, [3]Clinical Genetics Service, Austin Hospital, Melbourne, VIC, Australia, [4]Neuropsychiatry Centre, The Royal Melbourne Hospital, Melbourne, VIC, Australia, [5]Department of Neurology, The Royal Melbourne Hospital, Melbourne, VIC, Australia, [6]Eastern Cognitive Disorders Clinic, Box Hill Hospital, Melbourne, VIC, Australia, [7]Melbourne Genomics Health Alliance, Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne, VIC, Australia, [8]Department of Pathology, The Royal Melbourne Hospital, Melbourne, VIC, Australia, [9]Neurology Department, Monash Medical Centre, Melbourne, VIC, Australia, [10]Neurology Department, Calvary Healthcare Bethlehem Hospital, Melbourne, VIC, Australia and [11]Memory Disorders Clinic, Austin Hospital, Melbourne, VIC, Australia

Background: About 15% of cases of young onset dementia (YOD) are caused by an autosomal dominant genetic variant. People with YOD often experience long diagnostic delays, including delays in referral to specialised genetics departments and lengthy multi-step genetic testing. *Aims:* This study aims to improve access to genetic counselling and reduce diagnostic delays by implementing genetic counsellor roles and whole genome sequencing within tertiary dementia clinics. This presentation will focus on implementation challenges/successes from the perspective of the genetic counselling team, using illustrative case examples. *Methods:* This study uses a multi-site type 2 hybrid implementation-effectiveness design. Case examples will be examined, supplemented by qualitative data from semi-structured interviews with patients, relatives, and health professionals. *Results:* Although families are facing overwhelming emotional, social and practical changes during the diagnostic process for YOD, many are motivated to find an exact diagnosis and are worried about hereditary risk. Implementation successes include continuity for patients/families, greater ability for complex collaborative case discussions around timing, consent, family tensions, and clinical

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

considerations. Implementation challenges include the need for a highly flexible approach with multiple interactions with care team and families, and practical workplace issues such as gaining Honorary appointments, clinical rooms, and hospital systems access. *Conclusions:* Genetic testing and counselling for YOD has practical challenges and is occurring at a time of high strain for families, within complex hospital pathways. Outcomes from this study will help inform ongoing implementation of genetic counselling and genomic testing for dementia care.

Assessing Barriers and Enablers to Optimal Ongoing Support and Risk Management in People With Cancer-Predisposing Pathogenic Variants

Jack Wheeler[1], Stephanie Best[2,3,4], Abdullah Al Mahmud[5], Shivani Tyagi[5], Abdur Forkan[6], Alexandra Lewis[1], Nilmini Wickramasinghe[7,8], Rohit Kaul[6], Aisha Ward[1], Shane Joachim[6], Prem Jayaraman[6] and Alison H. Trainer[1,2]

[1]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and Royal Melbourne Hospital, Melbourne, VIC, Australia, [2]Faculty of Medicine, Dentistry, and Health Sciences, The University of Melbourne, VIC, Australia, [3]Victorian Comprehensive Cancer Alliance, Melbourne, VIC, Australia, [4]Australian Genomics, Murdoch Children's Research Institute, VIC, Australia, [5]Centre for Design Innovation, Department of Architectural and Industrial Design, Department of Communication Design, School of Design and Architecture, Swinburne University of Technology, Melbourne, VIC, Australia, [6]Department of Computing Technologies, Swinburne University of Technology, Melbourne, VIC, Australia, [7]Iverson Health Innovation Research Institute, Swinburne University of Technology, Melbourne, VIC, Australia and [8]Department of Health Sciences and Biostatistics, School of Health Sciences, Swinburne University of Technology, Melbourne, VIC, Australia

Background: Escalation of germline genetic testing has rapidly increased the number of individuals identified as carriers of cancer-predisposing pathogenic variants. However, knowledge of pathogenic variant status cannot reduce cancer-related morbidity and mortality without individuals engaging in personalised and ongoing risk management support. This study seeks to identify the barriers and enablers to accessing optimal care for individuals with a known hereditary cancer syndrome. *Methods:* A phenomenological approach was adopted. Cancer-unaffected adults with a pathogenic variant in a cancer predisposition gene were invited to participate in a semi-structured focus group discussion or personal interview. Audio recordings of each session were transcribed verbatim before an inductive, reflexive thematic analysis was undertaken. *Results:* Twelve individuals participated in the study. All participants had previously undergone genetic testing at the Peter MacCallum Cancer Centre and had no personal history of cancer. Five key themes were identified: a desire for two-way communication to support continuity of care; time is a significant barrier and patients value the ability to seek advice/information/ support immediately; difficulty in navigating logistics and processes of the healthcare system; a preference for a single source of trusted information and services relevant and specific to them, and; an appreciation of the importance of communicating genetic information to genetic relatives, and support to enable this. *Conclusions:* Despite being managed in a tertiary setting, this engaged cohort still experienced significant barriers to optimal ongoing care. Our study suggests that patients desire targeted information and support to enable optimal risk management.

ActionPlan: A Behaviour Change Theory Informed, Specialist Curated Online Resource to Support Cancer Prevention and Early Detection in Individuals at High Genetic Cancer Risk

Jack Wheeler[1], Cass Hoskins[1], Aisha Ward[1], Sue Fawcett[3], Stephanie Best[2,4,5] and Alison H. Trainer[1,2,3]

[1]Parkville Familial Cancer Service, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia, [2]School of Health Sciences, University of Melbourne, VIC, Australia, [3]Clinical Genetics Service, The Royal Women's Hospital, Melbourne, VIC, Australia, [4]Department of Health Services Research, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia and [5]Australian Genomics, Murdoch Children's Research Institute, Melbourne, VIC, Australia

Introduction: With escalation in germline genomic testing, it is important to consider that identifying pathogenic variants is only a surrogate outcome and individuals still encounter barriers to optimal care. Key to achieving improved health outcomes requires high-risk individuals to understand their management options and access optimal care. This study aimed to: (1) Develop a resource (ActionPlan) targeted to consumer-determined priorities. (2) Evaluate consumers' perspectives on ActionPlan usability and intention to use. *Methods:* We co-developed ActionPlan with a wide range of stakeholders using a mixed-methods approach. Consumers identified informational needs — healthy lifestyle, supportive care, communication, reproduction/fertility, grief support, and cancer risks, as well as risk management recommendations. Specialists requested a clinical trial module. ActionPlan integrates behavior change theory (COM-B model) into content to support consumers pursue their optimal care. ActionPlan evaluation adopted the systems usability scale (SUS) and theory of planned behavior constructs. Responses were analysed using descriptive statistics and open-text analysis. *Results:* Data from 20 high-risk PV carriers demonstrated ActionPlan is easily used by consumers (SUS mean 84.3). Their most valued modules were 'interactive risk visualisation tools', 'cancer risk-reduction options', and 'cancer early detection'. 55% participants took action after reviewing Actionplan, including speaking to relatives (45%), focusing on lifestyle factors (27%). One participant initiated risk-reducing surgery. Most individuals would share ActionPlan with relatives (70%) and/or GPs(47%). *Discussion:* Theory-informed digital resources like ActionPlan have potential to increase equity of access to specialist curated resources, thereby improving clinical outcomes. ActionPlan impact on consumer empowerment is being assessed through a national hybrid-2 effectiveness implementation trial.

Store Now, Talk Later: Mixed-Methods Evidence for a DNA Storage Approach in Palliative Care

Jacqui Irving[1], Elisha Swainson[1], Erin Turbitt[1], Jane Phillips[2], Chris Jacobs[3] and Stephanie White[1]

[1]Graduate School of Health, Faculty of Health, University of Technology, Sydney, NSW, Australia, [2]School of Nursing, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia and [3]School of Health Sciences, Faculty of Health and Medical Sciences, University of Surrey, UK

Background: Genetic counselling and testing are being integrated into routine medical care, yet insufficient attention has been paid

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

to integrating genomics in palliative care. A limited evidence base means best practice guidelines are currently missing from the literature. *Aim:* To understand the views and experiences of clinicians involved in the care of people who have palliative care needs towards DNA storage, including the barriers to and facilitators of this approach. *Methods:* This study includes data derived from three data sets: qualitative data from genetic clinicians, qualitative data from palliative care clinicians, and quantitative data from genetic and palliative care clinicians. During the meta-inference, we integrated data using a joint display table to compare findings across common topics to generate the narrative summary. *Results:* Storing DNA can overcome some of the barriers to genetic counselling and testing for people near the end of life by delaying complex genetic discussions until a more suitable time. Though genetic clinicians are supportive of palliative care clinicians independently overseeing DNA storage, they want to retain control over genetic testing discussions and follow-up. Palliative care clinicians do not feel confident organising DNA storage but are interested in further education. *Conclusions:* Storing DNA, as opposed to organising genetic testing, appears to be the preferred approach for clinicians caring for people near end of life. However, the lack of relevant guidelines and education for palliative care clinicians is limiting the opportunity to integrate DNA storage into practice. Implementation and effectiveness research would further strengthen the evidence base.

Is Dietary Advice Given for Correction of Essential Fatty Acid Deficiency in PKU Adequate to Effect Change?

Amy Allia, Clare Williams, Liza Phillips, Anita Inwood, Michelle Lipke, Sally Smith and Janelle Nisbet

Queensland Lifespan Metabolic Medicine Service, Brisbane, QLD, Australia

Background: Due to a higher incidence of essential fatty acid deficiency in PKU, patients seen by the Queensland Lifespan Metabolic Medicine service have annual nutritional bloods that include an essential fatty acid profile. If deficiency is detected standard dietary advice is given and levels are retested the following year. *Aim:* To determine if standard dietary advice is correcting essential fatty acid deficiency. *Methods:* Current patients with PKU seen by the Queensland Lifespan Metabolic Service were included if they had consecutive essential fatty acid profiles available for 2022 and 2023. *Results*: 25 patients met the criteria, of these 68% (n = 17) had a deficiency of an essential fatty acid in 2022. Eight patients (47%) with deficiency in 2022 had their levels improve on retesting in 2023 and four no longer had a deficiency. 94% of the patients (n = 16) diagnosed with deficiency had been given dietary advice. Form of dietary advice was similar between groups with 43% of those with no improvement and 44% of those with improvement in essential fatty acid levels receiving verbal advice and the rest receiving written advice. *Conclusions:* Although our patients are being diagnosed with and receiving dietary advice for essential fatty acid deficiency we are not seeing a corresponding improvement in levels. There does not appear to be a difference depending on mode of advice. Adherence to diet therapy was not assessed and this may impact on results.

'This information is incredibly powerful': Experiences of Young Australians Participating in the DNA Screen Population-Based Genetic Screening Program

Amanda Willis[1,2], Florence Chiew[1,2], Mary-Anne Young[1,2], Steven He[1,2], Adam Brotchie[3], Jane Tiller[3], Paul Lacaze[3] and on behalf of the DNA Screen Investigator Group

[1]Clinical Translation & Engagement Platform, Garvan Institute of Medical Research, Sydney, NSW, Australia, [2]School of Clinical Medicine, Faculty of Medicine and Health, University of NSW, Sydney, NSW, Australia and [3]School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

Background: DNA Screen is an Australian population-based screening program that has tested 10,263 Australians aged 18-40 for genetic risk of hereditary breast/ovarian cancer (HBOC), Lynch syndrome (LS) and Familial Hypercholesterolemia (FH). This qualitative study explores the acceptability and participant experiences of this novel program. *Methods:* In-depth, semistructured interviews were conducted with people who participated and received results from DNA Screen. Recruitment was targeted to capture all categories of results. Data were analysed using an inductive thematic approach. *Results:* To date, 35 individuals have been interviewed with an average age of 32 years (range 18-40). Sixteen participants were male, 18 female and one non-binary. Participants received high-risk results for HBOC (n = 11), LS (n = 5) or FH (n = 4), or no high-risk results (n = 15). Most participants expressed positive attitudes towards preventive healthcare, which drove their participation and response to results. While high-risk results were challenging for some participants, the information was greatly valued and participants were happy with their decision to participate. Participants who received high-risk results reported that they planned to, or had already, accessed recommended risk management. Participants with no high-risk results were reassured, though aware that the result was not an 'all clear'. Most participants were very satisfied with DNA Screen processes, describing participation as simple and easy, although some roadblocks to accessing clinical care and additional support needs were reported. *Conclusions:* This study suggests that population genetic screening is acceptable to young Australians. The information provided by DNA Screen was valued and promoted a sense of empowerment for future health.

A Complex Presentation of Phosphoglycerate Kinase Deficiency

Greg Woodhead and Tahlee Minto

Royal Children's Hospital, Melbourne, VIC, Australia

Background: Phosphoglycerate kinase (PKG) deficiency, stemming from mutations in the PGK1 gene, is a rare X-linked metabolic disorder. Patients typically present with a spectrum of non-spherocytic hemolytic anemia, myopathy, and variable neurological manifestations. *Aim:* To describe an unusual case of PGK deficiency characterised by profound neurodevelopmental impairment, recurrent haemolysis and recurrent rhabdomyolysis. Additionally, this patient developed recurrent cholestatic jaundice and cholelithiasis. *Methods:* A male infant underwent trio exome sequencing for developmental delays, hypotonia and recurrent anaemia. A maternally inherited variant, *PGK1* c.164C>A, p.(Ala55Asp) was identified, and markedly skewed X-inactivation

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

was noted on maternal testing. Enzymatic testing confirmed the diagnosis. *Results:* A 4-year-old boy had longstanding developmental impairment, recurrent rhabdomyolysis and recurrent transfusion-dependent haemolysis. There was no clinical improvement with a high-fat, low-carbohydrate diet. At 4 years of age he developed recurrent episodes of jaundice with marked conjugated hyperbilirubinemia (395 umol/L; reference range (RR) <15umol/L) and deranged liver function testing (ALT 1334 U/L (RR <50), AST 307 U/L (RR 10-45 U/L) and GGT 196 U/L (RR <40 U/L)). He was initially treated with ursodeoxycholic acid without improvement. Magnetic resonance imaging demonstrated significant cholelithiasis and the patient underwent cholecystectomy with resolution of these episodes. *Conclusions:* The unique severity of this patient's phenotype underscores the complexity of PGK deficiency. Furthermore, the occurrence of cholelithiasis in paediatric PGK deficiency, as observed in this case, expands our understanding of potential complications associated with this rare disorder.

Acute Promyelocytic Leukemia With A Cryptic *PML::RARA* Rearrangement

Claire Wraith

Sullivan Nicolaides Pathology, Brisbane, QLD, Australia

Background: Acute promyelocytic leukaemia (APML) is a subset of acute myeloid leukemia, characterised by the *PML::RARA* fusion gene (present in approximately 95% of cases), and risk of disseminated intravascular coagulation (DIC). APML is considered a medical emergency, and urgent testing for *PML::RARA* by fluorescent in situ hybridisation (FISH) and reverse transcription polymerase chain reaction (RT-PCR) is imperative. However, rare cases of cryptic rearrangements have been described. *Case Presentation:* A 49-year-old male presenting with chest pain was referred for a full blood count (FBC), which revealed pancytopaenia with a left shift and blasts present. Flow cytometry indicated the blastic population was consistent with cells of myeloid origin, also revealing a small population of monoclonal B-cells. Bleeding studies showed elevated levels of D-dimer. Due to suspicion of APML, RT-PCR and FISH for *PML::RARA* was performed on bone marrow. FISH testing using MetaSystems t(15;17) dual fusion and *RARA* break-apart probes did not detect the rearrangement, however RT-PCR was positive for the PML::RARA fusion with BCR1 breakpoint. G-banded karyotype showed a population with trisomy 8, though t(15;17) was not seen. Bone marrow was tested using an alternative FISH probe (CytoCell FAST PML/RARα), which was positive for the *PML::RARA* rearrangement. The patient was diagnosed with APML with a cryptic *PML::RARA* rearrangement, and initiated treatment with arsenic trioxide (ATO). *Conclusions:* This is a rare case of APML with a cryptic *PML::RARA* rearrangement, and highlights the importance of molecular testing in suspected cases of APML.

A Complex Allele in the *TYR* Gene Results in a Pathogenic Haplotype: Uncovering Missing Heritability in Autosomal Recessive OCA

Bing (Ellie) Wu, Samuel Cotton and Andrew Dubowsky

SA Pathology, Adelaide, SA, Australia

Background: Oculocutaneous albinism (OCA) is an autosomal recessive disorder characterised by reduced production of melanin in the eyes, skin and hair. Biallelic pathogenic variants in the *TYR* gene account for a genetic diagnosis in ~42% of OCA cases. However, missing heritability poses a diagnostic challenge, particularly among individuals with milder phenotype. Identification in our laboratory of a 16-year-old female OCA patient homozygous for a pathogenic complex allele prompted review of unresolved historical cases. *Aim:* To identify the contribution of a pathogenic *TYR* gene haplotype in previously unresolved OCA cases. *Methods:* Patients with OCA and whom remain genetically undiagnosed following testing by our laboratory were selected. Next generation sequencing (NGS) data was manually reviewed for patients carrying *TYR*:c.575C>A and *TYR*:c.1205G>A. *Results:* NGS analysis revealed a patient homozygous for a pathogenic haplotype (*TYR*:c.[575C>A;1205G>A]) in the *TYR* gene. The two variants, which individually are frequent in the population (AF 31.5% and 24.7%), are rarely seen in cis as a complex allele (haplotype AF <2%). Manual review of historical data (182 ophthalmic cases, including 7 cases affected with albinism) did not find any additional patients from our OCA cohort in which both variants, in *cis* or *trans*, were detected. Surprisingly, the finding of both variants in only a single patient indicates a first for our cohort. *Conclusions:* Common polymorphisms in *cis* may form rare pathogenic complex alleles that risk being filtered by variant frequency thresholds. Of note, phasing these variants could be complicated by high background rates of compound heterozygosity, requiring a linkage-based approach.

Translating Pharmacogenomics and Precision Dosing in Major Depressive Disorder

Kathy H. C. Wu[1,2,3,4,5,6], Rosalind Moxham[1,2], Andrew Tjokrowidjaja[7], Alison McLean[1,2], Sophie Devery[2], Renee Smyth[2], Paul Fitzgerald[8], Anthony Rodgers[6], Anthony Harris[9,10], Sean Hood[11], Tim Usherwood[6,10], Jacquie Garton-Smith[12], Stuart Grieve[13], Michael Millard[14], Rupendra Shrestha[15], Deborah Schofield[15], Fatemeh Vafaee[16] and The ALIGNED Steering Committee

[1]School of Clinical Medicine, University of New South Wales, Sydney, NSW, Australia, [2]Clinical Genomics, St Vincent's Hospital, Sydney, NSW, Australia, [3]Disciplines of Medicine and Genomic Medicine, The University of Sydney, NSW, Australia, [4]School of Medicine, University of Notre Dame Australia, Sydney, NSW, Australia, [5]Garvan Institute of Medical Research, Sydney, NSW, Australia, [6]The George Institute for Global Health, Sydney, NSW, Australia, [7]School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia, [8]School of Medicine and Psychology, The Australian National University, ACT, Australia, [9]Westmead Institute for Medical Research, The University of Sydney, NSW, Australia, [10]Sydney Medical School, The University of Sydney, Sydney, NSW, Australia, [11]Division of Psychiatry, UWA Medical School, University of Western Australia, WA, Australia, [12] Health Networks, Department of Health, WA, Australia, [13]Charles Perkins Centre, The University Sydney, Sydney, NSW, Australia, [14]Department of Psychiatry, St Vincent's Hospital, Sydney, NSW, Australia, [15]Centre for Economic Impacts of Genomic Medicine, Macquarie University, Sydney, NSW, Australia and [16]School of Biotechnology and Biomolecular Sciences, University of New South Wales, Sydney, NSW, Australia

Background: Pharmacogenomics (PG) assesses multiple variants that influence pharmacokinetic (drug metabolism) and/or pharmacodynamic (drug receptor) responses. PG-guided prescription enables tailored treatment and may be beneficial in depression treatment where current pharmacotherapy is based on trial-and-error iterations. *Methods:* A retrospective review of 100 patients who underwent PG testing in a tertiary hospital setting along with a further 78 participants with depression/anxiety prospectively recruited from

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press

the community were conducted to investigate end-user experience, potential utilities, and costing implications of PG. Clinician and patient views were examined qualitatively and quantitatively. Outcome measures of the prospective study include number of medication changes, treatment response and symptom remission. *Results:* We report our 39-month experience, including clinician and patient perspectives on PG, and identified barriers to clinical adoption of PG. We propose an interdisciplinary care model to facilitate wider PG implementation. Of 100 patients who had PG testing in the retrospective study, 67% were taking a medication with an actionable drug-gene interaction. Findings from the prospective cohort will be presented. *Conclusions:* PG-guided therapy has the potential to reduce adverse drug reactions and improve patient outcomes, however, recent studies have shown less clinical benefit than anticipated. Small effect size conferred by PG alone may be overcome by a data integration approach to incorporate additional biomarkers of treatment response. The ALIGNED study, a multicentre double-blind randomised controlled trial will further identify biomarkers of treatment response, test the effectiveness and health economic benefits of PG in people with depression.

Rebels With a Cause: Embedding Genetic Counsellors in Queensland Specialists Clinics

Tatiane Yanes[1,2], Aimee Dane[3], Alison Rutstein[3], Pauline McGrath[4], Jennifer Berkman[1,5] and Aideen McInerney-Leo[1]

[1]Frazer Institute, Integrating Genomics into Medicine, The University of Queensland, Brisbane, QLD, Australia, [2]Queensland Paediatric Immunology and Allergy Service, Queensland Children's Hospital, Brisbane, QLD, Australia, [3]Cardiology Department, The Prince Charles Hospital, Brisbane, Australia, Brisbane, QLD, Australiav, [4]Metabolic Medicine and Neurosciences, Queensland Children's Hospital, Brisbane, QLD, Australia and [5]Dermatology Department, Princess Alexandra Hospital, Brisbane, QLD, Australia

There is an urgent need to develop innovative models of care to support the rapid expansion of genomic medicine. Several mainstreaming models have been established to improve access to genomic testing, namely (1) upskilling nongenetic healthcare providers, (2) *hub and spoke* model with genetic counsellors (GCs) based in clinical genetic services while attending specialist clinics, and iii) embedded models where GCs are employed directly by specialist clinics. In Queensland, there are now five GCs employed by specialist clinics across four separate Hospital and Health Services. This presentation aims to describe the Queensland experience in establishing genetic counsellor embedded services. In line with international standards, protocols have been developed to prospectively evaluate the services in relation to clinical, patient, healthcare provider, and economic outcomes. Preliminary data indicates that the GC embedded model improves genetic testing ordering practices, support of patient and family psychosocial needs, and is cost-effective. Embedding GCs also improved capacity to provide long-term a support beyond the immediate genetic testing. Personal reflections reveal the model of care has improved work autonomy and employment satisfaction. In nearly all cases, the GC was the first to be employed by the Hospital or Health Service, resulting in challenges related to availability of appropriate professional and operational line management, limited understanding of GC role, no established service models, and uncertain long-term funding. Nevertheless, the Queensland experience demonstrates the feasibility of embedding GCs in specialist clinics and serves as an exemplar for expanding this practice model to better support genomic medicine implementation nationally.

Expanding the Genetic Landscape of RETT Syndrome — Reevaluating the *CHD8*-Associated Disorders

Elaine Xinyu Zhang[1,2], Tim Sikora[1], Carolyn Ellaway[3,4], John Christodoulou[1,2,5] and Simranpreet Kaur[1,2]

[1]Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia, [2]University of Melbourne, Melbourne, VIC, Australia, [3]University of Sydney, Sydney, NSW, Australia, [4]Children's Hospital at Westmead, Sydney Childrens Hospital Network, Sydney, NSW, Australia and [5]Victorian Clinical Genetics Services, Royal Children's Hospital, Melbourne, VIC, Australia

Background: Up to 80% of rare diseases (RD) have a genetic origin. Despite advances in sequencing technologies, approximately 50% of individuals remain undiagnosed, highlighting the importance of ongoing functional genomic studies. *Aims:* We aim to identify and evaluate novel variants in known disease genes and novel candidate genes in RD individuals using bioinformatic and functional approaches. *Methods:* Genomic (exome/genome) sequencing was performed in sequencing naïve families and existing genomic sequencing data was re-interrogated using the *seqr* platform. Variants were filtered using phenotype-specific gene panels and expanded literature searches, before extensive curation across the genome, considering population frequency, predicted protein impact, and other *in silico* predictions. In vitro functional analyses including Western blots, quantitative PCR (qPCR), and proteomic analysis were conducted on candidate variants using patient material. *Results:* We present findings in an individual with a clinical diagnosis of atypical Rett syndrome (RTT). A heterozygous stop-gain variant in the Chromodomain-helicase-DNA-binding protein 8 (*CHD8*) gene, a known disease gene (OMIM 615032; [c.5017C>T, p.(Arg1673Ter)] was identified. The variant was absent in population databases, and was predicted to be 'pathogenic' by in-silico tools. Western blots demonstrated a significant reduction of CHD8 protein in patient fibroblasts comparing to those of the controls, which is being further validated via proteomic analysis. *Conclusions: CHD8* has pivotal function in neurodevelopmental processes. Our results suggest that the CHD8 phenotypic spectrum should be expanded to include RTT-like phenotypes. Ultimately, our work will advance our understanding of RD, restore reproductive confidence for families, and possibly translate to personalised treatments.

https://doi.org/10.1017/thg.2025.7 Published online by Cambridge University Press