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Abstracts for the 43rd Human Genetics Society of Australasia Annual Scientific Meeting

Plenaries and Orals

Plenary 1
Population Genomics and The UK 100,000 Genomes Project Experience

Richard Scott

Clinical Lead for Rare Disease, Genomic England, London, UK

The 100,000 Genomes Project was conceived in late 2012 to bring the predicted benefits of genomics to NHS patients and to foster genomic research and investment in the UK. Between 2013 and 2018, a network of 13 NHS England Genomic Medicine Centres recruited over 100,000 participants with cancer or from families with rare disease. By December 2018, the 100,000th genome was sequenced and analyzed data on more than 60,000 genomes have now been returned to NHS laboratories for reporting to patients. In parallel, genome and clinical data is available to academic and commercial researchers in a dedicated research environment. To deliver the 100,000 Genomes Project, Genomics England worked with NHS England to build not just the genomic, informatic and bio-informatic infrastructure needed but also to develop new clinical standards, pathways and approaches required to deliver the project across more than. In parallel, substantial investment was made in education of health professionals. Patients and participants views have been central to design of the project. From late 2018, the know-how and infrastructure are now being brought into mainstream clinical use through the new NHS Genomic Medicine Service.

Plenary 2
Genomic Variome Project

Stephen Robertson[1,2,3]

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As genomics becomes systematically incorporated into medicine across world, the most refined and mature genomic instruments are those generated using data obtained from populations from the Western hemisphere. As an appreciation of how different minority populations are in terms of the type and frequency of their genetic variation, it is has become established that many of these genomic tools underserve these people, an eventuality that serves to widen often already significant disparities and inequities in healthcare delivery. In Aotearoa New Zealand the nation's founding document, *Te Tiriti o Waitangi*, asserts as a central premise that the interests, rights and customs of Māori must be preserved, protected and promoted, a tenet that the government and its institutions have failed to uphold effectively. If healthcare genomics is not going to fail in a similar fashion, an understanding of the genetic variation embedded within the genomes of persons with Māori ancestry must be obtained, but in a manner concordant and consonant with Māori protocols and tikanga. The Aotearoa-New Zealand Variome project aims to achieve this objective with a Māori-led ethos and culturally informed governance, an aspiration that has defined significant differences between these protocols and what is considered to be best practice on the wider world scene.

Plenary 3
Mackenzie's Mission

Martin Delatycki[1,2], Edwin Kirk[3,4,5], and Nigel Laing[6,7,8] on behalf of the Mackenzie's Mission Consortium

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Mackenzie's Mission is a Medical Research Future Fund project of the Genomics Health Futures Mission. The project aims to screen 10,000 couples for their chance of having a child with an autosomal or X-linked recessive condition. Mackenzie's Mission is being conducted over 3 years. In 2019 the infrastructure for the project is being established. In 2020 screening will be in selected areas of NSW, WA, Victoria and ACT, expanding to all Australian states and territories in 2021. Six committees have been convened to prepare for starting screening: (1) Gene selection, (2) Laboratory, (3) Recruitment, (4) Education and Engagement, (5) Clinical and (6) Research. Over 2400 genes in which mutations cause autosomal and X-linked recessive conditions were examined and approximately 1300 genes will be included in the screening test. Recruitment of couples will be by health professionals and will mirror pre-pregnancy and pregnancy care. We aim to recruit couples in the public and private sectors, in urban and rural Australia and across a broad ethnic base. Couples will mostly enrol via a web portal and screening will be by cheek brush sampling. Testing will be by a panel extracted from whole exome sequencing in Victoria and NSW and by a panel in WA. Research outcomes will include uptake, incidence of high chance couples, reproductive decisions made by high chance couples, psychosocial, epidemiological, ethical, implementation research and health economics. The research outcomes will inform an application to the Medical Services Advisory Committee (MSAC) to fund a national reproductive screening program.

Plenary 4
The Ethical Implementation of Genomics in Population Health

Ainsley Newson

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Genome sequencing technology has now reached a point where its use in population health is moving from the hypothetical to the certain. Politicians' attentions have been captured and there is increasing health budget investment in genomics. Wide offers of sequencing can be imagined for healthy adults, for those living with an undiagnosed condition, for newborns, for future parents. There are a variety of considerations when determining whether to implement genomics in populations: epidemiological, clinical, economic, educational, psycho-social – and ethical. In this presentation I will contend that population genomics requires a public health ethics approach, rather than a more restricted clinical ethics gaze. Drawing on concepts from public health ethics, this presentation will suggest and defend an ethical framework for use in population genomics. An ethical framework provides 'scaffolding' for deliberation and debate. They are useful at all stages of implementation: before, during and after a new health intervention is proposed. Frameworks help to make values explicit, and are particularly useful for enabling non-specialists to bring in ethical thinking and reasoning into a policy problem. The ethical framework to be presented for population genomics will include consideration of relevant ethical issues such as genohype, harm and autonomy.

Plenary 5
Future of Genomic Medicine

Wendy K. Chung

Columbia University, New York, NY, USA

We are rapidly identifying the genetic bases for many monogenic conditions and can sequence a genome within days to diagnose patients. Given these advances in knowledge and capabilities, how can we efficiently and effectively integrate genomics into medicine across the lifespan and what are the gaps we need to fill to accomplish the goal of improved health and quality of life? We will review opportunities for diagnostic and predictive genetic testing for individual patients and populations and consider the catalysts for change. We will also consider how to scale the effective use of genomic information for prevention and treatment of genetically based diseases.

Plenary 6
Delivery of Ethical and Effective Genomic Healthcare

Christine Patch[1,2,3]

[1]Genomics England, London, UKABC University, Perth, WA, Australia, [2]Society and Ethics Research, Connecting Science, Wellcome Genome Campus, Hinxton, UK and [3]Sheffield Hallam University, Sheffield, UK

The 100,000 genomes project completed its mission of sequencing 100,000 human genomes at the end of 2018. Work is ongoing delivering results into the health care system. Learning from the project is integral to the development of a national Genomic Medicine Service within England. The project was underpinned by a commitment to the delivery of benefit to patients in the NHS, appropriate ethical consideration and review, transparency and meaningful patient and public engagement. In this presentation I will describe the iterative development of the consent processes within the project and the Genomic Medicine Service. I will discuss how engagement with participants, patients and public underpin the project. I will also consider the evolution occurring within genomics healthcare as the Genomic Medicine Service develops and reflect on developments in genomic healthcare in the UK from a genetic counseling perspective.

Plenary 7
It Doesn't Just Happen: Changing Healthcare

Clara Gaff[1,2]

[1]Melbourne Genomics Health Alliance, Melbourne, VIC, Australia and [2]Workforce and Education, Australian Genomics Health Alliance, Australia

Healthcare is a complex adaptive system, making change challenging to achieve. Preparing health systems for the use of genomic medicine in healthcare needs a multifaceted approach. The NIH have described implementation as the use of strategies to adopt and integrate evidence-based health interventions and change practice within specific settings. I will provide an overview of collaborative research underway to inform strategies for change and initiatives fostering workforce capability and knowledge translation.

Plenary 8
Mainstreaming in Cancer Genetics

Kathy Tucker

Prince of Wales Hospital, Sydney, NSW, Australia

Given the clinical utility of knowing germline mutation status of cancer predisposition genes and their influence on the real time clinical care of patients, there are now cancer types where all individuals with that tumor need germline mutation analysis for good clinical care – for example, epithelial ovarian cancer, pediatric anaplastic alveolar rhabdomyosarcoma, early onset pituitary adenomas. As a profession, cancer genetics has a responsibility to develop new models of care to deal with this. From the patient's perspective the easiest is oncology-led mutation analysis with referral of the patient and/or their family to genetics if abnormal results are identified, for further management. Novel alternatives such as phone or video consultation for either pre- or post-test counseling or online genetic counseling with patient-led exploration of particular topics in more depth are being trialled. Genetic counselors embedded into subspecialties is a model favored by some older clinicians at present but will not be sustainable long term. Upskilling of every medical student in the principles of genetics and family-based population health prevention is essential but still not part of any curriculum I know. Adding genetic modules as essential assessable components of the curriculum of specialist is currently under discussion with various colleges. While retrospectively adding genetics as mandatory training for general practitioners and specialists has not been favorably received, it is essential for us all to be actively involved in training genetic ambassadors in every specialty. Let us all embrace new models of care to ensure the safest most cost-effective care for all people.

Plenary 9
Chimeric Antigen Receptor T-cells: A Cell and Gene Therapy for Cancer

Robert Weinkove[1,2]

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Chimeric antigen receptor (CAR) T-cells are T-lymphocytes that have been genetically modified to express a protein (a CAR) that redirects

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their cytotoxic activity against an antigen of choice. Increasingly applied both commercially and in clinical trials, autologous CAR T-cells are licensed for treating relapsed and refractory B-cell lymphomas and leukemias, and show promising activity for myeloma and some solid cancers. Following lymphodepleting chemotherapy and administration, CAR T-cells expand within the recipient, the peak of expansion frequently being associated with cytokine-related toxicities, requiring specific clinical management. Among patients with certain B-cell malignancies, a substantial portion enter long-term remission after administration of CAR T-cells. CARs are typically encoded by a single gene comprising components of both the B-cell and T-cell receptors alongside one or more co-stimulatory domains. This modular design favors innovation, allowing redirection of CARs against alternative targets, the incorporation of alternative co-stimulatory domains, or the incorporation of 'on-off' switches to manage toxicities. Genetic modification is achieved using replication incompetent lentiviral and gamma retroviral vectors (used to produce the commercial products Kymriah® and Yescarta®, respectively), or with transposon/transposase systems. Future prospects for CAR T-cell therapies, and solutions to the regulatory, logistic and clinical challenges they present, will be discussed.

Plenary 10
CaPP3 and Risk Management of Familial Colorectal Cancer

Finlay Macrae

The Royal Melbourne Hospital, and University of Melbourne, Melbourne, VIC, Australia

Risk management is primary and secondary prevention. Primary prevention can be through diet, lifestyle and or chemoprevention. Most attention recently has been on chemoprevention, particularly aspirin. Australian guidelines, developed by Cancer Council Australia after a systematic review and now supported by NHMRC, endorse a world-leading position for all Australians to take daily aspirin between 50 and 70 years of age for prevention of colorectal (and other) cancers, outweighing its important cardiovascular preventative effects as well. CaPP2 provided the evidence for 600 mg of aspirin in Lynch syndrome. Optimal dose risk-benefit remains uncertain and is the rational for the CaPP3 dose non-inferiority trial (100, 300 vs. 600 mg) in LS carriers currently understudy in the UK, Australia, Spain, Finland and Israel. Overwhelmingly, other epidemiology also supports the recommendation for average risk reduction, at least for those under 70 years of age. The benefit emerges after a latent period of 4–11 years depending on risk. There have been no studies of aspirin to manage non-syndromic familial risk, but given its benefit in average and high risk, extrapolation is not unreasonable. Secondary prevention, characterized by early detection of curable cancers, is driven by screening. The Australian guidelines have also tailored the initiation of iFOBT and colonoscopy to a risk accepted for commencing iFOBT (50 in Australia) or 4- to 6-fold RR for colonoscopy, bringing new groups to colonoscopic surveillance such as two first degree relatives, or one first degree and two second degree relatives on *either* side of the family (https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Screening)

Plenary 11
Enhancing Responsibility in Research and Response-ability in Practice

Maui Hudson

University of Waikato, Hamilton, New Zealand

Genomic research has longstanding problems with diversity, especially for Indigenous peoples who made up only 0.05% of all genome-wide association studies in 2016. Indigenous populations worldwide face unique health challenges, inequities, and barriers to healthcare resulting in typically poorer health outcomes than non-Indigenous groups. While genomics research has greatly advanced health outcomes in mainstream populations, the dearth of relevant genomics research for Indigenous communities may actually increase health inequities. Unequal access to genomic technologies and lack of relevant population genetic variation data all contribute to limited relevance and reduced effectiveness of genetic and genomic research for Indigenous peoples. While researchers strive to improve their understanding of indigenous genomics they have a responsibility to follow a path that empowers indigenous peoples through community engagement and research partnership. Enabling indigenous led partnerships through investment in capacity building and infrastructure and supporting community control over the use of indigenous samples and genomic data are key pathways to building trust and confidence. This presentation will describe efforts to enhance levels of trust and accountability in genomic research alongside the need to improve responsiveness to indigenous whanau in clinical genetics.

Plenary 12
Indigenous People and Genomics in Australia

Emma Kowal

Alfred Deakin Institute, Deakin University, Melbourne, VIC, Australia

Indigenous people have often been excluded from genomics research for a variety of reasons, including their distrust of researchers and past negative experiences of research. Past investments in genomics are beginning to translate into a variety of treatments and prevention strategies to enhance human health. As the vast majority of genomics research has involved people of European ancestry, it is likely that these people will benefit most from precision medicine. In an Australian context, this means precision medicine may increase health disparities unless action is taken to engage Indigenous communities and researchers. This presentation will outline recent efforts in Australia among Indigenous leaders, researchers and communities to develop Indigenous-led genomics projects in collaboration with non-indigenous researchers. These initiatives aim to allow Indigenous people to access the benefits of genomics while minimizing risk of individual and group harms. I will focus on the National Centre for Indigenous Genomics (NCIG), the first Indigenous-governed genome facility in the world. NCIG developed in response to the challenge of managing a collection of 7000 blood samples collected from dozens of Indigenous remote communities mainly in the 1960s and 1970s and held at the Australian National University (ANU). I will outline the ethical, cultural and political challenges NCIG faced and consider the lessons for other countries with minority populations that may be at risk of exclusion from the benefits of 21st century genomics.

Plenary 13
Engaging with Indigenous Communities for Genetic Research: Benefits, Pitfalls and Lessons

Rebekah McWhirter

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Historical factors have led to a situation where some Indigenous peoples are understandably wary of participating in genetic research, and

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funding bodies, ethics committees and other gatekeepers like to see evidence of substantial community support before approving such research. Community engagement therefore forms the backbone of successful genetic research with Indigenous communities. How to engage will depend in part on the communities involved, although general principles can be discerned. Using our experiences in undertaking a genetic study of vulvar cancer among Aboriginal women resident in Arnhem Land as an example, we can see how engaging with communities throughout the research process can benefit both the communities and the project, identify potential pitfalls of this approach, and draw lessons for research with Indigenous communities and broader populations.

Plenary 14
Te Aho Matatū – Culturally Responsive Genetic Research

Karyn Paringatai

University of Otago, Dunedin, New Zealand

In 1964, an unusually high number of cases of diffuse gastric cancer over successive generations were noted within a Māori family located in the Eastern Bay of Plenty region of New Zealand. Their belief was that a mākutu (an infliction of physical and psychological harm/death through spiritual powers) had been placed on them for selling land for quarrying purposes, and this was their punishment. However, in 1997, the family began working closely with a team of geneticists at the University of Otago who discovered that a hereditary mutation in the *CDH1* gene was responsible for their deaths. Historically, research conducted on Indigenous communities has had little to no direct cultural benefit for the people that were being studied. Many Indigenous peoples are intergenerational victims of colonial oppression and marginalization, and genetic research can be seen as a new form of subjection and exploitation. However, the initial discovery of *CDH1* mutations and exploration of its prevalence was collaborative and its results affected the lives of hundreds of people. Over 20 years later the relationship is ongoing and is just as pivotal as it was in 1997. This presentation will look at my experiences as an Indigenous person who has a *CDH1* genetic mutation in engaging with genomic technologies and the personnel tasked with providing these services to Indigenous families. It will also provide an insight in to how genetic research with and for Indigenous communities requires true engagement and an understanding of and respect for Indigenous communities.

Plenary 15
Assessing the Effects of New Small Molecule-based Treatments

Peter Clayton

Inborn Errors of Metabolism, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, London, UK

The advocates of evidence-based medicine argue that the best way of determining whether a treatment is effective is through meta-analysis of randomized controlled trials and this is true if we are determining whether treatment is generally beneficial to a group of patients with the same diagnosis. In many inborn errors of metabolism, phenotype and severity are highly variable. While stratification can be applied to RCTs, it is pertinent to ask in the new era of Personalized Medicine, whether the physician's choice of treatment should be based primarily on the findings of RCTs. I would argue that, in treating some of our inborn errors, we have for many years been adopting a personalized medicine approach that is better for individual patients. We are often able to measure levels of a metabolite or metabolites which we have good reason to believe might cause disease if present at too high or too low a concentration. Our treatment is designed to correct this and we can follow the effect of treatment with measurements of metabolite concentrations that are not subject to placebo effects (metabolic profile correction trial (MPC trial). If we adjust the treatment to be just sufficient to bring metabolites into the target range we can assess whether there has been any spontaneous improvement. We can then assess whether outcome is better in patients whose metabolites have been brought into the target range (metabolic correction outcome trial (MCO trial). Examples of this approach will be drawn a range of inborn errors.

Plenary 16
Antisense Huntingtin-Lowering Drugs for Huntington's Disease: Where Are We Now, and What's Next?

Edward Wild[1,2]

[1]National Hospital for Neurology & Neurosurgery, UCLH, London, UK and [2]Huntington's Disease Centre, UCL Queen Square Institute of Neurology, London, UK

The monogenic inheritance of Huntington's disease (HD) makes it an appealing candidate for the development of therapies targeting processes close to its genetic cause. HD is caused by CAG repeat expansions in the *HTT* gene, which encodes the huntingtin protein; development of therapies to target *HTT* transcription and the translation of its mRNA is therefore an area of intense investigation. Huntingtin-lowering strategies include antisense oligonucleotides, RNA interference constructs and small molecules targeting mRNA, and zinc finger transcriptional repressors and CRISPR-Cas9 methods aiming to reduce transcription by targeting DNA. RG6042 (formerly HTT_{Rx}), an intrathecally-delivered antisense oligonucleotide that aims to lower huntingtin, is the first huntingtin-lowering drug shown to lower mutant huntingtin concentration dose-dependently in HD patient cerebrospinal fluid, in a phase 1/2 trial. An open-label extension and pivotal phase 3 trial are now underway. Other ASOs are already in early-phase human studies, while one virally delivered gene therapy approach was recently granted Investigational New Drug approval by the FDA and is expected to enter human trials in the coming months. Meanwhile, orally bioavailable small-molecule inhibitors of *HTT* expression have shown promising results in preclinical models. Recent progress in biofluid biomarkers of huntingtin-lowering and neuronal damage may facilitate the conduct of preventative clinical trials and eventually a personalized medicine approach to disease modification in HD.

Plenary 17
Drug Trials in Skeletal Dysplasias

Ravi Savarirayan[1,2]

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The management of skeletal dysplasia (inherited disorders of bone and cartilage) has been predominantly, like many other genetic conditions, symptomatic and reactive. This status quo is now being challenged by the promise of precision therapies, underpinned by

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advances in the understanding of disease pathogenesis, that can potentially alter the natural history of these disorders, and offer patients and families new options for better health. To assess the safety and clinical efficacy of these new disruptive products, we have been undertaking clinical trials in children with various forms of skeletal dysplasia. This talk will summarize the current state of play with these phase II and III drug trials, and will focus on potential new therapies for children with achondroplasia (including c-natriuretic peptide, tyrosine kinase inhibitors, soluble *FGFR3*), Schmid metaphyseal dysplasia (repurposing carbamazepine), and hypophosphatasia (recombinant alkaline phosphatase enzyme replacement) as exemplars of this brave new paradigm.

Plenary 18
Therapeutic Advances in the Management of Mitochondrial Disorders

John Christodoulou[1,2]

[1]Brain and Mitochondrial Research Group, Murdoch Children's Research Institute, Melbourne, VIC, Australia and [2]Department of Paediatrics, Melbourne Medical School, University of Melbourne, Melbourne, VIC, Australia

The mitochondrial proteome consists of around 1500 proteins, with more than 300 nuclear or mitochondrially encoded proteins and RNA molecules being critical for the efficient generation of ATP. It is not surprising that this genetic complexity should result in phenotypic complexity, creating challenges and opportunities for the diagnosis and management of disorders of mitochondrial energy generation. In recent years there have been efforts to improve the accuracy and timeliness of diagnosis of individuals with mitochondrial disorders, which has been greatly enhanced by the advent of genomic technologies into mainstream healthcare. The development of consensus general management guidelines will hopefully also bring consistency in the overall care of mitochondrial patients. With an improved understanding of the genetic and biological architecture of mitochondrial disorders comes the promise of more effective targeted therapies. However, the genetic and phenotypic complexity of this group of disorders, the paucity of good genotype-driven natural history studies and the lack of robust biomarkers make clinical trials for this group of disorders particularly challenging. In this presentation a brief overview of the clinical, biochemical and genetic features of mitochondrial disorders will be described. An overview of previous efforts in the development of pharmacological and other specific therapeutic interventions will be presented, and some new developments in the field will be highlighted. Finally, the lessons learnt from such efforts in other metabolic disorders, and the issues that need to be considered in the design of future clinical trials, will be described.

Sutherland Lecture
Translating Complex Genetics Into Practice: The Example of Breast Cancer Risk

Paul A. James[1,2,3]

[1]Parkville Familial Cancer Centre, Peter MacCallum Cancer Centre and the Royal Melbourne Hospital, Melbourne, VIC, Australia, [2]Genomic Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia and [3]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia

Predicting and managing cancer risk challenges the assumptions of the 'single gene' model of clinical genetics. The heritability of breast cancer is among the highest for solid tumors and the use of panel gene testing is well established and has been recommended by some for every breast cancer diagnosis or even population screening. At the same time germline sequencing of large case-control cohorts, segregation studies and detailed tumor analysis has begun to reveal the underlying complexity of the genetic contribution to breast cancer risk. An excess of rare loss of function variants points to a predisposition role for a number of genes, although in some cases this is a true moderate-risk effect (e.g. *ATM*, *CHEK2*), and for other genes the risk is limited to specific tumor types (e.g. homologous recombination pathway genes and triple negative disease). The excess of common minor risk variants, summarized in the polygenic risk score, is responsible for a greater proportion of attributable risk than conventional gene 'mutations' and the burden of rare, deleterious missense variation has the potential to be even more significant but defies attempts at easy interpretation. Most importantly none of these different domains of genomic risk acts independently and the traditional approach of interpreting genetic test results in isolation has contributed to inconsistency in the literature and delays in clinical translation. In contrast accepting breast cancer risk as a complex trait will allow for better personalized risk assessment and management, for individuals and at a population level.

Invited Speaker Presentation
The Confluence of Genomic Sequencing and Newborn Screening

Cynthia M. Powell

Department of Pediatrics and Department of Genetics, The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC, USA

Background: The **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT) program funded by NICHD and NHGRI is exploring the use of genomic sequencing in newborn healthcare. Sites are studying its use in critically ill newborns, healthy newborns, and for newborn screening. The **N**orth **C**arolina **N**ewborn **Ex**ome **S**equencing for **U**niversal **S**creening (NC NEXUS) project is examining the utility of genomic sequencing in newborns and children, some of whom were diagnosed with conditions through traditional newborn screening. *Methods:* Parents who consent to having their child's genome sequenced learn results of variants in approximately 466 genes associated with conditions determined to have childhood onset and medical actionability (called the Next-Generation Sequencing-Newborn Screening or NGS-NBS category). Those with diagnosed conditions have additional genes analyzed for those that are not in the NGS-NBS category but have some evidence of being associated with their condition. *Results:* One-hundred and six children have had their genomes sequenced, including 17 with previously diagnosed inborn errors of metabolism (IEM). Eighty-eight percent with IEM had molecular findings consistent with their diagnoses, including all with phenylketonuria (PKU) and medium chain acyl-CoA dehydrogenase deficiency (MCADD). Four children (4%) had additional reportable findings in the NGS-NBS category, including one female with known PKU who was identified with a likely pathogenic variant in the *OTC* (ornithine transcarbamylase deficiency) gene. *Conclusion:* Genomic sequencing can augment results of traditional newborn screening and may detect conditions not identifiable through current screening methods.

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Concurrent Sessions – Submitted Orals

Oral 1
From '9–5' to '24/7': Delivering Rapid Genomics at Scale in a Diagnostic Laboratory

S Lunke[1,2,3], S Eggers[2], J Risely[2], M le Moing[2], B Chong[2], D Phelan[2], M Fanjul-Fernandez[2], J Marum[2], S Sadedin[2], C Ieng[2], D Zammit[2], S White[2,3], J Christodoulou[1,2,3], S Best[1,4] and Z Stark[1,2,3]

[1]Australian Genomics Health Alliance, Australia, [2]Victorian Clinical Genetics Services, Melbourne, VIC, Australia, [3]University of Melbourne, Melbourne, VIC, Australia and [4]Australian Institute of Health Innovation, Macquarie University, Sydney, NSW, Australia

Introduction: Widespread implementation of genomic testing for critically unwell children requires scalable and reliable laboratory pathways to deliver genomic testing with rapid turnaround times (TAT) to meet clinical need in a consistent manner. *Aims:* To develop and implement a rapid TAT clinical exome pathway for critically ill children in a diagnostic laboratory. *Methodology:* Rapid TAT testing was implemented at VCGS across 2 successive cohorts totalling 150 patients using a process of continuous review and improvement. The aim for the first cohort was to deliver results in <21 calendar days, with the aim of the second cohort to deliver results <5 days. *Results:* The first cohort ($N = 40$, singletons) utilized improved communication and prioritization of cases within existing processes to achieve an average TAT of 16 calendar days (range 9–109 days), with a doubling of per test cost. This informed changes to the sequencing approach and instrumentation used, bioinformatics and analysis processes, a move to dedicated analysis teams of scientists and clinical geneticists, as well as out-of-hours sample processing. These revized processes have been applied to an additional 110 cases, with an average TAT of 3 calendar days (range 2–5 days), and a tripling of cost. This model has met clinical demand from multiple sites across Australia and we estimate it is scalable to process over 500 cases per year. *Conclusion:* Implementation of rapid genomic testing in existing diagnostic laboratory environments is feasible, but requires whole of system change and is critically dependent on out-of-hours processing, close clinical integration and adequate resourcing

Oral 2
The Changing Nature of Genomic Medicine: Australian Medical Specialists' Current Practice, Preparedness and Preferences

A Nisselle[1,2,3], B McClaren[1,2,3], E King[1,2,3], E Crellin[1,2,3], S Metcalfe[1,2,3] and C Gaff[1,2,3]

[1]Australian Genomics Health Alliance, Melbourne, VIC, Australia, [2]Murdoch Children's Research Institute, Melbourne, VIC, Australia and [3]The University of Melbourne, Melbourne, VIC, Australia

Background/Aim: Medical specialists are critical to incorporating genomic medicine into routine healthcare. We investigated their experiences and perspectives of genomic medicine and education needs to address preparedness to practice. *Methods:* Mixed-methods study, with in-depth interviews informing survey development. All samples included national specialists, at all career stages and public/private practice. *Results:* Thematic analysis of interviews ($n = 86$; 18 subspecialities) revealed wide-ranging current genomic medicine practice. Five domains were identified: participant characteristics; current genomics practice; proximity of genomic medicine; preparedness (knowledge, skills, confidence); and preferences for service models, roles and genomic continuing education (GCE). A survey question bank (45 items) was developed encompassing these domains. A Delphi process (22 experts – medical and genetic specialists, educators, implementation scientist) reviewed items for relevance, clarity and inclusion. The interim survey (25 items) was tested ($n = 6$) then piloted ($n = 41$). The final survey is being advertized to Australian consultants/trainees (March–July) via medical colleges, societies and social media. To date, $n = 72$ (21 sub-specialties); 59.7% currently incorporate genomics into clinical practice, 41.7% recently completed GCE, 35.3% feel prepared to practice genomic medicine. *Discussion/Conclusions:* Our data provide depth and breadth of medical specialists' perspectives on current genomic practice, preferences for future service models and GCE. While over half of respondents currently practise genomic medicine, under half have completed GCE and only a third feel prepared. Implementing genomic medicine requires multidisciplinary care and education at multiple levels; GCE should leverage opportunities such as peer-to-peer learning. The study will provide contextual data informing government and other stakeholders in determining implementation strategies.

Oral 3
Hearing Their Voices: The Economic and Psychosocial Impacts on Families Affected by Intellectual Disability

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Purpose: Data on the financial and psychosocial costs incurred by families affected by intellectual disability (ID) in Australia is scarce, thus limiting the capacity to value the benefits of effectively diagnosing and preventing ID through whole genome sequencing (WGS). We provide an update on the previously reported economic and psychosocial impacts of having a molecular diagnosis for moderate to severe ID and illustrate the impacts with family experiences. *Methods:* A survey instrument was developed to assess quality of life (QoL), a range of psychosocial factors, income, welfare, wealth, education, and family out-of-pocket costs. To date we have surveyed carers from 105 families regarding their experience caring for 174 people affected by ID in NSW and Victoria. Fifty of these families were offered WGS. *Results:* From preliminary data our diagnostic rate is 46%. Potential diagnoses were identified in a further 11% of families, requiring further investigation. The cost burden on families is $4.6 million per household, mainly due to lost income and out-of-pocket expenses. Cost to Commonwealth and State governments totalled $9.8 million including $2 million in welfare payments. This includes $51,000 in NDIS funding per patient annually. Carers reported significantly lower QoL and social connectedness compared to population norms ($p < .0001$). Most carers also experienced levels of stress, anxiety and depression indicative of a need for clinical intervention. Conclusion: Our study shows that families affected by ID experience significant burden. This data can be used to benchmark the potential benefits of having a molecular diagnosis on family coping and informed reproductive decision-making.

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Oral 4
Preparing for Mackenzie's Mission and Expanded Carrier Screening at Victorian Clinical Genetic Services (VCGS)

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Genetic carrier screening aims to identify the chance of a couple having a child with a recessively inherited genetic condition. Recently, Mackenzie's Mission was announced; a national project which aims to screen 10,000 couples for 500 severe early onset recessive conditions. VCGS conducted a pilot study to investigate an approach to couple-based expanded carrier screening (ECS). This study analyzed 14 couples; including 5 couples known to have an affected child or previously reported as having an increased reproductive risk. One hundred fourteen severe early onset recessive genes were analyzed using a next generation sequencing (NGS)-panel assay. Four couples were identified as increased risk. An increased risk result was unexpected for one couple due to the detection of a likely pathogenic CFTR variant which was previously not screened for. In contrast, two couples, known to have an affected child were not identified as increased risk. One was due to a likely de novo variant and the second involved a variant which was classified as VUS in a screening context (not reportable) but was classified as likely pathogenic in a diagnostic context (using additional evidence of an affected proband). Importantly, a number of unexpected results were encountered including: pseudodeficiency alleles, reduced penetrance and autosomal dominant variants. A parallel couple-based method utilizing NGS-technology is an efficient and scalable approach to population ECS, it does however constitute a significant change to carrier screening in Australia. This pilot study identified a number of important issues which can inform the implementation of Mackenzie's Mission and ECS in Australia.

Oral 5
Parent Decision-Making About Clinical Trials for Fragile X Syndrome

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Significant progress has been made in understanding mechanisms at the root of neurodevelopmental disorders such as Fragile X Syndrome (FXS). FXS is a pediatric-onset disorder and the most common form of inherited intellectual disability. Clinical trials investigating the safety and efficacy of drugs targeting the cause are anticipated. As such, parents of affected children will be faced with decisions about whether to enrol their child. Delineating parents' motivating and discouraging factors may improve the informed consent process and positively impact retention rates. We conducted a best-worst scaling experiment to prioritize parents' decisional factors for enrolling their child with FXS into a clinical drug trial. Eligible parents were recruited by the two largest organizations representing FXS families in the United States. Respondents prioritized 11 motivating or discouraging factors to trial enrolment by responding to 11 profiles in an online questionnaire. Data were analyzed using best-minus-worst scores. Respondents ($n = 354$) most frequently chose the 'best' factor to be a drug that targets the underlying mechanism of FXS, potentially addressing a range of symptoms. The possibility of the drug helping many people with FXS was also highly rated. Most often, respondents rated drug side effects as the 'worst' factor, followed by loss of access to the drug post-trial. Our novel study is among the first to investigate parent decisions about trial enrolment for a neurodevelopmental disorder. Investigators may benefit from our findings in guiding discussions with patients about trial enrolment. Aided by our results, those designing trials may incorporate patient-defined priorities into trial design.

Oral 6
Homozygous Inheritance of AAGGG RE in RFC1 Causes CANVAS

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Background: Cerebellar ataxia with neuropathy and bilateral vestibular areflexia syndrome (CANVAS) is an inherited cerebellar ataxia with no known genetic risk factors. *Hypothesis:* CANVAS is caused by a recessively inherited repeat expansion (RE). *Methods and Results:* Linkage analysis on four families affected with CANVAS identified a shared linkage region on chromosome 4. Whole exome sequencing of 25 affected individuals from 15 families did not identify plausible candidate variants with standard analysis pipelines. Subsequent analysis of whole genome sequencing (WGS) using

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two unrelated CANVAS individuals identified a recessively inherited intronic AAGGG RE in the gene Replication Factor C1 (RFC1), within the chr4 linkage region. This motif localized to the 3' end of an alu element and completely replaced the AAAAG motif present in the reference genome. This previously uncharacterized AAGGG RE has an estimated allele frequency of 0.03 (in-house controls). Repeat primed PCR confirmed the homozygous inheritance of the RE in 16 CANVAS families, but was negative for 5 CANVAS patients. WGS of these patients identified mutations that lead to genomic re-diagnosis with spastic ataxia of Charlevoix-Saguenay (SACS), SCA3 (ATXN3 expansion), SCA45 (FAT2) and a variant of unknown significance in ATXN7. The AAGGG RE shared a core ancestral haplotype in all but one patient and was estimated to have arisen in Europe over 25,000 years ago. *Conclusion:* This study identified the genetic basis of CANVAS and demonstrated that improved bioinformatics tools increase the diagnostic utility of WGS to determine the genetic basis of a heterogeneous group of clinically overlapping neurogenetic disorders.

Oral 7
Genetic and Cellular Characterization of Cortical Dysplasia Using Patient-Derived Brain Tissue

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The development of cerebral cortex involves multiple steps of neuronal proliferation, migration, and differentiation. Interruption to these processes during development can cause congenital brain malformation including focal cortical dysplasia (FCD). FCD is a leading cause of drug-resistant childhood epilepsy that often requires surgical intervention for seizure control. However, the genetic basis and pathogenesis of FCD remain poorly understood. Here, we analyzed a unique resource of patient-derived, resected brain tissue. Genetic analysis using deep targeted panel sequencing revealed low allele frequency, brain-specific somatic mutations in 8 out of 23 FCD cases. Further investigation in one case showed a 'mutation gradient', in which the highest level of mutation load was observed in the brain region with the strongest epileptic discharge and the most severe histopathology. Single cell laser capture confirmed the somatic mutation was restricted to abnormal cell types that cluster at the center of the FCD. We further demonstrate that surgical resection, limited to the center of the FCD, is sufficient for complete seizure remission ($n = 4$). To understand FCD at the transcriptomic level, we used single-nuclei RNA-seq to analyze fresh resected dysplastic ($n = 4$) and normal ($n = 2$) brain tissue. This analysis identified abnormal cell types that may represent a marker for FCD and potentially the site of seizure generation. Our results provide the first description of the cellular composition of dysplastic lesions at single cell level, support a change in surgical practice in some individuals with FCD and offer insights into the genetic basis of FCD and pathomechanisms underlying the associated epilepsy.

Oral 8
Pathogenic Variants in GPC4 Cause Keipert Syndrome

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Background: Glypicans are a family of cell surface heparan sulphate proteoglycans that regulate growth factor signaling during development and are thought to play a role in the regulation of morphogenesis. The gene encoding glypican 4 (GPC4) has not previously been associated with a human disorder. *Methods:* Exome sequencing identified individuals with likely damaging loss-of-function alleles in GPC4. We studied the spectrum of phenotypes in human subjects and in Gpc4 knockout mice, performed functional studies of recombinant GPC4 protein, and undertook phylogenetic analysis of GPC4. *Results:* We report 10 affected males from 6 kindreds with novel and predicted pathogenic variants in GPC4. Three males were from the Australian family that defined Keipert syndrome in 1973. Segregation analysis and X-inactivation studies in carrier females provided strong evidence that the GPC4 variants caused the condition, supported by functional studies of recombinant protein that showed that the truncated proteins were less stable than the wildtype. Clinical features of Keipert syndrome included a prominent forehead, flat midface, hypertelorism, broad nose, downturned corners of mouth, and digital abnormalities, whereas cognitive impairment and deafness were variable features. Studies of Gpc4 knockout mice showed evidence of the two primary features of Keipert syndrome: craniofacial abnormalities and digital abnormalities. Phylogenetic analysis demonstrated that GPC4 is most closely related to GPC6, which is associated with a bone dysplasia with phenotypic overlap with Keipert syndrome. *Conclusion:* Pathogenic variants in GPC4 cause Keipert syndrome due to loss of function, making GPC4 the third human glypican to be linked to a genetic syndrome.

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Oral 9
Human Sex Reversal is Caused by Duplication or Deletion of Core Enhancers Upstream of SOX9

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Background: Disorders of Sex Development (DSD) are conditions affecting development of the gonads or genitalia. Variants in two key genes, SRY and its target SOX9, are an established cause of 46, XY DSD, but the genetic basis of many DSDs remains unknown. SRY-mediated SOX9 upregulation in the early gonad is crucial for testis development, yet the regulatory elements underlying this have not been identified in humans. *Hypothesis:* Disruption of key SOX9 enhancers cause of DSD. *Methods & Results:* We analyzed Copy number variations (CNVs) in the upstream regulatory region of SOX9 in DNA from four patients with DSD, allowing us to define several minimal critical regions for sex-reversal. We redefined the upstream regulatory landscape of human SOX9. Using new patient data, we analyzed these genomic regions using bioinformatic and luciferase tiling approaches, to identify three putative enhancers 5′ of SOX9. In cell-based reporter assays these enhancers responded to different combinations of testis-specific regulators including SRY, SF1 and SOX9 itself. When combined, all three enhancers show synergistic activity, significantly increasing their individual enhancer activity. *In vivo*, deletion of these three enhancers in mice resulted in different outcomes ranging from: no apparent effect to reduced Sox9 transcription and complete sex reversal. *Conclusions:* This is the first study to identify SOX9 enhancers that, when duplicated or deleted, result in 46,XX or 46,XY sex reversal, respectively. These enhancers provide a hitherto missing link by which SRY activates SOX9 initiation, upregulation and maintenance in humans, and establish SOX9 enhancer mutations as a significant cause of DSD.

Oral 10
Multi-Gene Analysis Effectively Provides a High Diagnostic Yield and Resolves Differential Diagnoses in Neuromuscular Disorders

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Background: Molecular genetic testing for hereditary neuromuscular disorders has been increasingly used for clinical diagnoses to identify disease subtypes, complement histological studies, and inform clinical management and prognosis. *Aim:* We sought to use a large, unbiased, and more comprehensive dataset to assess the complexity of genetic analysis in neuromuscular disorders. *Methods:* Using high depth-of-coverage next-generation sequencing (NGS) with simultaneous detection of sequence variants and CNV detection, we tested 21,558 unrelated individuals for subsets of 266 genes associated with neuromuscular disorders. *Results:* A definitive molecular diagnosis was obtained in 23% of this cohort overall, with yields ranging from 8% among individuals with dystonia to 49% among those with a muscular dystrophy. Importantly, intragenic CNVs accounted for as much as 40% of all clinically significant variants, with 9% of them occurring as rare, private pathogenic variants. Even for classical disorders like Duchenne muscular dystrophy, at least 45% of clinically significant results in the *DMD* gene were identified through gene panels designed to address differential diagnoses rather than through the traditional approach of single-gene analysis. Lastly, we observed a range of 1–13 variants of uncertain significance (VUS) in 54% of individuals. Only 0.7% of these variants were later reclassified as clinically significant, providing insight into the types of additional evidence that support VUS resolution and informing expectations of reclassification rates. *Discussion:* These data provide useful guidance for clinicians using genetic testing to diagnose neuromuscular disorders and represent one of the largest studies demonstrating the utility of NGS-based testing for these disorders.

Oral 11
Evaluating Cost-Effectiveness of Exome Sequencing in a Prospective versus Historical Cohort of Complex Pediatric Patients

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Background: The diagnosis of children with complex genetic conditions places a significant economic burden on healthcare services. Studies measuring the cost of first-line exome sequencing (ES) against that of traditional diagnostic approaches are limited by the lack of well-defined comparative cohorts. *Aim:* To evaluate utility and cost-effectiveness of early ES in pediatric patients with severe, likely monogenic medical conditions. *Method:* Data, including diagnosis rate and investigation costs, was collected from a prospective cohort of 92 pediatric patients who underwent singleton ES over a 2-year period (2016–2017). Inclusion required patients to have two of the following: a condition with high morbidity or mortality, multisystem disease involving three or more organ systems, or severe limitation on daily function. For comparison, data was collected from a historical cohort of patients fulfilling the inclusion criteria who underwent standard investigations in the 2 years (2012–2013) prior to the availability of clinical exome sequencing. *Results:* Exome sequencing yielded a diagnosis in 40/92 (43%) compared with 21/91 (23%) in the historical cohort. ES directed management changes in 33% of patients compared to 14% receiving standard care, while producing a 4-fold reduction in invasive investigations. The average cost per diagnosis following ES was AUD$10,659 compared to the AUD$37,810 cost per diagnosis of traditional diagnostic investigations. *Conclusion:* Early exome sequencing reduces the cost per diagnosis by 2.5-fold while almost doubling the diagnostic yield of traditional approaches. It improves the care of patients with severe genetic conditions by directing management, resolving uncertainty, and mitigating the need for invasive investigations.

Oral 12
Implementing Clinically Validated Automated Genomic Variant Prioritization with Diagnostic Performance that Equals Human Experts

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Background: Analysis and interpretation of genomes (and exomes) are major challenges requiring bioinformatics and professional

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resources in limited supply. We have developed an automated variant prioritization framework, whose performance equals genomic diagnosis using human experts. *Methods:* Genome.One operates a NATA-accredited (ISO15189) whole genome diagnostic service in *Sydney, NSW, Australia*. A reference set of ~500 clinical referrals underwent bioinformatics using a precisionFDA Award-winning pipeline (Kinghorn Centre for Clinical Genomics). Tertiary bioinformatics used published tools (Seave), with every case analyzed by Doctoral genetics professionals. Additionally, a team of genetics experts performed variant review of selected non-trivial cases. We evaluated two automated pipelines: Moon (diploid.com), Eclipse (derived from Seave), and a combination of the two. Reference set concordance was required for all ACMG Class 4 and 5 variants, and desirable (but not required) for Class 3 variants. Discordant results were adjudicated by the variant review expert team. *Results:* Both automated pipelines performed nearly as well as human experts, identifying at least 88–98% of Class 4/5 and 60–75% of Class 3 variants. Applying both in combination equalled human experts, with 100% concordance for all Class 4/5 reportable variants and 75–81% concordance for Class 3 variants. The new approach resulted in up to order-of-magnitude reduction (median reduced from 225 to 6 variants) in interpretation time. *Conclusion:* An automated variant prioritization protocol has been developed, whose performance equals that of credentialed genetic diagnostic professionals. The pipeline is accredited for clinical diagnosis.

Oral 13
A National Approach to Rapid Genomic Diagnosis in Acute Pediatrics

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Background/Aim: Implementation of rapid genomic testing in neonatal and pediatric intensive care units (NICUs/PICUs) is gathering momentum, and requires the development of systems capable of consistent delivery across multiple sites. *Methods:* We developed a rapid genomic diagnosis program involving 10 Australian hospitals and two laboratories with the aim of providing test results in <5 days for acutely unwell pediatric patients with suspected monogenic disorders. Rapid exome sequencing (rES) was performed as trios when possible, and analysis utilized multidisciplinary expertise. Experience was shared between clinical sites, laboratories, and professional groups to enable collective learning. *Results:* The program considered 123 patients for rES over 10 months, and approved 114 (93%). Five families declined testing (4.4%), and nine (7.9%) were withdrawn due to change in clinical circumstances. Of 100 patients tested, 53 received a diagnosis. Twelve of the diagnoses (23%) were made using approaches augmenting standard ES analysis: mitochondrial genome sequencing, ES-based copy number analysis, matchmaking of emerging genes, reverse phenotyping and RNA analysis. Median time from hospital admission to consent was 6 days (range 0–64 days); median time from sample receipt to clinical ES report was 3 days (range 2–7 days). The total cost of testing was AU $1,123,000 (AU$11,230 per case). Changes in management following a result occurred in 77% of diagnosed patients and 10% of undiagnosed patients. *Conclusions:* We demonstrate the feasibility of a national, highly integrated clinical-laboratory approach to rapid genomic diagnosis, which delivers results within a timeframe relevant to acute pediatrics, while optimizing clinical utility and resource allocation.

Oral 14
Implementation of Exome Sequencing in a Clinical Diagnostic Laboratory Service

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As genetics and non-genetics health professionals embrace the potential of rapidly advancing genomic technology to diagnose patients with complex phenotypes, it is useful to audit the experience of offering exome sequencing in a clinical diagnostic context. In 2016 Victorian Clinical Genetics Services launched an accredited diagnostic exome sequencing service. Data from 839 diverse adult and pediatric patients from Australia and New Zealand were reviewed. Diagnostic results were issued for 337 patients, variants of uncertain significance were identified in 99 patients and 403 negative results were reported. The overall diagnostic rate was 40%, with a rate of 39% for singleton and 51% for trio analysis. Family segregation analysis was undertaken in 141 cases (17%) to clarify variant inheritance and classification. Phenotype-driven variant prioritization is used to target analysis and minimize incidental findings however variants unrelated to the patient's presentation were identified in 22 cases (2.6%), 7 of whom were CFTR carriers. Individual diagnostic rates calculated for each of the most common patient phenotypes included 39% for intellectual disability (38% of referrals), 38% for neurological conditions (16% of referrals), 36% for multiple congenital anomalies (5% of referrals) and 51% for eye conditions (5% referrals). These data may serve as a useful reference point for clinicians considering the diagnostic yield and utility of genomic testing for various phenotypes. Essential to the success of this complex testing approach is the integration of clinical and laboratory expertise throughout the process including test request triage, variant prioritization and multidisciplinary team data review prior to reporting.

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Oral 15
Exome Sequencing Enhances the Diagnostic Rate of Perinatal Autopsy: A Prospective Multicenter Clinical Utility Trial with Implications for Prenatal Diagnosis

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Exome sequencing (WES) enhances the diagnostic rate of perinatal autopsy: A prospective clinical utility trial with implications for prenatal diagnosis. *Objectives:* (1) To determine the utility of WES in perinatal post mortem for congenital anomalies. (2) To model the outcome of WES as a prenatal test. *Method:* Probands with congenital anomalies were referred by pathologists. They were enrolled for sequencing if their microarray was negative and their anomalies were considered to have a monogenic cause. WES was performed as an adjunct to routine perinatal autopsy and the diagnostic outcomes were compared. A geneticist reviewed the probands' antenatal imaging findings and recommended a gene list to model the clinical utility of prenatal WES. *Results:* The referred cohort numbered 131. Forty-nine (37%) were unsuitable for inclusion. The parents of 5 (4%) declined enrolment and 10 (8%) could not be consented. Sixty-seven probands (52%) were enrolled. Results are available for 65 probands (32 singletons and 33 trios). Autopsy identified specific diagnoses in 11 cases (17%). WES identified specific diagnoses ('pathogenic' or 'likely pathogenic' variants) in 23 cases - a diagnostic rate of 35%. The combined diagnostic was 38%. VUS were reported in 13 cases (20%). The rate of diagnostic or suspicious variants was 42%. Genomic diagnoses were obtained from 34% of singleton exomes and 36% of trio exomes. Antenatal sequencing in this cohort would have identified a diagnosis in 18 of 23 cases diagnosed by sequencing (78%). *Conclusion:* WES doubles the diagnostic rate of autopsy for congenital anomalies and supports the prenatal use of genomic sequencing.

Concurrent Session 1 – Australasian Association of Clinical Geneticists

AACG Oral 1
The Diagnostic Trajectory of Families Undiagnosed After Singleton Exome Sequencing

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Background: Over 50% of individuals with rare genetic disease remain undiagnosed after exome sequencing (ES), yet optimal strategies for additional testing after a non-diagnostic ES result are unclear. *Aim:* We aimed to describe the diagnostic trajectory of families undiagnosed after exome sequencing. *Methods:* We performed a retrospective descriptive audit on the diagnostic investigations undertaken in a cohort of 93 families without a molecular diagnosis after clinical exome sequencing. We collected data on all diagnostic investigations, in addition to translational sequencing performed at The Broad Center for Mendelian Genomics. We evaluated the reasons for not identifying the diagnosis in the initial clinical exome. *Results:* A molecular diagnosis was established in 43/93 (46.2%) families. Family-based ES reached a diagnosis in 37/89 (41.6%) families, family-based whole genome sequencing and RNA-sequencing in 2/9 (22.2%) families, high-density array in 2/32 (6.3%) families, and re-analysis of the initially unsolved ES data in 2/9 (22.2%) families. We identified 17 (39.5%) diagnoses in novel disease-genes, 2 (4.7%) diagnoses in known disease-genes with expanded phenotypes, and 24 (55.8%) diagnoses in known disease-genes with known phenotypes. The major contributors to the diagnoses in known genes were family-based ES allowing for ease of variant detection (58.3%), and literature published after the initial ES (29.2%). Unsolved cases continue on their diagnostic trajectory with additional genetic and non-genetic testing, including invasive investigations. *Conclusion:* Our findings suggest that family-based ES is effective in achieving a diagnosis following a non-diagnostic singleton exome and that adjunctive translational methods are useful when a novel hypothesis is queried.

AACG Oral 2
What to Do With a Negative Exome?

N Tan[1], R Stapleton[1], Z Stark[1,2], S White[1,2], M Delatycki[1,2], A Yeung[1,3,4], M Hunter[3,4], D Amor[2,5,6], N Brown[1,2,5,7], C Stutterd[1,7], G McGillivray[1], P Yap[8], M Regan[3,4], B Chong[1], M Fanjul Fernandez[1,2], J Marum[1], D Phelan[1], S Lunke[1] and T Tan[1,2]

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Background: Individuals with suspected monogenic disease remain unsolved after exome sequencing (ES) for reasons including technical challenges and difficulty in variant interpretation. *Aim*: To evaluate systematic reanalysis of singleton ES data for unsolved cases. *Methods:* Data from unsolved cases referred for clinical ES at Victorian Clinical Genetics Services between 01/2016 and 03/2017 was systematically reanalyzed. First reanalysis at 4–13 months after the initial report looked at genes newly associated with disease since the original analysis; second reanalysis at 9–18 months looked at all disease-associated genes. At 25–34 months we reviewed the status of all cases and collated the strategies which solved cases through means other than reanalysis of singleton ES data. *Results:* Fifty-six unsolved cases were referred for syndromic (45%) and non-syndromic (3.5%) neurodevelopmental conditions, multiple congenital anomalies (12.5%), and single system disorders (39%). Reanalysis of existing ES data alone did not yield new diagnoses. Over the same timeframe, nine new diagnoses were obtained (16%): two intragenic deletions not tractable by ES but detected on array (ATAD3A/3B, NIPBL); two missense variants with low coverage in the original singleton ES, detected on trio ES/GS (CHD7; SCN8A); one in-frame deletion detected with a low variant fraction on singleton ES, highlighted as a de novo variant of interest on trio ES (WDR45); and four novel gene

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discoveries (unpublished). *Conclusion:* All additional diagnoses in this study were derived from strategies other than reanalysis of singleton ES data, illustrating the need to implement a multifaceted strategy for cases remaining unsolved after singleton ES.

AACG Oral 3
Vesicular GABA Co-Transporter Variants are Associated with Genetic Epilepsy with Febrile Seizures Plus (GEFS+)

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Background: Genetic epilepsy with febrile seizures plus (GEFS+) is a familial epilepsy syndrome in which patients from the same family have phenotypes ranging in severity from febrile seizures (FS) to developmental and epileptic encephalopathies, such as Dravet syndrome. While GEFS+ has a genetic etiology, only a small proportion have a known pathogenic variant in one of the few known genes. *Methods:* We performed whole-genome sequencing (WGS) for three members of a GEFS+ family. Whole-exome sequencing data of a further 1330 epilepsy patients, including 57 with FS/Febrile Seizures Plus and 452 with genetic generalized epilepsies, was interrogated. Three hundred sixty-five patients with FS or GEFS+ were Sanger sequenced for the candidate gene identified from WGS. Variants were validated and familial segregation examined by Sanger sequencing. *Results:* A missense variant in *SLC32A1*, coding for the vesicular GABA co-transporter VGAT, was identified in all three family members. The variant was predicted to be damaging by multiple prediction algorithms, was not present in the gnomAD database and co-segregated with the phenotype in the family. Variants in *SLC32A1* were identified in three further unrelated patients, including one co-segregating with the phenotype in a second GEFS+ family with 12 affected individuals. The other two variants were seen in three siblings with GEFS+ and a patient with focal epilepsy and FS. *Conclusions:* Missense variants in *SLC32A1* are a novel genetic determinant of GEFS+. These variants are likely to alter GABA transport into synaptic vesicles. The examination of further epilepsy cohorts will elucidate the full genotype-phenotype spectrum of *SLC32A1*.

AACG Oral 4
Exploration of Interactions between Genetic Health Professionals and Laboratory Specialists in Clinical Genomic Sequencing

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Despite widespread use of genomic sequencing (GS) in clinical care, there has been little exploration of actual experiences of genetic health professionals (GHPs) using these new technologies in their practice. To address this, semi-structured interviews were conducted with 31 clinical geneticists and genetic counselors from 30 institutions across Europe, Australia and Canada to explore their experiences requesting GS from laboratories and receiving reports for their patients. Data was analyzed using inductive content analysis. Participants described a spectrum of interactions between GHPs and laboratories. These ranged from those requesting GS exclusively from laboratories affiliated with their genetic service, to those without access to GS 'in-house' who instead send patient samples to varying external laboratories. Those that use in-house services described close working relationships with laboratory personnel, which leads to better communication, more clinical involvement in the analysis/interpretation process, and reporting of fewer, yet more relevant variants. In contrast, those that use external laboratories discussed being less involved in the analysis/interpretation, which may increase the number of variants of uncertain significance reported. These GHPs often 'shop around' to identify the external laboratories that provide the best overall service, taking into account factors such as cost, turnaround time and level of detail provided on reports. These results help us understand the challenges GHPs are experiencing in interpreting GS results from laboratories, which has important implications for clinicians' training and also laboratory reporting practices.

AACG Oral 5
Genetics of Functional Bowel Disorders: Looking for Genes Where the Sun Don't Shine

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Background: Functional gastrointestinal disorders (FGIDs) affect 1 in five people, with symptoms including dyspepsia, abdominal pain, constipation and diarrhea, translating into remarkable healthcare costs. Despite this, FGID pathophysiology is under-investigated, which hampers the development of effective therapies. At least for irritable bowel syndrome (IBS), the most common FGID, a hereditary component has been demonstrated, though powered genetic studies have been lacking. *Aim:* With the bellygenes initiative, we use large population-based biobanks and cohorts to study IBS predisposition: this is a multinational project supported by EU BBMRI-LPC that aims to study IBS, bowel symptoms and genotype in a target population of >800,000 Europeans. *Methods and Results:* Through GWAS studies and their meta-analyses, we focus on multiple IBS definitions and relevant endophenotypes spanning questionnaire data, healthcare records (ICD codes), and clinical material from tertiary neurogastroenterology centers worldwide. Through these studies we show that (1) rare and common sucrase-isomaltase (SI) variants increase IBS risk because of their reduced carbohydrate digestion capacity; (2) ion channel activity and specific ion channel genes (*SCN5A, TRPM8*) are important for bowel motility (stool frequency) and IBS characterized by constipation; (3) a locus on chromosome 9q31.2, known to influence age at menarche, is also associated with IBS risk and harder stools in women; (4) several loci, containing plausible candidate genes, strongly associate with variation in the frequency with which people open the bowels (stool frequency). *Conclusions:* These results implicate genetically predisposing pathways that are therapeutically actionable in IBS, thus providing preliminary rationale for patients stratification and additional treatment options.

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AACG Oral 6
Population Genetic Testing for Breast and Ovarian Cancer Susceptibility

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Background: Population-based testing for specific BRCA founder mutations in high-risk populations, such as the Ashkenazi Jewish population where the mutation prevalence ranges between 1.1% and 4.5% has been demonstrated to save more life-years and quality-adjusted life-years compared to a family history-based testing approach. *Aim:* The aims of this study are to: (1) determine the prevalence of pathogenic mutations in an unselected cancer-free Western population, and assess the rate of uptake of genetic counseling, risk reduction surgery and cascade testing in mutation-positive families; and (2) use these data to inform a health economic model specific to the Australian population. *Method:* Since 2014, population-based genetic testing of 11 HBOC genes has been offered to 5910 cancer-free unselected women recruited into the LIFEpool cohort study while attending a government-funded population breast surveillance program. *Results:* To date, 38 of 5910 women (0.64%) carried a clinically actionable mutation (BRCA1 $n = 6$, BRCA2 $n = 15$, PALB2 $n = 14$, ATM (c.7271T>G) $n = 3$). The 38 women ranged in age from 24 to 77 years, with an average age of 57 years. Forty-two percent of mutation carriers did not have a first-degree relative with breast or ovarian cancer, and 91% accepted referral to an FCC. Uptake of cascade testing and risk-reducing surgery mirrored families identified through standard clinical practice. *Conclusion:* HBOC genetic testing was well accepted and identified families with mutations, who would not otherwise have presented to a familial cancer clinic. The findings indicate the clinical utility of identifying a mutation in this setting parallels the current model of clinical practice. The cost effectiveness is still under investigation.

Concurrent Session 2 – Australasian Society of Genetic Counsellors

ASGC Oral 1
Genetic Testing for Familial Motor Neurone Disease (MND): Insights and Challenges

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Background: Motor neurone disease (MND) is an adult-onset neurodegenerative condition, with an average survival of 2.5 years after symptom onset. Genetic counseling and/or testing is increasingly recommended to be offered to all individuals with MND given the presence of known pathogenic variants in up to 70% of familial and 10% of apparently sporadic cases. Despite no changes to medical management, genetic testing may be important for future drug trials and for relatives considering predictive and/or reproductive genetic testing. Few studies have explored how individuals decide whether to pursue testing, nor the testing uptake rate. *Methods:* Qualitative in-depth semi-structured interviews with individuals from Australian familial MND families explored experiences of familial MND, and factors that influenced genetic testing decision-making. Interviews were analyzed using an inductive approach. *Results:* Thirty-four individuals from 24 families were interviewed and included patients ($n = 4$), spouses ($n = 4$), and asymptomatic at-risk relatives ($n = 26$). Life stage, experience of disease, costs, research opportunities, and attitudes to familial MND and/or reproductive options influenced decision-making. Some patients and relatives experienced difficulty gaining accurate information from their health professionals about the costs and implications of genetic counseling or testing, resulting in a reluctance to proceed. *Conclusion:* This study provides new insight into the Australian experience of genetic testing and counseling for familial MND. It highlights the need to work together with other health professionals to ensure the complexities of genetic testing decision-making, and referral pathways are better understood.

ASGC Oral 2
Expanded Genetic Carrier Screening – Lessons Learnt From the First 130 Couples

Z Milgrom

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Background: Genetic carrier screening is entering mainstream obstetrics. Professional guidelines state that information on carrier screening should be offered to all women planning or in the first trimester of pregnancy. A challenge faced by healthcare practitioners and consumers is how to access affordable, efficient and simple testing. *Methods:* We have developed an end-to-end service delivery model, offering genetic counseling and next generation sequencing-based testing via a digital platform, at an affordable price. Here we report the results of the first 130 couples accessing this service. Consumer feedback was obtained by questionnaire and phone interviews. *Results:* Of all couples tested, 79% were referred by a healthcare professional, 38% were pregnant at the time of testing, and 8% had a known family history of a recessive disorder. Reported ethnicity was Caucasian in 50%, with the remainder reporting diverse ethnic backgrounds. Of all individuals tested, 71% were identified as being a carrier of one or more disorders. When results from both partners were combined, 10% of couples were at risk of having a child with a severe recessive disease. In addition, 10% of couples were at risk of a child having a recessive disorder with low penetrance, for which prenatal testing was not indicated. An incidental finding with possible health implications was reported in 10% of individuals tested. Ninety-six percent of individuals were extremely satisfied with overall experience and 97% of couples felt empowered by the testing process. *Conclusion:* Expanded carrier screening can be delivered successfully using a digital platform and couples screening model.

ASGC Oral 3
General Practitioners and Genomics: Their Views on Practice and Education in Australia

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Background and Aim: General practitioners (GPs) face particular challenges in translating genomics into primary healthcare,

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considering the broad nature of generalist practice and the changing landscape of consumer-led testing. In this genomics era, it was timely to explore Australian GPs' current practice and educational needs. *Methods:* We convened a national task force to guide this qualitative study, including practising GPs and representatives of medical colleges and Australian Genomics Health Alliance. GPs were recruited from all states in Australia by convenience or snowball sampling. Semi-structured interviews ($n = 28$) were conducted and transcribed. Data was analyzed thematically and co-coded to ensure methodological rigour. *Results:* Current roles for GPs in genomics are diverse and context-dependent. GPs do encounter genomic testing in their practice, but do not always recognize the genetic nature of tests. Often GPs refer patients to genetic services or specialists but can also be asked to assist patients with consumer-led tests. All GPs interviewed think genomics will impact future practice; and they believe continuing education and 'just-in-time' resources will support their confidence in genomics. However, there was limited awareness of existing resources (RACGP Genomics in General Practice). Relevance to practice underpins education preferences for topics and mode of delivery. *Conclusion:* GPs interviewed often underestimated their current practice in genomics, and recognized the need to upskill to prepare for its increasing impact. GPs are a diverse group with varied needs and learning preferences. To have impact, a multipronged approach needs to drive educational strategies, and widespread dissemination of relevant resources is crucial.

ASGC Oral 4
Ethical Implications of Population-Scale Genomic Screening

J Tiller[1], L Zhang[1], Y Bao[2], M Riaz[1], D Liew[1], X Zhuang[2], D Amor[3], A Huq[4,5], L Petelin[6], M Nelson[7], P James[4,5], I Winship[4,5], J McNeil[1] and P Lacaze[1]

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We recently found (Zhang et al., GiM, 2019) that population genomic screening of young adults would be highly cost-effective, possibly approaching cost-saving, for the Australian health system. While recognizing the enormous public health potential of population genomic screening, in considering the implications of these findings we have identified a range of ethical and service issues which must be considered. Associating government investment with disease prevention, especially where reproductive decisions are involved, raises ethical challenges. 'Routinization' of testing may lead to expectations that individuals will undertake testing or make certain decisions after receiving test results (including surgery or termination of pregnancy), compromizing the values of informed consent and individual autonomy. Further, normalization of testing risks stigmatizing high-risk individuals and reducing societal acceptance of disability. Achieving informed consent at scale will require careful re-thinking of current genetic-counseling models. Genetics services, already stretched, will require significant resourcing to manage the number of at-risk individuals identified. Associated preventative interventions (such as surveillance and surgery) will need additional funding to deal with rapidly expanding demand. Unresolved issues around insurance discrimination and privacy issues remain in Australian law, which must be adequately resolved to ensure public engagement with a national screening program. These issues have been recognized as priority issues by the Australian Genomics Health Futures Mission, yet have not yet been adequately addressed at the policy level. This presentation will discuss these critical and timely issues in the context of the implementation of population-scale screening in Australia.

ASGC Oral 5
Acceptability and Feasibility of a Pre-Clinic Psychosocial Screening Tool in an Australian Clinical Genetics Setting

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Clinical genetics services are experiencing increasing referrals meaning new ways to meet demand without compromizing patient care are required. The Genetic Psychosocial Risk Instrument (GPRI) is a validated tool that screens patients undergoing genetic testing for increased psychological risk. This study aimed to investigate the acceptability and feasibility of the GPRI to clinical staff and patients attending an Australian clinical genetics service. Patients (145/154, RR = 94%) recruited from the genetics service at the Peter MacCallum Cancer Centre and Royal Melbourne Hospital completed the GPRI in the waiting room alongside a survey about GPRI acceptability. The GPRI was then scored and provided to clinical staff prior to each appointment. Once patient recruitment ceased, staff (14/26, RR = 54%) completed a similar survey. Descriptive statistics and regression analyzes were used to analyze the patient data, and descriptive statistics were employed for staff surveys. Patients felt the GPRI was relevant (65%), easy to understand (92%), and it reassured them that their concerns would be addressed (63%). All patients were accepting of completing the GPRI before their appointment, regardless of their level of psychological risk. Staff disagreed that reviewing the GPRI was too time consuming (85%) or difficult to interpret (79%). Most (85%) believed utilizing the GPRI improved patient care through helping to identify patient needs, and all were willing to use the GPRI routinely. These findings demonstrate the GPRI is a highly acceptable tool to patients and staff in this setting. Further studies will indicate whether the tool leads to improved patient care.

ASGC Oral 6
How Do Adolescents and Young Adults Experience Genetic Testing for Li-Fraumeni Syndrome?

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Background: Li-Fraumeni syndrome (LFS), caused by germline mutations in TP53, confers high multi-organ cancer risk from childhood. For young people (aged 15–39 years), the process and

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implications of genetic testing for LFS transpire across a complex developmental trajectory. Yet, the psychosocial needs of young people who face LFS are poorly understood and could have implications for their supportive care. Aim: We explored how young people experience the process and implications of genetic testing for LFS while traversing adolescent and young adult development. *Methods:* Using interpretive description, we conducted semi-structured interviews with young Australians with, or at 50% risk of, a germline TP53 mutation. We carried out team-based iterative thematic analysis to increase rigour and develop findings. *Results:* Thirty young people participated (mean age 25.5 years; 26 TP53+ve; 4 at 50% risk) and primarily underwent genetic testing to reduce uncertainty and access cancer risk management; genetic testing represented a critical means to regain control over LFS. Young people tested during cancer treatment ($n = 11$) commonly misinterpreted the severity of an LFS diagnosis because they were preoccupied with survival. Young people's autonomous decision-making for testing was complicated by reliance on family, and simultaneous testing among siblings was common for younger participants. Genetic testing for LFS forced young people to navigate developmental tasks beyond their life stage, and re-evaluate already completed tasks (e.g., parenthood). *Conclusion:* Young people undergoing genetic testing for LFS have unique psychosocial needs that are linked to the developmental tasks of their life stage, and require developmentally appropriate genetic counseling.

Concurrent Session 3 – Australasian Society of Inborn Errors of Metabolism

Invited Speaker
Bile Acid Disorders

Peter Clayton

Inborn Errors of Metabolism, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, London, UK

The number of disorders of bile acid synthesis continues to increase. For an infant with cholestatic liver disease or the clinical picture of a peroxisomal disorder, a diagnosis can be achieved using urine negative ion electrospray mass spectrometry (without chromatographic separation). After 1 year, diagnosis usually requires quantitative determination of atypical bile acids. Traditionally this was achieved by GC-MS following deconjugation and derivatization but many laboratories are turning to LC-MS/MS to quantitate bile acids.

As well as presenting with cholestatic liver disease and fat-soluble vitamin malabsorption in infancy, bile acid synthesis disorders can present with neurological disease and/or liver disease in older children and adults (often without a history of neonatal cholestasis). We have much to learn about why not all infants get liver disease. Neurological disease is probably in part due to the fact that cholestenoic acids are important signalling molecules in the CNS. The oxysterols that accumulate in Niemann-Pick C disease can be converted to bile acids and measurement of 3β,5α,6β–trihdroxy-cholanoic acid and its conjugates in plasma or blood spots can provide a means of diagnosis of NPC. The liver disease and fat-soluble vitamin malabsorption in 3β-hydroxy-Δ5-C_{27}-steroid dehydrogenase deficiency and Δ4-3-oxosteroid 5β-reductase deficiency respond very well to treatment with cholic acid and/or chenodeoxycholic acid and liver disease in one child with oxysterol 7α-hydroxylase deficiency responded to chenodeoxycholic acid. Dementia and neurological dysfunction in cerebrotendinous xanthomatosis respond to treatment with chenodeoxycholic acid. The effectiveness of bile acid supplementation in peroxisomal disorders is variable.

Invited Speaker
Extreme Phenotype Sampling and Whole Genome Sequencing of Niemann-Pick Type C Disease in Australasia

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Niemann-Pick type C (NPC) disease is one of more than 6000 Mendelian diseases for which there is no cure. These diseases are inherited in a monogenic nature caused by loss-of-function mutations in one gene; however, there is extensive variation in the onset and progression of these diseases. We hypothesize there are genetic variants that modify the *NPC1* gene that confers 95% of NP-C disease cases, and ultimately regulate the onset and progression of NP-C disease. Relative to the extensive success of genome and exome sequencing in identifying disease-causing variants, there has been little success in identifying variants that modify Mendelian disease progression since a large cohort of samples to represent all the possible pairwise interactions in a genome is required to achieve statistical significance. Most NP-C patients are diagnosed as late infants and die before or during adolescence. To complement our extensive clinical characterizations of rare cases of adult onset of NP-C disease, here we will compare whole genome sequences of pediatric and adult onset patients. We anticipate the variants that associate with disease severity can be effective therapeutic targets to treat NP-C disease given the direct interaction with the disease-causing Npc1 gene. We will discuss the ongoing analyses of these sequences, including an extreme phenotype sampling pipeline that integrates mathematical modeling of genetic polymorphisms and extensive clinical records to overcome the statistical challenge of working with small sample sizes inherent to rare diseases.

ASIEM Oral 1
Outside the Exome: The Role of CNVS, SVS, Deep-Intronic and 'Silent' Mutations in Mitochondrial Disease

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Mitochondrial disease (Mito) is a heterogeneous group of disorders resulting from defective cellular energy generation with an estimated minimum birth prevalence of 1 in 5000. Currently over 300 (nuclear and mitochondrial DNA encoded) genes are known to cause Mito; all resulting from defective cellular energy generation, either by primarily or secondarily affecting the oxidative phosphorylation system. Exome sequencing has revolutionized the diagnosis of Mito, with 30–60% of reported patients now receiving diagnoses. However, this means that ~50% of patients are still unable to be diagnosed with this technology, either due to the genetic cause being an unidentified novel disease gene or because the mutation is refractory

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to current technologies. Since 2012, an average of 22 novel Mito disease genes have been identified every year, however in 2018 this number seemed to drop significantly for the first time. We expect that the next 'wave' of diagnoses will be due to an expansion of the mutational spectrum for known disease genes; particularly as newer whole genome sequencing (WGS) technologies become better utilized such as linked-read and long-read WGS. Currently, within the literature ~8% of known Mito genes have mutations outside those readily prioritized by Exome sequencing. Our research has thus far identified pathogenic deletions, duplications, complex rearrangements, gene conversions, deep-intronic and 'silent' splicing mutations in 16 known Mito genes. Here, we present examples in which 10X Genomics and Oxford Nanopore WGS and RNA analyses have aided in the diagnosis of challenging mutations in *ACAD9, NDUFAF6, SERAC1, NDUFV1* and the *ATAD3* gene cluster.

ASIEM Oral 2
Mitochondrial Disease in New Zealand: A Nationwide Prevalence Study

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Background: The complexities of Mitochondrial Disease make epidemiological studies challenging, yet this information is important in understanding healthcare burden and addressing service and educational needs. Existing studies focus on single referral centers, phenotypes or genotypes and estimate prevalence as 1 in 5000. New Zealand's (NZ) size and partially integrated national healthcare system make it amenable to a nationwide prevalence study. *Aim:* Estimate the prevalence of molecularly confirmed and suspected mitochondrial disease on 31st December 2015 in NZ. *Methods:* National and local ethics approval was obtained. Cases were identified using adult and pediatric endocrine, genetics, neurology, metabolic, ophthalmology list servers and databases. Laboratory databases were searched for positive genetic results. The National Minimum Dataset was interrogated for mitochondrial-like presentations between 2000 and 2015. Clinical notes were reviewed. Those with a diagnosis of 'mitochondrial disease' who were alive, living in NZ on the prevalence date were included. These were divided into molecularly confirmed and clinically suspected. Official NZ estimated resident population data was used to calculate prevalence rates. *Results:* 723 unique NHI's were identified. 505 were excluded. The minimum combined prevalence rate for mitochondrial disease was 4.7 per 100,000 (95% CI [4.1. 5.4]). The minimum prevalence rate for molecularly confirmed and suspected disease was 2.9 (95% CI [2.4. 3.4]) and 1.8 (95% CI [1.4. 2.2]) cases per 100,000 respectively. *Conclusion/Discussion:* Within the limitations of this study, comparison to similar prevalence studies performed by specialist referral centers suggests mitochondrial disease is likely underdiagnosed in NZ. This highlights a need for improved education and referral pathways for mitochondrial disease in NZ.

Concurrent Session 4 – Australasian Society of Diagnostic Genomics

Invited Speaker Presentation
A Customisable Analysis Pipeline for Identification of Clinically Relevant Genetic Variants in Next Generation Sequencing Data

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The introduction of large scale next generation sequencing into clinical practice creates new challenges regarding the classification of potentially pathogenic genetic variants. Aside from the technical challenges involved (sufficient depth and breadth of coverage for target regions) there is the challenge of identification of known or novel pathogenic variants. As these variants are found among a host of common and rare polymorphisms, the identification of clinically relevant variants is time consuming and fraught with the potential for analysis induced false negatives. This is especially the case in larger datasets and further complicated in conditions or disorders where a multitude of genes or mutation sites within a gene may be responsible for symptoms or important for treatment recommendations. Here I present the details of an approach I developed in a working NATA-accredited DNA diagnostics laboratory, to rapidly facilitate the diagnosis of neurological conditions and to enable 'pathogenic', 'likely pathogenic' and 'variants of unknown significance' to be flagged for subsequent validation. This pipeline uses custom, curated gene lists to categorize variants into specific analysis tiers and to subcategorize them based on standard parameters to facilitate the rapid interrogation of potentially pathogenic variants by human operators. Numerous publicly available databases are used to assist with variant classification. Curation processes allow robust logging of parameters and database and software versions. A static report is automatically generated during the annotation and filtering step using RMarkdown. A Shiny-based web environment was implemented, providing a layer of interaction and visualization not possible with static reporting. In practice this approach greatly improved the time to identification and validation of suspected variants, going from 4–8 to 1–2 weeks. Overall, these tools provide a simple, customizable and entirely open source method to identify genetic variants that may be of clinical importance in a variety of genetically important conditions.

ASDG Oral 1
Detecting Repeat Expansions with Sequencing Data: Implications for Novel Discoveries and Rapid Genetic Diagnosis

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Repeat expansion detection with both whole genome and whole exome sequencing data (Tankard et al., AJHG 2018) is now a reality

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(Bahlo et al., F1000Research). We have been using our validated pipeline on research genomes and exomes coming in through the laboratory and have made several novel repeat expansion discoveries, as well as rapidly genetically diagnosing repeat expansions. We found individuals with: (1) confirmations of clinical diagnoses (e.g. DM1), (2) rare repeat expansions not available as standard tests in Australia (e.g. SCA36), (3) different repeat expansions to those expected (incorrect clinical diagnosis) (e.g. SCA3 instead of CANVAS), and (4) novel repeat expansions (RFC1/CANVAS, Rafehi et al., *BioRxiv* 2019, Cortese et al., *Nat Genet* 2019). Unlike putative pathogenic SNVs, validation of rare and novel repeat expansions remains difficult, both in publications and in NATA accredited settings and represents a challenge going forward for clinical genetic testing. Recent discoveries of several new repeat expansions (Rafehi et al., BioRxiv, 2019) have catalyzed a resurgence of interest in repeat expansions. New repeat expansions, once identified in the genome and able to be described by location, can be readily added to repeat expansion bioinformatic discovery methods and pipelines. These novel repeat expansions and already known repeat expansions, such as the HTT and C9orf72 expansion, which can now be easily found with the new bioinformatic tools available, will translate into rapid genetic diagnosis for hundreds of individuals in Australia and thousands world-wide.

ASDG Oral 2
Whole Genome Sequencing Reveals Structural Gene Rearrangements and Novel Splicing Variants in the Retinal Dystrophies

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The inherited retinal dystrophies (IRDs) are a clinically and genetically complex group of disorders which primarily involve the rod and cone photoreceptors, collectively affecting 1/3500 people worldwide. While targeted capture and panel-based strategies have been delivering molecular diagnoses in the majority of IRD families tested, approximately one in three families remain unsolved and unable to obtain personalized recurrence risk and clinical management information. We performed whole genome sequencing (WGS) (TruSeq Nano-DNA 30x) in 64 IRD families with a view to also explore gene-associated non-coding genomic DNA regions which could be missed by targeted capture panel-based approaches. Libraries were sequencing on the Illumina HighSeq X Ten. Variants were filtered and prioritized using population allele frequencies, in silico pathogenicity and splicing prediction tools before ACMG guideline classification. Overall, molecular diagnosis was achieved in 40 of 64 families (63%). Furthermore, analysis of WGS data identified variants potentially missed by current panel-based clinical testing strategies in at least six families (9–10%). Analysis of WGS data in a family with stationary cone photoreceptor dysfunction identified a double-hit mutation with an OPN1MW c.648T>C p.Cys203Arg hemizygous missense change and a gene-fusion event involving the *OPN1LW* and *OPN1MW* opsin genes within chromosome Xq28. We also identified two other novel splicing variants predicted to affect natural gene splicing, with one involving a new candidate vitreoretinopathy gene. While targeted capture panel-based methods are proven to be successful in achieving an efficient molecular diagnosis, this study highlights the benefits and clinical value of whole genome approaches in highly heterogeneous disease.

ASDG Oral 3
Genomics Education in the UK: What Can We Learn?

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Genomics education for the health workforce is a priority since genomic information is increasingly used in routine healthcare. The current structure of genomics education for scientists and genetic/genomic counselors in the UK is markedly different from Australasia. The NHS 'Modernizing Scientific Careers' (MSC) scientist training program (STP) was established to deliver broad training across a range of pathology disciplines over a 3 year period. Work-based learning complements a part-time Masters level academic program, culminating in registration as a clinical scientist. Technicians, designated 'healthcare practitioners', train over 2 years while completing a BSc academic program and can register as a technologist on completion. The MSC training scheme for healthcare scientists began in the UK in 2009. Alongside the 100,000 Genomes initiative, funding has been made available for genomics training for the NHS workforce, delivered by Health Education England (HEE). An MSc in genomic medicine was introduced in 2015, with funding committed to 2023. The STP has become genomics rather than genetics focused and has expanded to include specialisms in Clinical Bioinformatics (Genomics) and Genomic Counseling, introduced in 2016. There is now a Higher Specialist Scientific Training (HSST) scheme incorporating a doctoral level academic program, designed to deliver candidates for consultant scientist posts. The UK and Australasia are approaching genomic education for scientists and genetic counselors differently. The pros and cons of the UK training schemes can be used to inform vital discussion of future directions to ensure that Australasia has a robust workforce fit for practice in the genomic era.

ASDG Oral 4
Quality Control is Critical for Genomic Analysis

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Background: The process of generating data through next generation sequencing (NGS) is a complex procedure where errors can occur at any stage of analysis. It is important to have quality control (QC) steps in place, to ensure sample provenance, data integrity, and accurate downstream analysis that are consistent with standard laboratory practice. *Aim:* To summarize important QC steps in genomic analysis pipelines and provide examples where standardized procedures identified data discrepancies. *Method:* Exome data was generated using the ThermoFisher Ion AmpliSeqTM Exome RDY kit and an Ion Proton Sequencer. Genomic data QC metrics generated include TS/TV, het/hom, synonymous/non-synonymous, gender and kinship relationships. These post-sequencing QC steps are embedded in Genome Analysis Interface Annotation (GAIA), an accredited NGS tertiary analysis pipeline. Where any data discrepancies were identified, appropriate investigations were employed – including audit procedures and genotyping of samples to confirm identity. *Results:* We present a summary of the types of errors and QC solutions developed through the

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analysis of more than 1000 exomes. Sample contamination, incorrect gene nomenclature and incorrect zygosity were identified in three families (1%). Diagnostic results not meeting quality thresholds were also flagged through a clinically responsive and flexible bioinformatic pipeline. *Discussion:* Although at low frequency, it is critical that appropriate genomic QC analysis protocols are employed to identify errors in complex analysis pipelines.

Concurrent Session 5: Australasian Association of Clinical Geneticists

AACG Oral 7
Human Medical Genetics and Genomics Competencies for the Contemporary Medical School Graduate

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Introduction: Since 2008 the Human Genetics Society of Australasia 'Core capabilities in genetics for medical graduates' document has guided medical genetics curricula in New Zealand. Rapid advances in genomic science mean current medical genetics curricula require reevaluation. To determine competencies for future New Zealand medical graduates we collated international human medical genetics curricula and sought expert opinion to determine relevant curricular content. *Methods:* International medical genetics curricula were identified online and collated into 13 themes, with repetitions removed. Twenty-six New Zealand experts (clinical geneticists, scientists, clinical educators) added missing competencies. With a survey-based, two round Delphi process experts determined which competencies should be retained and which eliminated. *Results:* Experts reached consensus on retaining 58/60 (97%) of competencies to be learned in at least 'some depth' after two Delphi rounds. Competencies were added to include Maori health concepts, including taking an appropriate genetic history, understanding cultural tenets connected to whakapapa (genealogy), an understanding of DNA samples and genomic data being taonga (sacred), and the application of genetic data to Maori and other indigenous populations. Competencies in interprofessional skills, pharmacogenetics, clinical reasoning, and information management were refined. Less knowledge about specific laboratory methodologies was recommended. *Discussion:* Competencies for medical students have expanded over the last decade, to include indigenous health, this is reflected in the new competencies proposed. The large number of competencies recommended may not be achievable during medical school, and some competencies may be better situated in years 1–4 postgraduate clinical years curricula.

AACG Oral 8
The Ethics of NIPT: Women's Experiences and Attitudes on Expanding the Reach

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Non-invasive prenatal testing (NIPT) can screen for conditions such as Down syndrome. It is highly accurate and low risk. Some countries publicly fund NIPT, although Australia does not. This study aimed to investigate the attitudes of women who have undergone NIPT towards possible expanded future uses, and their experiences with the test. One thousand women who had undergone the percept™ NIPT test were contacted and asked to complete a survey. The number of complete responses received was 209. Responses underwent content analysis and descriptive data analysis. Women generally reported an interest in using NIPT for early-onset medical conditions that severely impacted quality of life. They were also interested in testing for neurodevelopmental disorders such as autism. Respondents stressed the importance of accuracy of the test. Concerns were raised about using NIPT for non-medical traits such as intelligence. Respondents indicated that termination of pregnancy was not their only reason for testing, particularly in the case of reporting fetal sex. Positive experiences with NIPT were generally reported, with some room for improvement in pre- and post-test counseling. Most respondents indicated an interest in undergoing NIPT again. The findings of this study indicate women support widening of the scope of NIPT if it becomes practicable. However, they do not support its blanket use for all traits and conditions. This has ramifications for decisions about how NIPT should be expanded as technology allows. We will discuss the ethical implications of these findings. Positive experiences support the further integration of NIPT into the healthcare system.

AACG Oral 9
Reproductive Preferences in Parents with Lived Experience of Caring for their Children with Intellectual Disability

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Introduction: Genomic technologies are increasing diagnostic rates in children with intellectual disability (ID) improving risk assessment and reproductive choice. The EPIC-ID study, the Economic and Psychosocial Impacts on Carers of children with ID, provides an opportunity to explore parental reproductive decision-making. *Method:* Counselor delivered survey to a retrospective cohort of parents of children with ID, exploring recurrence risk perception, previous reproductive experiences, and preferences regarding carrier testing and reproductive options. *Results:* Of the 41 participants, most had 2 or more adult children with moderate-severe ID and 27 (66%) had obtained a genetic diagnosis after completing their family. 28/41 (68%) reported that they would have had carrier testing, if available. Perception of recurrence risk was high: 33/41 estimated their perceived chance was 50–100%. The most acceptable reproductive option was pre-implantation genetic diagnosis (66%); 23/41 (56%) would have prenatal testing and 14/41 (34%) would consider ending an affected pregnancy. Of the 16/41 (39%) who would continue an affected pregnancy; four would have carrier testing and seven, prenatal testing. Of the three mothers who had prenatal testing in previous pregnancies, two ended an affected pregnancy and one would have ended the pregnancy, if affected. There were no significant differences in choice based on perceived risk, severity or number of affected children. *Conclusion:* Personal

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beliefs appear as important as lived experience in determining prenatal choice. This study highlights the difficulty parents of children with ID face when making reproductive decisions and especially in regard to ending an affected pregnancy.

AACG Oral 10
Preimplantation Genetic Diagnosis (PGD) for Retinoblastoma Survivors: Cost-Effectiveness and Quality of Life Improvements

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Background: Retinoblastoma (Rb) is a pediatric cancer, leading to loss of vision, eye(s) or life. Approximately 40% of patients have a heritable form of the disease. Offspring of these individuals have a 50% risk of inheriting the disease. Regular monitoring is required, with aggressive and invasive treatments, from birth to age 18. The numerous procedures under general anaesthetic, impact the patient, family and hospital resources. Preimplantation genetic diagnosis (PGD) offers reproductive choices for individuals with a heritable mutation, and costs of genomic sequencing are rapidly declining, with increasing availability of reproductive technologies. *Aims:* We undertook a cost-effectiveness study to determine the costs IVF and PGD and retinoblastoma and quality of life improvements, from diagnosis to age 18. *Methods:* We modelled the cost of reproductive technology, number of affected/unaffected births, and quality of life gains, for parental uptake rates of PGD from 0–100%. We included the costs of hospital visits from 0–18 years, and three cycles of IVF and PGD (1 fresh, 2 frozen). *Results:* Compared to standard care (i.e. natural pregnancy), PGD resulted in a cost-saving of $2,747,294, for one hundred couples with a 50% uptake rate. PGD also resulted in fewer affected ($n = 56$) and unaffected ($n = 78$) live births compared with 71 affected and 83 unaffected live births. *Conclusions:* IVF and PGD was always less expensive, with higher quality-of-life compared with taking the natural pregnancy approach. Affordable and accessible PGD will lead to savings for families and health systems for families with heritable retinoblastoma.

AACG Oral 11
Comparison Between Preconception Carrier Screening for Spinal Muscular Atrophy and Treating It with Nusinersen: A Cost-Effectiveness Analysis

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Spinal muscular atrophy (SMA) is an inherited neuromuscular diseases and a leading genetic cause of infant mortality. The recent approval of nusinersen as the first disease-modifying therapy for SMA that may extend quality and quantity of life represents a major milestone. However, it is a high cost orphan drug. Preconception carrier screening followed by preimplantation genetic diagnosis (PGD) for those at risk of having a child with SMA offers an alternative path to have a baby without SMA. The aim of this paper is to analyze if preconception carrier screening (PCS) for SMA is cost-effective compared to standard care and treatment of SMA with nusinersen. We developed a cost-effectiveness model based on the number of babies born each year in New South Wales. The number of babies that are likely to be born with SMA was estimated based on the published incidence rate of SMA of approximately 1 in 11,000 live births. The cost-effectiveness of PCS followed by PGD with IVF for those couple who are at the risk of having a child with SMA was separately compared with standard care for SMA and treating SMA with nusinersen. The incremental cost per additional life year gain for PCS compared to standard care for SMA was estimated at around $37,800. When compared to treating SMA with nusinersen, PCS would provide both substantial savings and more life years. Preconception carrier screening for SMA would be highly cost-effective compared to treating with SMA, but reproductive choices of individuals also need to be considered.

AACG Oral 12
Maximizing the Minimum Gain: Ensuring Equity of Access to BRCA Testing

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As BRCA mutations impact on cancer treatment, prognostication and familial risk assessments, equitable access to testing is of social importance. The association between BRCA mutations and the development of triple negative(TNT) breast cancer diagnosed <50 years, or high grade serous ovarian cancer diagnosed <70 years defines a cohort of women who warrant BRCA testing based on tumor-pathology alone. Comparing the characteristics of those women referred to the familial cancer clinics(FCC) to those who were not, can identify and quantify inequitable access to testing at a population level. A retrospective data cross-match was undertaken of all women with BRCA-related cancers (defined by ICD –O- and ICD10 codes and immunohistochemistry) reported to the Victorian cancer registry from 1/1 2008 to 31/12/2014 against the subset referred to the Victorian FCCs. All incident cases were categorized as either 'Referred' or 'Not-Referred'. Individual-level parameters relating to year and age of diagnosis, survival, socio-economic indexes, geographic location (ARIA code), and region of birth were available. Logistic regression (LR) analysis was undertaken using 'Not-referred' as outcome variable. The results demonstrate an inequitable and inefficient referral process as multivariate analysis demonstrated increased age at diagnosis, tumor grade, decreased length of survival, and increased socio-economic disadvantage significantly decreased referral of HGSO cases, while increased age of diagnosis, grade, survival and non-Australian status decreased TNT referral. These findings led to the EMBED study, which circumvents current barriers to FCC referral by integrating the cancer registry directly in the FCC referral process. Both the LR results and description of EMBED will be discussed.

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Concurrent Session 6: Australasian Society of Genetic Counsellors

ASGC Oral 7
Taking a Family Health History: What Shapes the Aboriginal and Torres Strait Islander Story?

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Genetic Services in Australia follows a Western model of care based on evidence and an accurately documented family health history. As genomic medicine move into mainstream healthcare however, it is important to reconcile whether this model of care resonates with all members of the community. Our study targeted one of the most disadvantaged groups in our community, those who identify as an Aboriginal and/or Torres Strait Islander. It is well documented that health and wellbeing from the Aboriginal and Torres Strait Islander Community's perspective extends beyond the combination of signs measured by a medical test. Health is inclusive of mental wellbeing, social, emotional, spiritual and cultural connections, and therefore it is important to explore whether genetic concepts such as family health history align with this or not. Using semi structured interviews during which time a three-generation pedigree was documented by a genetic counselor, our study explored kinship, biological relationships and understanding of genetic health conditions in the Aboriginal and Torres Strait Islander Community. Qualitative analysis of 19 interviews with participants revealed how this community's cultural beliefs intersect with the model of care provided by genetic services. Results show that working with the Aboriginal and Torres Strait Islander Community does require clinicians to adapt their practice by providing more time, being aware of historical and cultural events and exercizing sensitivity to the unique issues that can be encountered during the documentation of a family health history.

ASGC Oral 8
Developing Guidelines for Genomic Researchers Partnering with Aboriginal and Torres Strait Islander People of Queensland

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Substantial investment both nationally and within Queensland means genomics is rapidly moving from a research activity with niche clinical applications to a technology that will become part of every-day healthcare. The past experience of Aboriginal and Torres Strait Islander peoples across scientific endeavour, including genomics, has frequently been damaging. This experience plus the complex ethical and social implications of genomics has resulted in limited number of genomics research projects exploring topics important to Aboriginal and Torres Strait Islander peoples. This lack of genomic research has direct implications for healthcare. For clinical genomic services to provide meaningful analyses, reference genomic databases and research that represent Aboriginal and Torres Strait Islander population are needed to provide frequency of genomic variants in the population and how they relate to disease profiles. To assist researchers in developing genomics research projects with Aboriginal and Torres Strait Islander peoples and communities this project aimed to develop a set of guidelines that are based on stakeholder consultation. The consultation process consisted of two workshops held at five locations across Queensland in July/August 2018 and February/March 2019. The workshops involved people from the research community, health services, ethics, health policy sector, and members of the Aboriginal and Torres Strait Islander community. Here we will presented an overview of the resulting document Genomics Research: Guidelines for genomic research involving Aboriginal and Torres Strait Islander Peoples of Queensland.

ASGC Oral 9
Parent Experiences with Ultra-Rapid Genomic Sequencing in Pediatric Acute Care

G Brett[1,2,3], M Martyn[2,3,4], M de Silva[1,2,5], K Boggs[5,6,7], A Baxendale[5,8], S Borrie[5,8], S King-Smith[5,9], S Ayres[1,3,5], L Gallacher[1,2], F Lynch[2,3,5], J Pinner[6], S Sandaradura[7], M Wilson[7], C Barnett[8], C Patel[10], A Vasudevan[11], E Krzesinski[12,13], S Lunke[1,2,5] and Z Stark[1,2,5]

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Background: Emerging evidence that rapid turnaround times impact the clinical utility of genomic testing in acute pediatrics is driving widespread adoption. However, little is known about the experience that parents of critically unwell infants and children have during the testing process and beyond. *Methods:* Participants were recruited as part of the Australian Genomics Acute Care study, a national rapid genomic diagnosis program for infants and children admitted to intensive care with suspected genetic conditions. Pre- and post-test counseling was provided by genetic health professionals. Over 95% of parents offered testing gave consent. Results were available within 5 days of sample receipt. Parents were surveyed >12 weeks after results return. We explored parental experiences with consent processes, perceived impact of testing on child health, relationships and reproductive decisions. This questionnaire included the Decision Regret, Short Form Genetic Counselling Outcomes and PedsQL Family Impact Module scales. *Results:* From 21 respondents in the first 6 months (RR = 54%), most felt they received enough information during pre-test ($n = 21$, 100%) and post-test ($n = 18$, 86%) counseling. No respondents reported decisional regret regarding testing. Perceptions varied about the benefits of rapid genomic sequencing for the child. The majority of respondents ($n = 13$, 62%) were extremely concerned about the condition occurring in future children, regardless of their actual or self-perceived recurrence risk. Eight respondents (38%) reported the test impacted their reproductive plans. *Importance:* Understanding parental experiences, opinions, and the short and long term impacts on families will guide the design and delivery of rapid genomic diagnosis programs.

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ASGC Oral 10
Ethical Challenges in Genomic Testing in the NICU: Clinicians' Views

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Background: The increasing use of genomic testing in neonatal intensive care units (NICU) gives rise to ethical issues. However, little is known regarding views of healthcare providers on the ethical aspects of this application of genomic testing. *Aim:* To explore the views of Australian clinical geneticists regarding ethical issues surrounding the use of genomic testing in the NICU. *Methods:* Semi-structured interviews with purposively-invited participants were audio-recorded, transcribed, coded and analyzed using thematic analysis. *Results:* Eleven Australian clinical geneticists participated, with data saturation reached. Four themes were identified: (1) Informed consent: the craft is in the conversation – encapsulating the challenges in obtaining true informed consent, and pre-test counselling; (2) Whose best interest and who decides? – balancing clinical utility and potential harms of the test, emphasizing parental interests in deciding which kinds of results to receive; (3) The winds of change and ethical disruption – while professional expertise is vital to clinical decision-making and oversight of mainstreaming, participants also expressed concern over the size of the genetics workforce and (4) Finding solutions – the available resources and mechanisms to prevent and resolve ethical dilemmas, such as adequate genetic counseling, teamwork and use of external ethics and law expertise. *Conclusion:* These findings highlight the ethical complexities associated with genomic testing in the NICU. They suggest the need for a workforce that has the necessary support and skills to navigate the ethical terrain, drawing on relevant concepts and guidelines to balance the interests of young children, their carers and health professionals.

ASGC Oral 11
Genetic Counselors in the NICU and PICU: Experiences from the Australian Acute Care Genomics Project

M de Silva[1,2,3], G Brett[1,2,3], S Ayres[1,2], A Baxendale[4], S Borrie[4], K Boggs[1,5,6], A Springer[1,7,8], K Rose[7,8], F Cunningham[7,8], H Curd[7,8], T Davis[9], L Fowles[10], L Hunt[10], F Lynch[1,3,11], M Wilson[5,12], Z Stark[1,2,3] and L Gallacher[1,2,3]

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Background: The Acute Care Genomics (ACG) project provides rapid (turnaround time of <5 days) genomic testing to acutely unwell infants and children with suspected monogenic disorders across 10 Australian hospitals. Of the first 100 cases enrolled, 52% received a diagnosis, with a change in management in 75% of those diagnosed. Five families declined participation in the project. Genetic counselors (GCs) formed an integral part of the multidisciplinary ACG team. *Methods:* We examined the interactions of the GCs with this patient cohort and describe our observations of the emerging role of GCs in neonatal and pediatric intensive care units. *Results:* Overall, GCs spoke with families in 91/121 (75%) pre-test and 74/118 (63%) post-test encounters, with an average duration of 53 and 42 min respectively. Where GCs were involved, the average number of contacts per family was two (range 1–6); the level of GC involvement varied across recruitment sites. GCs facilitated informed decision-making and consent, provided psychosocial support, and managed the logistics of recruitment, often acting as a conduit for communication between bedside clinicians and the laboratory. Common challenges encountered during this period included logistics, (lack of) preparation time and practising in the intensive care environment. Given the distressing nature of many of the diagnoses, GCs provided guidance and peer support to each other and the clinical team more broadly, through individual discussions and focussed, interactive workshops with multisite participation. *Conclusion:* Lessons learned are important for future service planning, as well as in ongoing efforts to mainstream genomic testing more broadly.

ASGC Oral 12
Clinical Leadership and Genomics – What Works?

S Best[1,2], J Long[1], Z Stark[2], C Gaff[2,3,4], J Braithwaite[1] and N Taylor[5]

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Transitioning genomics from research into clinical care will challenge current health service delivery. Understanding how clinical leaders can steer health services through this change is imperative if the benefits of genomic medicine are to be realized. *Aim:* To identify clinical leadership qualities and behaviors required to navigate the move of clinical genomics from research into clinical care. *Methods:* We designed two semistructured interview schedules to identify determinants of implementation of clinical genomics using two theoretical frameworks: (1) Theoretical Domains Framework, for non-genetic medical specialists, and (2) The Translation Science to Population Impact framework, for those working at service level. Sixty-two people working with Australian and/or Melbourne Genomics were identified: 37 people responded (clinical $n = 16$, service decision makers $n = 21$) and were interviewed in 2018. Data were managed with NVivo 11 software and coded thematically. *Results:* Participants reported a disruption of the traditional medical hierarchy impinging on the coveted consultant 'elite' status. More established participants recognized the loss of the 'expert leader' role and the need to support younger, often more knowledgeable, colleagues. The need for new approaches to knowledge gathering, humility, and to embrace failure, were reported as essential requirements for clinical leaders. *Discussion/Conclusion:* Our findings demonstrate how the status quo in service provision is being challenged by the implementation of genomics. Upsetting conventional structures and nurturing rapidly developing clinicians, requires considered leadership. Clinical leaders need to be supported towards team decision-making and learn strategies about how to access knowledge as required.

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Concurrent Session 7: Australasian Society for Inborn Errors of Metabolism

ASIEM Oral 3
Growing Up with a Hidden Disorder: An Ethnography of the metabolic condition MCADD in New Zealand

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Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) is an inborn error of metabolism that was included in newborn screening programs in New Zealand in 2006. Once diagnosed, children may never become symptomatic due to ongoing treatment, which is as simple, and as complicated as eating regularly. This nationwide New Zealand study examined the daily lived experience of the first generation of children to be diagnosed with MCADD via expanded newborn screening. Patients were recruited via Starship's Metabolic Services Team in Auckland. It used a variety of anthropological methods to capture 31 children's perspectives across the age range, from newborn to age 10, along with those of family members and health professionals. These methods include participant observation, 524 semi-structured interviews, photovoice, metaphor sort technique, body mapping, and storyboarding. I show that a body diagnosed with the potential for illness has as much capacity to transform a young life as illness itself. The diagnosis creates a medicalized body in need of preventative treatment, while outpatient clinics and hospital admissions help construct the impression of a pathologized body. The 4 year study found that personhood, as embodied and situated, is affected by the experiential, sensory knowledge of MCADD treatment (feeding and hospitalization) in the first few years of life.

ASIEM Oral 4
Baby Beyond Hearing, Using Genomics as a Newborn Screening Tool

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Genomics has the potential to be a powerful newborn screening tool, this is being investigated internationally. Genomic tests are increasingly available in Australia and additional findings can be analyzed and inform future health. This study aimed to explore parents' interest in receiving additional findings from genomic testing and determine factors influencing decision-making about the scope of results desired. Families that consented for exome sequencing to investigate deafness in their child were eligible. They were provided with a decision aid and a genetic counseling session. Participants could choose (A) no additional results; (B) additional results for childhood onset genetic conditions with a known treatment; or (C) additional results for childhood onset conditions with or without a known treatment. All families completed surveys about their decision-making at recruitment and after return of results. One hundred and six families participated, of which 72 (68%) chose to receive additional findings: 29 (27%) opted for choice B and 43 (41%) opted for choice C. Decisional conflict and anxiety levels were lower in those who chose to receive additional findings but similar between groups B and C. Intolerance of uncertainty was highest in the choice A group. Eighty percent of participants used the decision aid and 74% made a decision before their appointment however 23% consented to a different option post genetic counseling. Four participants had additional results returned, of which two required further management. This study highlights the interest in additional findings from genomic sequencing and emphasizes the importance of choice as families desire different levels of information.

ASIEM Oral 5
Newborn Screening of Severe Combined Immune Deficiency in NZ

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Severe combined immune deficiency (SCID) is ideal for newborn screening (NBS), it has 100% mortality by 1 year old, yet upon hematopoietic stem cell transplant before 3.5 months the long-term survival rate is 95%. A simple DNA test quantifies the number of T-cell receptor excision circles (TRECs) in the blood, which are inversely proportional to disease risk. Both in-house qPCR and the commercial EnLiteTM end-point PCR methods for TREC quantification were investigated. A tight go-live date enforced implementation of the EnLiteTM method. A conservative cut-off of 25 TREC copies/μl blood was initially used and all positives referred for Flow Cytometry confirmation. However, both this threshold and number sent for confirmation were too high, so in consultation with clinicians a second card for borderline results was introduced and the cut-off reduced to 18 TREC copies/μl. Many other lessons were learned. The repeat rate, although consistent with other countries, is still highly variable. Issues with PCR plate sealing, likely caused by inconsistencies in the plate manufacture; and with reagent stability, from long term storage of kits exacerbated by long transit times from the manufacturer to NZ have been identified. Since the introduction of SCID NBS in December 2017, ~78,000 babies have been screened, detecting two patients with critical T-cell lymphopenia (TCL) requiring immune reconstitution: one with SCID and one with complete athymia. Secondary targets of clinical significance include patients with multisyndromes with variable TCL requiring initial immunological monitoring. These results align with the expected population frequency of SCID of 1:50–100,000.

Concurrent Session 8: Australasian Society of Diagnostic Genomics

ASDG Oral 5
Identification and Characterization of Predisposition Genes and Mutations in Familial Hematological and Pan-Cancer Families

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Approximately 6500 Australians are diagnosed with leukemia or other hematological malignancies (HM) each year and 10–15% of

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these are attributed to familial hematological malignancies (FHM). Since the establishment of the Australian Familial Haematological Cancer Study (AFHCS) in 2004, we have recruited over 200 families, and have comprehensively analyzed genomic profiles to identify candidate germline mutations that predispose to HM. We and collaborators have discovered predisposition genes *GATA2* (MDS/AML) and PAX5 (ALL), and have also reported families with *RUNX1*, *DDX41* (MDS/AML), *CEBPA* (AML) and *SAMD9L* (ALL) mutations. In ~20% of AFHCS families tested, we have identified a predisposing gene mutation and have strong candidates for another ~20%. The majority of unresolved cases include families with lymphoma who often also present with non-HM solid tumors. Segregating variants in a number of DNA damage repair (DDR) genes *BRCA/FANC* genes (e.g., PALB2, BARD1) in families with a history of lymphoma and solid tumors signify a pan-cancer (P-C) phenotype. The discovery of P-C genes, such as DDR genes in HM, suggests that the prevalence of FHM may be higher than the purported 10–15% of HM. Through AFHCS, we aim to ascertain the prevalence of genetic predisposition to HM and P-C, develop functional models to provide evidence for pathogenicity of novel candidate genes/mutations, and provide families with a solution to their predisposition. Improved understanding of the pathogenic mechanisms of inherited blood cancers will help unveil therapeutic targets to benefit clinical practice.

ASDG Oral 6
A Clinic Based Multidisciplinary Review for Variants of Uncertain Significance Identified in Cancer Susceptibility Genes

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The identification of a genetic variant of uncertain significance (VUS) can be challenging for both patients and genetic health professionals. As access to genetic testing improves and larger gene panels are available, the number of VUSs is increasing leaving patients and their families uncertain about their cancer risks and reducing the clinical benefit of testing. Classification of variants incorporates diagnostic laboratory based assessment using ACMG guidelines and clinical information, including variant segregation within families, histopathology and somatic variant tumor profiles. To bring together these clinical and diagnostic elements and help manage this complex group of patients, a new multidisciplinary forum was developed at the Parkville Familial Cancer Centre to provide opportunity for the classification and clinical management of VUSs to be reviewed. This multidisciplinary group consists of senior molecular scientists, curation specialists, geneticists, genetic counselors, gastroenterologists, consultant oncologists and has links to national and international variant research consortium. Results are issued by the laboratory using their usual protocols to avoid delay and are only referred for variant review by the clinic after being reported and issued. In the 12 months since its inception, 61 VUSs have been presented from familial cancer centers in Victoria and Tasmania resulting in 12 VUSs (20%) being reclassified as pathogenic or likely pathogenic, 3 reclassified as benign and 7 determined to be highly suspicious. Multidisciplinary review of patients with a VUS within a familial cancer clinic has been a valuable forum to reclassify variants improving the quality of information provided to patients and their families.

ASDG Oral 7
Somatic Mutation Testing for Cancer Services in Queensland Public Hospitals

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Background: The Laboratory introduced Next Generation Sequencing (NGS) methodology into routine somatic cancer genetic testing of FFPE specimens in 2016. The results of testing help to guide treatment therapy decisions for melanoma, lung cancer (NSCLC) and colorectal cancer patients. *Method:* Our NATA accredited (ISO15189) assay uses the TruSight 26 panel that includes selected exons from 26 genes (Illumina). It is a targeted panel that is focussed on actionable variants that have strong clinical utility in solid tumors. The assay has an analytical sensitivity of 97.3%, a variant detection threshold of 3% and a minimum read depth of 1000 fold. The assay has also been recently NATA accredited for use with Thinprep specimens from endobronchial ultrasound lung biopsies. *Results:* Somatic genetic testing was performed on 6516 FFPE and a small number of Thinprep specimens between 2016 and 2018. Two-thirds of FFPE specimens were tested by NGS with the remainder, lower-quality specimens, tested by real-time PCR. Thinprep extracted DNA was of better quality and produced better results with NGS than FFPE extracted DNA. Somatic variants (Tier I to III) were reported in 59% of specimens tested by NGS. Benign and likely benign variants (Tier IV) were not reported. *Conclusions:* The somatic cancer panel covered 98–100% of OncoKB actionable/druggable alterations for melanoma, lung cancer (NSCLC) and colorectal (excluding fusions and CNVs), as of March 2019. The NGS assay has a variant detection frequency comparable to large pan-cancer datasets and is a cost-effective solution for routine genomic cancer testing with high clinical utility.

ASDG Oral 8
Whole Genome Sequence Analysis of Patients with Suspected Hereditary Cancer

A Davidson[1,2], U Dressel[2], F Newell[1], H Mar Fan[3], E Tudini[1], S Kazakoff[1], R Koufariotis[1], J Shamsani[1], Australian Genomics, The Inherited Cancer Connect Partnership (ICCon)[4], P James[4], G Mitchell[5], R Ward[2,6,7], J Pearson[1], A Spurdle[1] and N Waddell[1]

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Cancers may be driven by inherited germline variants, often recognized when multiple individuals within families present with cancer phenotypes that are considered characteristic for a given gene or genes. Such presentations are termed hereditary cancer predisposition syndromes (HCPS). Unfortunately, the underlying causes for many HCPS remain unknown. A project conducted by Australian Genomics and the Inherited Cancer Connect (ICCon) partnership, aims to analyze the germline whole genome sequences of 190 patients presenting with clinical features of a HCPS who have previously undergone uninformative clinical genetic testing. Our analysis includes the identification of germline variants, including single-nucleotide, small insertions and deletions, copy-number and structural events, within a reviewed gene panel. These genes have disease-associated variants which are considered clinically actionable within the context of familial cancer. To date, we have recruited 87

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participants of which 54 have undergone whole genome sequencing. Consequently, we have reviewed more than 600 rare variants for potential association with cancer. Approximately, 10% of these variants were discussed at multi-disciplinary team meetings; the majority were reported as variants of uncertain significance, and several as likely pathogenic. These findings have also triggered requests for functional assays to aid variant interpretation, and further detailed clinical examination to assess the relationship between identified variants and patient presentation. We hope that identifying these variants will increase our understanding of the role that germline variation has in hereditary susceptibility to cancer, and in doing so identify better ways to manage patients with otherwise unexplained hereditary cancer.

ASIEM Dietetic Workshop

Ketogenic Diet in McArdle Disease: A Case Study

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Background: McArdle Disease (Glycogen Storage Disease Type V, GSDV) is an inborn error of muscle glycogen metabolism caused by mutations in PYGM, and subsequent myophosphorylase deficiency. Patients present with exercise intolerance, myalgia, and are at risk of recurrent rhabdomyolysis. The ketogenic diet (KD) may reduce glycogen synthesis and replenish acetyl-CoA for the tricarboxylic acid cycle from ketone bodies, thus providing alternative muscle energy. Although patients with McArdle disease increasingly advocate for use of the KD, treatment efficacy is not well established. *Case:* A 56-year-old man presented with a lifelong history of exercise intolerance, myalgia, probable rhabdomyolysis, and subtle shoulder girdle muscle weakness and wasting. He was a keen athlete and exercized regularly. Creatinine kinase (CK) level was 2559 U/l. He was homozygous for the common PYGM mutation c.148C>T. Pre-exercise carbohydrate intake did not improve symptoms, thus the KD was initiated on request of the patient. *Results:* KD provided: 82% total energy (TE) from fat, 6.5% TE from carbohydrate, 18% TE from protein. Median blood ketones were 1.2 mmol/l (range 0.4–4.1). Increased fat intake improved ketosis and a ketogenic ratio of ≥1.6:1 precipitated ketones >2 mmol/l. Subjective improvements in fatigue, myalgia and exercise tolerance with faster progression to second wind phenomenon were reported. Median CK was 1867 U/l (range 874–6175); with an observed increase in CK following isometric training. *Conclusion:* McArdle disease patients report symptomatic improvement on the KD. Further research into the application and effectiveness of the KD in this condition is needed.

ASIEM Allied Health & Nurses Session

Invited Speaker Presentation
Dietetic Challenges in Managing Glycogen Storage Diseases (GSD) – Focusing on GSD I and III

Rachel Skeath

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Introduction: Dietary management of GSD types Ia, Ib and III necessitates implementation of a finely balanced regimen that meets requirements for metabolic stability while avoiding over treatment. Consideration must be given to how this often intensive feeding plan can be incorporated into everyday life. Inclusion of high protein intakes or the ketogenic diet add further challenge in GSD III. Aim: Produce a descriptive summary of the dietary management of our GSD patient cohort: Ia ($n = 6$) Ib ($n = 5$) and III ($n = 12$) and discuss the challenges of management. Implementation of ketogenic diets into current GSD III management has also been considered. *Method*: Data on route of feeding, cornstarch intake, protein intake (GSD III) and growth were collected. Management of infants was given particular attention. *Results:* 22/23 patients follow a higher centile for weight than height (difference in height and weight z-score ranges 0.01–3.26, median 1.58). Only 1/11 with GSD Ia or Ib does not require a feeding tube; this patient does not have an overnight feed. No GSD Ib has a gastrostomy. Patients with GSD III achieve a protein intake of 10–29% energy requirements. Breast feeding with supplements of glucose polymer is possible in infants. *Conclusion:* There is still progress to be made in improving outcomes in GSD I and III. Multi-factorial dietary management plans must be practical if latest recommendations are to be successfully implemented and reported benefits achieved.

Continuous Glucose Monitoring in Hepatic Glycogen Storage Disorders: A Systematic Review

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Hepatic glycogen storage disorders (GSD) are characterized by enzyme defects that affect blood glucose homeostasis. Despite these patients being highly susceptible to severe hypoglycemia, use of continuous glucose monitoring (CGM) in this population is less common. This review aimed to summarize existing use of CGM in patients <20 years with hepatic GSD subtypes (0; I; III; VI; IX; GLUT 2), to determine if it could improve glucose control versus the standard self-monitoring blood glucose (SMBG) method. The search strategy was conducted across four databases in October 2018, and updated in April 2019, using key terms relating to GSD, CGM, SBGM, and pediatrics. Studies were selected using a set inclusion and exclusion criteria. Our search identified that of the five studies retrieved, the quality of the evidence was low. Studies contained a small number of patients from single-centers and mostly focused on the usability and functionalities of CGM as a monitoring tool. CGM across all studies, revealed unrecognized periods of hypo- and, or hyper-glycemia, with incidence varying in degree and duration over the day. When combined with dietary intake data, CGM lead to statistically significant improvements in metabolic parameters including reduced frequency of hypoglycemia; reduced liver size; decreased triglycerides; decreased lactic acid; and improved liver markers. Routine CGM use could also be an effective education tool leading to improved quality of life and reduced hospital admissions. Future coordinated systematic research using standardized methodologies is warranted to establish CGM as the accepted management of hepatic GSD, as it has for diabetes mellitus.

The Use of Tetrahydrobiopterin IN PKU: The Victorian Experience

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Background: Patients with phenylketonuria (PKU) that show responsiveness to tetrahydrobiopterin (BH4), may have a more liberalized diet. RCH Melbourne has funded and used BH4 for PKU

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since 2002, however BH4 will soon be prescribable on the Australian Pharmaceutical Benefits Scheme (PBS) in doses up to 20mg/kg/d. We aim to describe responsiveness, dietary intake and growth of patients treated with (BH4PKU) and without BH4 (DPKU). *Method:* Since 2012, longitudinal retrospective and prospective clinical data of growth (weight, height, BMI z-score) and dietary intake (protein type and quantity) has been collected on patients from medical records and clinic appointments documented in a metabolic database (VICIEM). *Results:* Since 2002, 87 new patients with elevated phe > 360 µmol/l have been treated at RCH. 65/87 were loaded/tested with BH4 and 28/65 (43%) showed responsiveness; mean phe reduction 49.4% (SD 17.7). Of these 9/20 BH4PKU patients are on 'normal' diet, while 11/20 still require some natural-protein restriction. No significant relationships were observed between degree of BH4 responsiveness and natural-protein intake, or between BH4 dose and natural-protein intake in children <10 years. In BH4PKU patients, natural-protein intake (g/kg/d) was significantly higher at 2, 3, 4, 5 ($p < .001$), 7 ($p = .011$), and 9 years ($p = .034$) and synthetic-protein intake (g/kg/d) was significant lower at 2,3,4,5 ($p < .001$), 7 ($p = .001$) and 10 years ($p < .001$), compared to DPKU patients. BMI z-score was not significantly different. *Conclusion* The PBS listing of Kuvan® will allow an increased BH4 dose and potential dietary liberalization in our patients allowing further analysis of the dose-diet relationship.

Concurrent Sessions – Top Poster Presentations

Poster Oral 1
P29. Screening Strategies for Recruitment and Result Reporting to Maximize Utility of Whole-of-Life Genomics

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Background: Population genetic screening has traditionally been offered in the setting of education supported by face to-face genetic counseling and consent, followed by specimen collection. Community Genetics programs have also offered group genetics education, followed by individual consent and specimen collection. Models for result reporting can be individual or couple-based, with additional potential reflex testing for couples. Each model has advantages and disadvantages, which will vary from the perspective of the use-case (diagnostic, reproductive, pharmacogenomic, predisposition), patient, consumer, laboratory, clinician and funder. *Aim:* To determine if an optimal model exists to meet all likely use-cases and stakeholders. *Methods:* We modelled a range of recruitment and reporting strategies: Pretest online or group education and counseling: Individual, Couple (1-step concurrent, 2-step sequential, or reflex)['1C2SorR'] or Group Recruitment: Individual, or Couple (1C2SorR); self-selected or referral by healthcare provider. Analysis: Individual, or Couple (1C2SorR). Result reporting: Individual, or Couple (1C2SorR). Posttest counseling: Individual, Couple (1C2SorR) and pan-test. *Results:* We identified the models likely most appropriate to achieve informed consent, optimal yield, clinical utility and efficiency for the different scenarios. *Conclusion:* While sequencing costs remain high, the optimal strategy will be one where genomic data is tested once and stored in a secure repository, with periodic reanalysis generating various report types to maximize utility at minimum cost. The ideal solution appears to be 'collect and test once', followed by a lifelong mixture of education and reporting strategies as needed. This model met all scenarios.

Poster Oral 2
P94. Improving Communication of Genetic Results in Families with Hypertrophic Cardiomyopathy: A Randomized Controlled Trial

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Background: In the setting of hypertrophic cardiomyopathy (HCM), genetic results provide invaluable information, allowing at-risk relatives to undergo predictive testing. Communication to at-risk relatives is currently not ideal, with 20–40% of relatives uninformed about relevant genetic information. *Aim:* Improving knowledge of a genetic result may positively impact on communication to at-risk relatives. We aimed to determine if a genetic counselor-led intervention using a communication aid for delivery of HCM genetic results improves ability and confidence. *Methods:* This was a prospective randomized controlled trial. Consecutive HCM patients were invited to participate. Once consent was obtained they were randomized to receive their genetic result via the intervention (with communication aid) or control arm (usual care). Primary and secondary outcomes were measured using a survey comprised of a number of validated scales. The primary outcome was the ability and confidence of the proband to communicate genetic results to at-risk relatives. *Results:* The a priori primary outcome did not show statistically significant differences, though the majority of probands in the intervention group achieved good communication (13/22 [59%] vs. 10/20 [50%], $p = .26$). Genetic knowledge scores were consistently higher among the intervention group (19/22 [86%] vs. 12/20 [60%], $p = .05$). Importantly, among the cohort we found 29% of at-risk relatives were not informed of a genetic result. *Conclusion:* We show evidence that a communication tool has a positive impact on family communication. Research to further develop this to support communication in HCM families is needed.

Poster Oral 3
P124. 'The Benefit that Comes from My Existence': Patients' Experiences of Consenting to a Cancer Rapid Autopsy Program

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CASCADE, an Australian-first cancer rapid autopsy program, was established in 2012 to enable functional and genomic analyses on metastatic tissue. Patients with metastatic disease are recruited to CASCADE when they have no further curative treatment options available. Little is known about patients' experiences of consenting to a rapid autopsy at the end-of-life, and the implications of consenting to this unique research program. This study aims to explore patients' experiences of consenting to CASCADE, and the personal and familial implications of this decision. Using a qualitative approach, we conducted interviews with CASCADE patients.

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Recruitment for interviews is ongoing and is mediated by clinicians who recruit for CASCADE. We used thematic analysis, coding interview transcripts inductively and independently, then compared coding to identify themes, concepts, and ideas, to generate the findings. To date, 10 interviews have been conducted with patients who have consented to CASCADE. Most had agreed to participate with little deliberation: their decisions were based on altruism and a wish to benefit others, a desire to reciprocate for the care they had received, and an unfulfillable aspiration to donate their organs. Consenting to CASCADE created a space during end-of-life to discuss death with their support network but otherwise minimally impacted their everyday living. Patients expected that their families would respect their wishes and agency. Despite this, some patients had not disclosed enrolment in CASCADE to their parents to minimize distress. These findings suggest that discussions about rapid autopsy were acceptable to our participants and consenting offers meaning during the end-of-life.

Poster Oral 4
P83. Pregnancy Outcomes Following the Detection of Early Fetal Edema on Pre-NIPT Ultrasound

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Aims: To investigate the incidence of structural and chromosomal abnormalities in cases of fetal edema identified at pre-NIPT ultrasound. *Methods:* A retrospective cohort study at a tertiary ultrasound practice in Melbourne, Australia, including all women undergoing pre-NIPT ultrasound examination of fetuses with crown-rump length (CRL) of 28–44 mm. Ultrasound examinations between January 2013–November 2018 where subcutaneous edema or fetal hydrops were reported were included. Information on conception mode, obstetric ultrasound examinations, prenatal screening, genetic testing and pregnancy outcome were collected. Fetal edema was classified into isolated nuchal edema, generalized subcutaneous edema or fetal hydrops. Classification was conducted independently by two experienced operators, blinded to pregnancy outcomes. *Results:* 10,478 pre-NIPT scans were performed and fetal edema was reported in 104 cases (1.0%). Pregnancy outcomes were available in 93 cases. Chromosomal anomalies were identified in 21.5% (20/93), and structural anomalies with normal microarray were identified in another four (4.3%) cases. Seventy-one infants (76.3%) were liveborn (66 with normal ultrasounds and phenotypically normal infant at birth, one with monosomy X, two with major fetal anomalies, two with variants of unknown significance). Miscarriage occurred in four cases (4.3%), and termination of pregnancy occurred in 18 cases (19.4%, 16 with chromosomal abnormalities and two with major structural anomalies). Cases where edema resolved at 11–14 weeks had a significantly lower adverse outcome rate than those with NT $\geq$ 3.5 mm (11.8% versus 70.6%, $p < .001$). *Conclusion*: Fetal edema in early pregnancy is associated with a high incidence of structural or chromosomal abnormalities, and these rates increase with progressive severity.

Poster Oral 5
P108. The Expanding LARS2 Phenotypic Spectrum: HLASA, Perrault Syndrome with Leukodystrophy, and Mitochondrial Myopathy

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Background: LARS2 encodes mitochondrial leucyl-tRNA synthetase, which attaches leucine to its cognate tRNA. LARS2 variants are associated with Perrault syndrome, characterized by premature ovarian failure and hearing loss, and with an infantile lethal multi-system disorder: hydrops, lactic acidosis, sideroblastic anemia (HLASA) in one individual. Recently we reported LARS2 Perrault syndrome cases with leukodystrophy. Here we describe bi-allelic LARS2 variants associated with a HLASA-like phenotype in two unrelated individuals (P1, P2), an adult with Perrault syndrome and leukodystrophy (P3), and a child with mitochondrial myopathy, lactic acidosis, and developmental delay (P4). P1 and P2 survived multi-system disease in the neonatal period; both have developmental delay and hearing loss. *Methods:* Bi-allelic LARS2 variants were identified by exome sequencing of P1-P4. *In vitro* amino-acylation assays were performed using recombinant LARS2 variant proteins. For P4, respiratory chain enzyme activity assays, immunoblot, immunohistochemistry and electron microscopy were performed on muscle biopsies. *Results:* Amino-acylation assays showed the P1-P4 LARS2 variants had reduced catalytic efficiency in attaching leucine to its cognate tRNA. P1 and P2 LARS2 variants had a more severe effect on amino-acylation compared to P3 and P4 variants. One of the P4 variants had a lower affinity for ATP while the other variant had reduced affinity for leucine. Analysis of P4 muscle biopsy showed reduced LARS2 and complex I protein levels, reduced complex I activity, and an unusual form of degeneration. *Conclusion:* Bi-allelic LARS2 variants are associated with a broad phenotypic spectrum. These HLASA-like cases partially bridge the spectrum between lethal HLASA and Perrault syndrome.

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Poster Oral 6
P149. What Exactly Do We Know About Functional Constraint on Genes Associated with End-Stage Kidney Failure?

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Large-scale high-quality exome sequencing data have allowed for the interrogation of low-frequency variations and their predicted pathogenicity. The accuracy of identification is useful for appropriate clinical interpretation as mutations that occur in constrained regions are more likely to be deleterious; therefore, it is hypothesized that in certain genes, selective constraint diminishes observed functional variation. Using data from the Exome Aggregation Consortium (ExAC), combining exome sequencing in 60,706 patients, we examined functional constraint acting on genes associated with end-stage kidney failure (ESKF) by comparing the frequency of synonymous, missense, and loss-of-function (LoF) mutations against their respective selection-neutral expected values, taking into account gene length, read depth, and local sequence context. A set of ESKF-associated genes were identified from clinical data on pediatric patients in Boston Children's Hospital and the Children's Hospital at Westmead. We compared these values across genes identified by transcriptomic analysis to be highly tissue-enriched in kidneys and those associated with chronic kidney disease (CKD) by GWAS. Our results show stronger negative selection in ESKF-associated genes than in CKD-associated genes across LoF mutations ($p < 4.0e-06$). Among missense mutations, AD ESRF-associated genes are under more selective constraint than kidney-expressed genes ($p < .004$). As expected, CKD-associated, ESKF-associated, and kidney-expressed gene sets had similar z-score distributions for synonymous mutations ($p =$ n.s.). Selective pressure was identified most strongly across LoF mutations, suggesting that frameshift, nonsense, and splice-site disruptions are likely to be deleterious in the context of ESKF. In contrast, genes highly enriched for renal tissue experience minimal negative selection, suggesting tolerance of variation.

Poster Oral 7
P49. Western Australian Health Professionals' Attitudes to and Knowledge About Expanded Preconception Carrier Screening

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Background: Expanded preconception carrier-screening has been increasingly discussed and implemented over recent years. Some have warned of limited clinical utility, while others argue that preconception carrier screening improves reproductive choices. We investigated the attitudes and knowledge of Western Australian health professionals in relation to preconception carrier screening and where their concerns lie. *Methods:* We analyzed the relationship between knowledge, attitudes and intentions to participate in preconception carrier screening using logistic regression, in 203 health professionals in Western Australia. *Results:* Almost all participants have high genetic knowledge but knowledge did not correlate with intentions to take the test. Participants were less informed about probabilities and result interpretation than key carrier-screening concepts. Although 60.6% of participants had a positive attitude to the test, researchers and diagnostic scientists were more concerned about discrimination and confidentiality issues ($p \leq .05$) while genetic counselors were worried about doing more harm than good ($p = .04$). Predictors of taking the test include having a positive attitude, being a non-practitioner, not being a parent and not religious ($p \leq .05$). Of the 76% of participants who would use the test, 95% indicated that they prefer to screen for both childhood lethal and chronic debilitating conditions. *Conclusions:* Preconception carrier-screening is perceived positively by WA health professionals with a high level of intention to use it if it was available. Practitioners would be effective at administering the test provided they have access to support such as a genetic counselor to clarify doubts. Pilot studies of carrier screening will address concerns identified in this study.

Poster Oral 8
P101. Modeling the Mitochondrial Disease Sengers Syndrome Using Human Embryonic Stem Cells

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Background: Sengers syndrome is a potentially fatal mitochondrial disease characterized by hypertrophic cardiomyopathy, congenital cataracts, lactic acidosis, and exercise intolerance. This disease is caused by mutations in the acylglycerol kinase (*AGK*) gene. The enzymatic activity of AGK functions in mitochondrial lipid homeostasis. Additionally, AGK is a subunit of the mitochondrial TIM22 protein import complex and facilitates mitochondrial carrier protein biogenesis. *Aim:* This project aims to model and investigate the molecular and cellular pathogenesis underlying Sengers syndrome using human embryonic stem cells (hESCs) differentiated to clinically relevant cardiomyocytes. *Methods:* AGK-/- hESCs were generated using CRISPR/Cas9 gene editing technology, and validated for pluripotency and karyotype. Mutants were characterized by genetic (DNA and RNA) and immunoblot experiments. Selected clones were differentiated into cardiomyocytes and further functional analyses performed including calcium imaging and electron microscopy experiments. *Results:* DNA sequencing and cDNA studies identified multiple hESC clones with AGK mutations causing a frameshift and premature stop codons, or splicing defects. In hESCs with bi-allelic AGK mutations, the TIM22 complex was not detected by BN-PAGE. Preliminary results indicate that cardiomyocytes derived from AGK-/- hESCs display an irregular beating pattern and abnormal calcium handling compared to controls. Furthermore, samples analyzed by electron microscopy suggest that mutant cardiomyocytes possess disorganized myofibrils. *Discussion/Conclusion:* The AGK-/- hESCs have the potential to provide clinically relevant tissue samples for further investigations of disease pathomechanisms, with future experiments including proteomic and lipidomic analyses of mutants. Ultimately, these cells could be used to facilitate pre-clinical studies testing potential treatments for Sengers syndrome.

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Poster Oral 9
P128. The Practice of Engaging Aboriginal and Torres Strait Islander Communities in Genome Research

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Australia's National Health Genomics Policy Framework recognizes the obligation to ensure that Aboriginal people and Torres Strait Islanders (Australia's First Peoples) are at the forefront of developments in precision medicine and the broader integration of genomics onto the healthcare system. Indigenous inclusion in this area has requirements that go beyond general principles for Indigenous health research. This need exists for historical reasons and to maintain an enduring connection between patients, participants & communities and their contribution to the biospecimens and data that underpin genomics. The National Centre for Indigenous Genomics (NCIG) has developed a framework that addresses these requirements through strong Indigenous governance, enduring community engagement with stored material & genomic data, and rigorous data management systems. We present an Indigenous perspective on the community engagement component of this framework, describing the practical application of 'doing the right thing'; proceeding at 'the pace of trust'; obtaining informed consent as part of an enduring relationship; acknowledging cultural perspectives; understanding the diversity of views and practices within and between communities; respecting the need for community ownership and enabling community involvement in research. This Indigenous methodology for community engagement has been developed through action research involving communities participating directly in genomic research. In combination with NCIG's Indigenous governance and data management systems, it provides a model for Aboriginal people and Torres Strait Islanders to play a leading role in the future development of genome science and precision medicine in Australia.

Poster Oral 10
P68. Breast Screening in Young Women with NF1: Psychological Impact and Development of an Educational Resource

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Background: Women with Neurofibromatosis type 1 (NF1) have a moderately increased lifetime risk of developing breast cancer (18%); however, estimated 10-year breast cancer risks between ages 30 and 50 are comparable to those with *PALB2, CDH1* and *BRCA2* high-risk gene mutations. Consequently, EviQ guidelines recommend annual breast screening from 35 years. It is important to investigate the impact of breast screening, and provide appropriate support given NF1 is associated with learning difficulties and other cancer risks. *Aims:* (1) Assess the psychological impact of breast screening in young women with NF1. (2) Develop and evaluate an educational resource. *Methods:* Women with NF1 (30–47 years) enrolled in a single-center pilot breast screening study were invited to: (1) complete patient-administered validated questionnaires prospectively (including questions on experience) at four time points; (2) evaluate an educational brochure retrospectively via semi-structured telephone interviews. *Results:* Participant experiences ($n = 21$) were mostly positive. Preliminary results suggest screening may lower clinically relevant anxiety and cancer worry (with some expressing reassurance), though these concerns may increase with recall. Most were satisfied with the screening process. Issues most frequently reported were discomfort, not being reassured and inadequate information regarding the process of additional testing for suspicious lesions. Barriers to future screening included fear of results and time off work. An easy-to-read brochure was developed, and evaluation is underway. *Conclusion:* Understanding psychological issues and barriers to screening in young women with NF1 will inform development of improved screening protocols and educational resources, to better support NF1 patients who undergo early breast screening.

Poster Oral 11
P144. Biallelic Variants in *EFEMP1* in a Man with a Pronounced Connective Tissue Phenotype

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Connective tissue disorders are a broad spectrum of diseases that affect multiple structures including skin, vasculature and joints. We present here an individual with signs of a severe connective tissue disorder including multiple and recurrent abdominal and thoracic hernia, myopia, hypermobile joints, scoliosis, and thin translucent skin. Routine genetic testing did not provide a diagnosis, therefore we utilized whole exome sequencing. Candidate variants were found in three genes; however we prioritized a pair of compound heterozygous loss-of-function variants in *EFEMP1* (NM_001039348.3: c.320_324delTGGCA and c.615T>A). *EFEMP1* encodes fibulin-3, a member of the fibulin family of glycoproteins. This group of extracellular matrix proteins are important for the integrity of elastic tissues including dermis, retina, fascia and vasculature; and other family members are associated with connective tissue disorders. To our knowledge, loss-of-function of *EFEMP1* has not been described in humans before, however the Efemp1 knockout mouse displays a remarkably similar phenotype to the affected individual. Others have shown that knockout of Efemp1 in the mouse results in multiple herniation events, pelvic organ prolapse and premature ageing due to the loss of elastic fibre integrity in the visceral fascia. Using qPCR, we showed that dermal fibroblasts from the affected individual express a negligible amount of *EFEMP1* transcript, a significant reduction compared to control ($p < .001$). We therefore conclude that loss of *EFEMP1* function in this individual is the cause of a novel connective tissue disorder, and can perhaps explain similar cases in the literature.

Poster Oral 12
P19. ROSAH Syndrome: An Autosomal Dominant Ocular and Multisystem Disorder with Causative Variant, ALPK1 P.THR237MET

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Background: We ascertained a three generation autosomal dominant family with features of retinal dystrophy, optic nerve edema,

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splenomegaly, anhidrosis and headaches, and named the condition ROSAH syndrome, with the identification of four other similarly affected families. Independent genome and exome sequencing, identified the same causative variant in ALPK1 in all five families. *Aims:* The aim of this project was to undertake phenotypic and functional studies to characterize additional inflammatory, ciliary and centrosomal abnormalities in this condition. *Methods:* ROSAH syndrome patients heterozygous for ALPK1, c.71°c > T, [p.Thr237Met]), underwent further phenotypic investigations characterizing inflammatory components in the condition and ophthalmic investigations. Cytokine, centrosomal and primary ciliary analyses were conducted from human fibroblast samples. HeLa cells were subject to overexpression of mutant and wildtype ALPK1, and ALPK1 knockdown. ALPK1 isoform characterization was undertaken in human and mouse tissues. *Results:* Additional features indicated innate immunity dysfunction with marked susceptibility to viral infections, and indication of other abnormal inflammatory responses. Primary ciliary and centrosomal abnormalities in cell culture investigations suggested a possible gain of function disease mechanism. ALPK1 isoform differences were identified in human and mouse retina providing additional insight to disease mechanisms. *Conclusions:* Heterozygous abnormality in ALPK1 leads to the multisystem ROSAH syndrome through impact on retinal and other tissues. There are indicators of innate immune system dysfunction as well as primary and photoreceptor cilia and centrosomal abnormalities, and a likely gain of function disease mechanism.

Poster Oral 13
P129. Telomere Length in Skeletal Muscle and Leukocytes, and Aerobic Fitness

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Background: Telomeres shorten due a lack of telomerase activity and progressive cellular replication. As such, telomere length (TL) is indicative of cellular replicative reserve and biological age. Current evidence indicates TL is associated with healthy living and suggests that a higher aerobic fitness is associated with longer telomeres. *Aims:* The aim of this study was to investigate the relationship between TL in a minimally proliferative tissue (skeletal muscle) and a highly proliferative tissue (leukocytes). Second, to explore the relationship between TL and markers of aerobic fitness in both tissues. *Methods:* We measured TL (T/S ratio) in leukocytes and skeletal muscle from 82 recreationally active healthy men (age = 31.4 ± 8.2; BMI = 25.3 ± 3.3) from the Gene Skeletal Muscle Adaptive Response to Training study. Using an integrated fitness score (Watt peak, lactate threshold, and citrate synthase activity), we ran robust linear models to examine if TL was associated with aerobic fitness scores or chronological age. *Results:* Telomeres were longer in skeletal muscle than in the leukocytes ($p < .001$, 95% CI [0.33, 0.45]). TL in skeletal muscle and leukocytes were correlated ($r^2 = .35$, $p = .002$). Aerobic fitness was not correlated with TL in skeletal muscle ($r^2 = .006$, $p = .8$) or leukocytes ($r^2 = -.006$, $p = .8$) even after adjusting for age (skeletal muscle $p = .8$; leukocytes, $p = .7$). *Discussion:* These data suggest that aerobic fitness is not associated with TL in blood or skeletal muscle at least in a recreationally active, younger cohort of men (18–45 years of age). The moderate correlation indicates synchrony in the length of telomeres between highly and minimally proliferative tissue.

Poster Oral 14
P43. A Novel Method for Gene and Region Prioritization Based on Human Phenotype Ontology (HPO) Terms

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A large number of variants are often detected per sample for clinical constitutional tests using whole exome and whole genome sequencing (WES and WGS). Traditional approaches to identify causative variants from these involve filtering stages but these still leave a large number of candidate variants to be reviewed. To help prioritize variants, we have developed a statistical method that computes a significance value for causality for each gene based on HPO terms (PMID: 30476213) associated with the sample. Phenotypes associated with each gene are identified using the phenotype-gene association data curated by the Monarch Initiative (monarchinitiative.org). Combining this information with the phenotypes associated with the sample, we can estimate the significance of having a genetic variant within a gene which has been associated with many of the sample phenotypes. Different weights can be set to each of the sample phenotypes to increase the significance of genes associated with more highly weighted phenotypes. We expanded the concept to come up with an 'event'-based significance, Significance Associated with Phenotype (SAP) score. Here, we combine all the genes covered by a larger event (e.g. a CNV) to identify events that might be affecting a set of genes that are in consensus for the set of observed phenotypes reported for the sample. We will provide some example cases where this scoring system has been used to prioritize variants and will calculate both sensitivity and specificity of the approach using resolved cases.

Poster Oral 15
P131. Early-Career Doctor Recommendations for Competencies in Genomics

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Introduction: The skills required by early career doctors to competently engage with genomic medicine may be rapidly changing due to advances in genomic science and increased public awareness of genomic testing. To assist with the development of fit-for-purpose curricula in medical genomics, we explored the opinions of early career doctors about current knowledge and skill requirements for medical genomics. *Methods:* Fifteen early career doctors (1–6 years postgraduate) and three general practitioners in Wellington, New Zealand were interviewed. Interviews were transcribed and analyzed by inductive and deductive thematic analysis. Emerging themes were identified, grouped to form broader categories, then reanalyzed and further defined. *Results:* Interviewees thought there was a limited role for general doctors in clinical genomics. They identified their main roles as being to identify patients with genetic disorders and refer appropriately, and to explain genetic disorders to affected people. They recommended a genomic curriculum be immediately relevant to day-to-day practice, focusing on genetic and genomic consultation skills (communication to support patient perspectives; patient education; family history taking), information management, clinically applicable scientific knowledge (inheritance; patient identification), and cultural aspects of genetics and genomics. *Discussion:* Early career

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doctors have a traditional view of their role in genetics (detect-refer-educate) and suggested a curriculum to support this. They did not identify a change in the role based on the recent advances in pharmacogenomics and personal genomic testing. This information has utility for assisting with the development of fit-for-purpose undergraduate and postgraduate medical genetics curricula.

Special Interest Group Meetings
Australasian Society of Genetic Counsellors

Invited Speaker Presentation
Genetic Counseling to Genomic Counseling a Perspective from Europe

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Medical genetics is at an exciting transition point partly due to technological advancement. Large genome sequencing projects are being instigated across the world. One example of this in the UK is the 100,000 Genomes Project which has directly impacted on the reorganization of genomic healthcare particularly in the laboratory domain. Across Europe as the volume of genomic information and its impact on patients and families is increasing the importance of genetic counseling as an activity is being recognized. In this presentation developments in the UK and Europe will be used to illustrate how genetic counseling as an activity and as a profession is becoming relevant to the whole of genomic healthcare and all health professionals. This needs a close examination of the action of genetic counseling in order to maximize any benefits to patients and families particularly those with rare inherited Mendelian disorders.

Providing Culturally Sensitive Services to a NZ Māori Whānau Affected by Lynch Syndrome

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Background and Aim: Members of this large Māori whānau (family) are known to the Genetic Health Service New Zealand (GHSNZ) and New Zealand Familial Gastrointestinal Cancer Service (NZFGCS) due to their strong history of colorectal and endometrial cancer. Genetic testing identified an MLH1 class 3 variant of unknown significance according to ACMG guidelines: NM_000249.3: c.827T>G, p(Ile276Arg). We aimed to facilitate segregation testing in a culturally appropriate manner. *Methods:* A hui (group meeting) was organized and attended by the GHSNZ, NZFGCS, and multiple members of this whānau in October 2017. Culturally sensitive genetic counseling was provided to whānau willing to participate in segregation testing. The variant was also recognized to be present in multiple other Māori and Pasifika whānau known to GHSNZ. Segregation data was submitted to the InSiGHT variant database, and the variant was reclassified in March 2018 as a class 5 pathogenic variant. *Results and Discussion:* We communicated with individuals who had been seen previously by the GHSNZ and NZFGCS to arrange predictive testing for wider members of this whānau. Whānau continue to be referred, with approximately 27 unaffected individuals having received predictive testing to date. This case demonstrates the benefit of collaboration between our national services in order to help clarify the genetic risk and appropriate surveillance for New Zealand families affected by gastrointestinal cancer. This case also reinforces the importance of recognizing and utilizing the data held by a clinical genetics department which provides services to an ethnically unique population.

Genetic Counseling and Risk Management for a Transgender (Female to Male) BRCA2 Mutation Carrier

J Mansour

Tasmanian Clinical Genetics Service, Hobart, TAS, Australia

Anna is a 24-year-old female *BRCA2* carrier who requested a genetic counseling appointment to review risk management options and surveillance recommendations. Anna learnt that she was a *BRCA2* carrier when she was 18. At the appointment, Anna advised that in recent years she had been married and divorced, experienced depression (unrelated to her *BRCA2* carrier status), and now identifies as transgender (female to male). She wanted to discuss risk reducing surgery as a preventative measure, but to also support steps towards gender reassignment. Anna wanted prophylactic bilateral mastectomy without reconstruction and bilateral salpingo-oophorectomy to avoid menstruating and to feel less female. We discussed that prophylactic mastectomy would not be considered controversial, but oophorectomy would be contra-indicated for a person of her age due to the risks associated with surgically induced menopause. We discussed the option of contraception to avoid menstruating and reviewed the evidence that supported the safety of hormone based contraception in *BRCA* carriers. We also discussed whether it would be safe for Anna to explore testosterone therapy as a *BRCA2* carrier. Follow-up inquiries have confirmed the uniqueness of this case from a counseling and risk management perspective. However, there evidence that the number of transgender people seeking medical support and hormone treatment is increasing. Therefore it is likely that the number of transgender BRCA carriers will increase in time, and it would be helpful to have an understanding about the unique counseling issues and the safety of treatment options and hormone therapies available to them.

Invited Speaker Presentation
Measuring Patient Outcomes from Genetic Counseling: Recent Developments

Marion McAllister

Centre for Medical Education, School of Medicine, Cardiff University, Cardiff, UK

Measuring outcomes from genetic counseling and testing is challenging because the patient benefits can be unclear, and often, there are no direct health benefits. A range of measures has been used to evaluate genetic counseling and genetic testing. The Genetic Counselling Outcome Scale (GCOS-24) is a 24-item patient-reported outcome measure developed to evaluate genetic counseling and testing interventions, grounded in extensive qualitative research. GCOS-24 has good psychometric properties and has been applied to evaluate genetic counseling and testing internationally. In this presentation, I will review the range of outcome measures that has been used to evaluate genetic counseling and testing, with a particular focus on GCOS-24, and describe some recent developments. A shorter form of GCOS-24 would be less burdensome for respondents and could be used where genetic testing is done outside clinical genetics services. I will describe a recent study to develop a six-item form of GCOS-24. The six-item scale was re-named The Genomics Outcome Scale (GOS). Correlation between GCOS-24 and GOS is good ($r = .838$, 99%

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confidence), indicating that GOS maintains the ability of GCOS-24 to capture the underlying construct of empowerment, while providing a less burdensome scale for respondents. GOS would benefit from further psychometric validation, in particular assessment of test-retest reliability and responsiveness. I will also describe some other developments that extend the reach of the GOS internationally.

Familial MND and FTD: Identifying the Need for a New Genetic Counseling Model of Care

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Background: Motor neurone disease (MND) and frontotemporal dementia (FTD) are adult-onset neurodegenerative conditions with clinical and genetic overlap. Genetic counseling and/or testing is increasingly recommended for all individuals with MND or FTD. In Australia this often occurs within a multidisciplinary neurologist-led clinic, rather than a clinical genetics service. Genetic counselors need to be advocates and educators, facilitating the integration of genomics into other healthcare disciplines, such as neurology. *Methods:* We present three illustrative cases that highlight patients' and families' varied experiences of genetic counseling for familial MND/FTD, and differences in lab reporting. *Results:* Case 1 highlights that genetic testing can be appropriately conducted outside of a clinical genetics unit, but challenging cases benefit from genetic counselor input. Case 2 demonstrates the varied responses of health professionals to MND/FTD genetic testing and the need for further education about the complexities of genetic testing decision-making. Case 3 highlights that inconsistent results between laboratories can occur and therefore the limitations of our current knowledge should be discussed pre-test to ensure informed decision-making. *Conclusion:* The cases demonstrate the complex genetics and counseling issues that frequently arise in familial MND and FTD. For patients and families to receive consistent and evidence-based care, clinical guidelines require updating and other health professionals require education and support to manage the challenging issues that can arise. To meet the needs of patients with MND or FTD, their families and health providers, we are conducting a research study aimed at developing a new model of genetic counseling in mainstream care.

Changes in Perception of My Role as a Genetic Counselor throughout a Difficult Case

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Background: CW was referred by her GP as generally well, with a query of Wilson's disease (WD) based on reduced ceruloplasmin which is an unreliable test in isolation. I triaged the referral for a clinical geneticist appointment and provided advice to the GP regarding clinical diagnosis and management in the interim. When I subsequently phoned CW to conduct her intake I discovered a steep decline in her health had occurred. Despite clinical confirmation of WD, the GP made no referrals to recommended specialists and instead began Cu chelation with a drug not approved for that purpose and administered intravenous vitamin cocktails resulting in B6 nerve toxicity. I rapidly coordinated multiple specialist appointments for CW and eventual hospital admission; however, many of her symptoms were irreversible. *Discussion:* The complex psychosocial and medical needs of CW and her family pushed the boundaries of my role and extended my skills as a genetic counselor. I used a model of informed shared decision-making to negotiate treatment options with CW and constantly implemented the counseling skills of contracting and re-framing to identify and work towards CW's over-arching goals. Throughout this case I often felt powerless and frustrated. In exploring these feelings I discovered a concept known as moral injury which helped me to reframe my experience and reinvigorate my dedication to genetic counseling. This case also demonstrates that while the field of genetics is in a constant state of change, the core competencies of genetic counseling remain critical to providing patient-centered care.

Pharmacogenomics as an Element of Precision Healthcare: The St Vincent's Experience

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The Clinical Genomics Unit (CGU) at St. Vincent's Hospital Sydney has been routinely offering pharmacogenomics (PGx) testing since May 2018. PGx testing is a form of personalized medicine which detects potential drug-gene interactions (DGIs), by screening for alleles that are known to be associated with significantly altered drug metabolism (pharmacokinetics) and/or receptor function (pharmacodynamics). Testing has been carried out through a USA-based company, involving analysis of 27 genes with DGI information for >300 medications. Potential utilities of PGx include pre-emptive usage allowing future point-of-care guidance on choice/dosage of medication based on one's genotype; and to facilitate PGx-guided mental illness treatment which has been shown to lead to improved response/remission versus control. As of April 2019, 38 patients have undergone PGx testing, with the following indications: (1) Polypharmacy: currently prescribed ≥5 medications; (2) Patients with mental illness to guide pharmacotherapy; (3) Patients with altered/adverse drug reactions. Results showed that 6 patients (16%) and 18 patients (47%) had at least one high-risk, and moderate-risk DGI respectively, for medications they were currently taking. An average of 12 high-risk and 50 moderate-risk DGIs were identified per patient. PGx testing in our cohort has (1) guided pain management and mental illness pharmacotherapy, (2) provided explanation and confidence in treatment of a patient post lung transplantation who needed an exceedingly high dose of immunosuppressant for which he was found to be an ultra-metabolizer, and (3) identified a patient to be a non-metabolizer for an antidepressant leading to drug level monitoring to avoid toxicity/adverse reactions.

Moratorium on Genetic Test Results and Life Insurance: Everything You Need to Know

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Historically, Australian life insurance companies have been permitted to discriminate on the basis of genetic test results. Despite international

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trends towards banning or restricting this practice, Australian insurance companies, until recently, have opposed any restriction on disclosure of genetic results. As a result, there have been reports of consumer fears around insurance deterring uptake of clinical genetic testing and reducing participation in medical research in Australia compromizing progress in genomic medicine. In 2016, we formed the Australian Genetic Non-Discrimination Working Group to address the issue of genetic discrimination in Australia especially in life insurance. The group advocated for regulatory change by undertaking research, generating media interest and lobbying directly to the federal government. This included giving evidence at public hearings for a national Parliamentary Inquiry into the life insurance industry. In early 2018, the Parliamentary Inquiry recommended an urgent ban on using genetic results in life-insurance underwriting. The recommendations identified the UK's genetics and insurance moratorium as the most appropriate model. In late 2018, the Financial Services Council (FSC), the peak insurance body in Australia announced that it will implement a self-regulated moratorium with financial limits to commence in July 2019. This talk will cover the functional aspects of the proposed industry-led moratorium, including the regulatory mechanism, the limits on its operation, current concerns with the model, and a comparison with the UK moratorium. It will also cover practical aspects of implications for clients and matters for clinical services to consider.

Genomics + Legal System Involvement

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Genetics of Learning Disability (GOLD) Service, Hunter Genetics, Newcastle, NSW, Australia

Our genetics unit was approached by a Sydney law firm asking if we would be willing to see a family who lived within our area. A 22 year old male with severe intellectual disability (ID) had been ordered by the Supreme Court to have genomic testing. The family had been involved in a legal battle for >15 years suing medical personnel and a health service as they believed that a traumatic birth was responsible for their son's ID. The family were currently with their third legal firm and strongly resented being ordered to have genomic testing. We (geneticist + genetic counselor) visited the family at home and organized genomic testing (WGS). Testing revealed the client had a pathogenic mutation in a rare but known ID gene. The case discussion will include implications for the entire family, difficulties experienced during initial consult (home visit) and the follow up management/care provided.

Evaluation of Advantages and Challenges of Panel Testing in Cancer Genetics: A UK Case Report

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NGS panels for cancer susceptibility are part of routine care. Although they may be a cost-effective method to concurrently test multiple cancer susceptibility genes, the rate of identifying variants of unknown significance (VUS) and incidental findings may be high. Hence, there is much debate over the importance of clinical utility in panel testing. We report a family with a strong incidence of lobular breast cancer (LBC). Panel testing in two affected siblings reported the p.(Val242Gly) high-risk ATM variant and a class-4 *CDH1* variant (c.2343A > T). Germline CDH1 mutations confer a high risk of hereditary diffuse gastric cancer (HDGC) and LBC. With no HDGC family history, interpretation of these results was complex. The CDH1 variant was re-curated and reclassified to a VUS. Since the p.(Val242Gly) ATM variant is not typically associated with LBC, the cancer susceptibility in this family is still unclear. Comparisons can be drawn between NZ and the UK regarding the management of *CDH1* germline mutations. Owing to a founder effect in the Māori population, NZ is experienced in the management of CDH1 mutations. *CDH1* was recently excluded from the UK familial breast cancer panels due to its relevance in cases of LBC only. HDGC experience in the UK is limited to a few specialized centers, with families identified only due to a strong family history of LBC, resulting in difficulty in risk interpretation. The management of HDGC/LBC family members is critical and complex. This case highlights the challenges presented in interpreting variants in families with no history of HDGC.

'I Don't Know What to Do with Hope'

Christina M. Buchanan, Claire M. Stewart, Miriam J. Rodrigues and Richard H. Roxburgh

Department of Neurology, Auckland Hospital, Auckland, New Zealand

Scenario: You are a woman in your late 60s, whose husband recently passed away from Huntington disease. You have two gene-positive sons, who've known their status for nearly two decades. You were your husband's caregiver, and plan to support your sons in their certain decline. Your sons are also under no illusions as to what to expect based on their father's final years. Now it appears there is a targeted molecular therapy that could change outcomes for Huntingon sufferers. The plans you've had in place for decades have been uprooted and shaken. You have been moved from a dark but certain future to consider an uncertain future you don't know the colour of. Here I will present the case of Lucy*, described above. I will share her thoughts on the announcement of the Phase III clinical trial using huntingtin-lowering antisense therapeutic RG6042.

Working with a 'Rebellious' Patient within the Huntington's Disease Pre-Symptomatic Testing Framework

Nikki Gelfand[1] and Michael Fahey[2,3]

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Presymptomatic genetic counseling before testing for conditions such as Huntington's disease (HD) is considered necessary to ensure that patients feel informed and supported throughout. A degree of client engagement would be essential for the processes to be successful. We discuss a case of pre-symptomatic counseling where engagement was actively avoided by a client requesting pre-symptomatic testing. This case description highlights the challenges in working with a client who demanded his right to autonomy with strong verbal and non-verbal refusal to engage. During 4 months of contact, neither rapport nor connection was established. After thorough discussions and supervision both internally and externally, considering his mental health and motivations to test, we felt we had no right to deny him his wishes. During this process, the genetic counselor expressed feelings of anger, frustration and manipulation. Ultimately we questioned how we had contributed to this man's life, or possibly his death.

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Interesting Case Study: Termination of Pregnancy for Autism Risk

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Sarah was referred to the clinical genetics service at 11 weeks gestation. She was 42 years of age and pregnant with dichorionic diamniotic (DCDA) twins. Sarah conceived using assisted reproductive intrauterine insemination. Sarah has a son with high functioning autism and her identical twin sister also has a son with autism. Sarah was aware of the increased chance of autism in subsequent children, which is reportedly up to ~25% chance if the child is male. She previously sought advice from an IVF service about sex selection for a female using preimplantation genetic screening as a risk reduction strategy. Sarah was requesting diagnostic testing for age related chromosomal abnormalities and fetal sex with a view to terminate a male fetus. Additionally, Sarah was incredibly anxious about a twin pregnancy and wanted a fetal reduction if both fetus's were female. This case raised some ethical and moral dilemmas from a personal and professional perspective and highlighted the challenges non-directive counseling presents.

Screening for SCA Using NIPT – Reflection and Practice Implications

Joanne Kelley

Genetic Counselor, Genetics Department, Mercy Hospital for Women, Melbourne, VIC, Australia

Noninvasive prenatal testing (NIPT) has unequivocally changed the landscape of prenatal screening. Testing for sex chromosome aneuploidy (SCA) was introduced in 2012, providing women with information previously unknown in the screening domain. Despite sound understanding of biological principles underlying discordant and false positive results for NIPT, particularly for the common autosomal aneuploidies, the inclusion of SCA has resulted in many challenging counseling scenarios in our genetics department. Providers of NIPT deliver varying degrees of result interpretation and transperancy, which coupled with the unique biological phenomena associated with SCA make counseling for SCA both interesting and challenging. Particular cases have resulted in reflective discussion and practice modification. Our current practice incorporates not only the potential underlying causes of a FP SCA result, but also addresses that the SCA karyotype identified from screening, may differ to the SCA karyotype that the fetus or baby is determined to have.

Australasian Association of Clinical Genomics

Invited Speaker Presentation
Genetic Basis of Congenital Anomalies

Wendy K. Chung

Columbia University, New York, NY, USA

The genetic basis of congenital anomalies is complex. We have studies three of the most common and birth defects: congenital heart disease, congenital diaphragmatic hernia, and esophageal atresia/trachea esophageal fistulas. In each of these congenital anomalies, de novo genetic variants play account for a substantial fraction of the identifiable genetic cases. In some cases, the same gene can cause more than one congenital anomaly in the same individual. In other cases, the same gene can cause different anomalies in different individuals. In many cases, the conditions caused by de novo genetic variants also influence brain development and function and are associated with neurobehavioral manifestations. Comparisons across anomalies and with neurodevelopmental conditions provides a richer understanding of the fundamental processes of development and the types of genes that are fundamental to human development.

Invited Speaker Presentation
The Evolving Role of the Clinical Geneticist in the UK Following the 100,000 Genomes Project

Richard Scott

Clinical Lead for Rare Disease, Genomic England, London, UK

The role of the clinical geneticist has evolved considerably in the UK in response to the 100,000 Genomes Project and more generally to the technological advances, reducing costs of genomic testing and the move to deliver genomics as part of 'mainstream' medicine. In this talk, I will reflect on the areas of greatest change over the past 5 years and those that are likely to change most over the next 5 years.

Australasian Society of Inborn Errors of Metabolism

Invited Speaker Presentation
Dietary Management of Methylmalonic Acidemia (MMA) MUT0 through Renal or Liver Transplant: Three Case Studies

Rachel Skeath

Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Background: Despite intensive medical treatment and adherence to dietary management, morbidity is high in MMA mut^0. Liver transplant offers potential stabilization of metabolic control with reduced frequency of decompensations, but is not a cure. Long-term complications include chronic kidney disease, especially in those with high methylmalonic acid excretion. Possible explanations include toxicity from metabolic derangements and dehydration (either chronic due to frequent vomiting and poor feed tolerance, or acute in times of intercurrent illness and metabolic decompensation). *Aim:* Summarize dietary management of MMA through renal and liver transplant. *Method:* Two patients with MMA mut^0 who underwent living-related donor kidney transplants and one patient who underwent a cadaveric liver transplant are described. *Results:* Prior to renal transplant both patients received a period of hemodialysis, three times per week, to achieve metabolic stability in the run up to transplant. This necessitated regular adjustments to fluid and electrolyte intake. Peri-operative nutritional management in all cases focused on providing adequate energy. Parenteral nutrition of glucose and lipid (3.6–8.5 mg/kg/min glucose, 1–1.4 g/kg lipid) was given during the renal transplants and intravenous dextrose (6–8 mg/kg/minute) during the liver transplant. Insulin sliding scale was commenced in response to hyperglycemia in all cases. Protein was reintroduced as PN after 24 h and enteral feeds commenced by day 2–6 post-transplant. Post-operative management of renal transplant involved frequent fluid adjustments. Following liver transplant, oral intake has dramatically improved. All continued on a protein-restricted diet. *Conclusion:* Management through transplant requires planned and coordinated input across the multi-disciplinary team.

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Invited Speaker Presentation
Nutritional Management of the Extremely Preterm Baby

Frank Bloomfield

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Babies born extremely preterm (<28 weeks' gestation) and/or extremely low birth weight (<1000 g) can be described as facing a nutritional emergency. Continuous placental nutrition is interrupted yet the usual body stores to support transition to extrauterine life have not yet been laid down. Organ systems, including the gastrointestinal tract, liver and kidney, are immature meaning parenteral nutritional support is essential, for several days or even weeks. Postnatal faltering growth failure is almost universal and poor growth is correlated with poorer neurodevelopmental outcomes. Survival of extremely preterm babies has improved dramatically over the past few decades based upon extensive research. However, there are few high quality data supporting optimal nutritional approaches. This can lead to unnecessary restrictions on provision of adequate nutrition due to fears about risk of necrotizing enterocolitis, uremia and hyperammonemia. This presentation will review the challenges of providing sufficient and optimal nutrition to extremely preterm babies including provisional data from the largest randomized controlled trial in this area.

Invited Speaker Presentation
Disorders of Vitamin B6 Metabolism: What's New?

Peter Clayton and Philippa Mills

Inborn Errors of Metabolism, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, London, UK

Three disorders are now known to present with vitamin B6-responsive neonatal epileptic encephalopathy: ALDH7A1 deficiency, pyridox(am)ine phosphate oxidase (PNPO) deficiency and deficiency of the pyridoxal-phosphate binding protein (PLPBP, PLP homeostatic protein, PROSC). However, these disorders can cause epilepsy with onset as late as adolescence, a dystonic movement disorder, a disorder similar to mitochondrial encephalomyopathy and to systemic manifestations such as anemia, hypoglycemia and lactic acidosis. A newly identified disorder, pyridoxal kinase deficiency presents with childhood onset sensorimotor neuropathy and optic atrophy. This disorder responds well to treatment with pyridoxal phosphate. ALDH7A1 has been most commonly diagnosed biochemically by measurement of the urine-aminoadipic semialdehyde/creatinine ratio. However, preliminary results suggest that 6-oxo-pipecolic acid may be a more stable metabolite and a potential biomarker for neonatal screening (Wempe MF et al. J Inherit Metab Dis. 2019). PNPO deficiency can be diagnosed by measuring the activity of the enzyme in dried blood spots. Activity was very low in two siblings homozygous for p.R116Q mutations in PNPO; one is asymptomatic, the other presented with PLP-responsive infantile spasms. The explanation for this variability is not clear. Long-term treatment of PNPO deficiency with PLP can be associated with deranged liver function tests, cirrhosis and hepatocellular carcinoma. PLP is a reactive aldehyde that can react with sulphydryl and amino groups and can modify proteins and DNA. The inborn errors of B6 metabolism are showing us that there are important homeostatic mechanisms that keep the cellular concentration of PLP low while allowing it to be delivered to PLP-dependent enzymes.

Expanding the Utilization of Mass Spectrometry in Diagnosing Inborn Errors of Lysosomal Metabolism

Brett McWhinney

Department of Chemical Pathology, Analytical Chemistry Unit, Pathology Queensland, RBWH, Brisbane, QLD, Australia

The mucopolysaccharidoses (MPS) are a group of inherited metabolic disorders arising from a deficiency in any 1 of the 11 lysosomal hydrolases required for the degradation of glycosaminoglycans (GAGs). Oligosaccharidoses are disorders in the breakdown of complex carbohydrate side chains of glycosylated proteins characterized by an accumulation of undegraded oligosaccharides (OS). The deposition of undegraded GAGs/OS in the lysosomes of affected cells, leads to a cascade of intracellular abnormalities and ultimately clinical manifestations instructive of the MPS/OS phenotype. Current limitations in the diagnosis of lysosomal storage disorders (LSD) include the lack of fast, accurate and relatively inexpensive tests. The diagnosis of MPS and OS is typically made by urinary electrophoresis, which is time consuming, requires a large volume of urine (up to 6 mL) and prone to interference, leading to positive results in unaffected individuals. For many LSD, enzyme tests require 5–10 ml of blood to confirm the diagnosis. Over the last decade Mass Spectrometry based assays have been increasingly used to overcome these issues due to its specificity and sensitivity. Two recent publications have utilized Mass Spectrometry, one for MPS and the other for OS. We have significantly streamlined both these assays by utilizing automation and standardizing processes to increase sample throughput, improve turn-around-time and significantly reduce sample volume requirements. This presentation will give an overview of the improvements in performance and the specificity and sensitivity of both assays.

Invited Speaker Presentation
The Potential of MRNA Therapy for Inborn Errors of Metabolism Including MMA

Heidi Peters

Royal Children's Hospital, Melbourne, VIC, Australia

There is an increasing number of new novel therapeutic approaches to the treatment of many rare and complex inherited metabolic disorders. One exciting approach has been the development of exogenous delivery of messenger RNA (mRNA) aimed at restoring or augmenting proteins following systemic delivery. The mRNA is packaged in lipid nanoparticles and delivered intravenously. It is taken up into the cell and the released mRNA utilizes the cells own machinery to be translated into functional protein. This approach was first explored nearly 20 years ago, however it has only been with advances in delivery and mRNA chemistry that it is now moving into clinical trials. It represents an attractive therapeutic alternative as the technique can be broadly applicable to numerous disorders and particularly IEM. One limitation has been that the liver is currently the main target organ. While it would be ideal to also target the CNS, for organic acidemias such therapy represents potential for significant advances in the management of these devastating conditions. Methylmalonic aciduria (MMA) due to deficiency of the enzyme methylmalonyl coA mutase ($mut^{0/-}$) results in presentation with metabolic acidosis, hyperammonemia and variable neurological complications. In the long term patients develop renal failure. Current therapy has been with dietary

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modification, caloric supplementation and carnitine therapy. Despite this the condition is associated with significant morbidity and mortality. Liver and or kidney transplantation have been considered in some patients. Such approaches provide improved metabolic control, however risk of disease complications particularly involving the CNS remain. Such treatments are invasive, carry associated risks of complications and rely on donor availability. The ability to restore enzyme function in the liver using mRNA, to act as a 'metabolic sink' would provide an important treatment alternative either in the acute setting or a metabolic decompensation or for long term metabolic control. Delivery of mRNA in mouse models of MMA have demonstrated improvement in both biochemical and phenotypic features of the condition. The potential for mRNA therapy will be discussed along with its particular application to organic acidemias and MMA.

Invited Speaker Presentation
Genetic Engineering Approaches to the Treatment of Urea Cycle Disorders

Ian E. Alexander

Gene Therapy Research Unit, Children's Medical Research Institute, Faculty of Medicine and Health, The University of Sydney and Sydney Children's Hospitals Network, Sydney, NSW, Australia

After 25 years of incremental development, gene transfer and genome editing technologies have finally reached a *powerful inflexion* point bringing many difficult or impossible to treat diseases within therapeutic reach. Major successes to date have been achieved in organs systems including the hematopoietic compartment (HSC and T cells), the central nervous system, the eye and the liver. All have involved the use of recombinant viral vectors and gene addition strategies, but the development of user-targeted nucleases has put the field on an exciting trajectory towards targeted genome editing. While proof-of-concept is now well established, the key ongoing challenge is to continue to extend the therapeutic reach of contemporary technology. For example, the first successful liver-targeted gene therapy was for hemophilia B. This reflects the fact that in this condition, involving a secreted protein (FIX), therapeutic success can be achieved by genetically modifying as few as 3% of hepatocytes. For the majority metabolic/genetic liver diseases, however, a much higher proportion of hepatocytes will need to be modified. In urea cycle disorders (UCDs), clinical and experimental evidence suggest that for robust therapeutic effect this value may be as high as 30%. This therefore places a 10-fold higher demand on the delivery technology. Vectors based on adeno-associated virus (AAV) are currently the leading system for *in vivo* gene delivery and the best available system for targeting the liver. Indeed recent advances in AAV capsid technology, the protein shell carrying the vectors' therapeutic DNA cargo have led to the development of new AAV variants capable of delivering genes to the human liver with unprecedented efficiency. The earliest of these variants have reached the clinic, but the only active gene therapy trial for a UCD, ornithine transcarbamylase deficiency (OTC) is using relatively older technology. This trial involves adults and is currently undergoing vector dose escalation in search of unequivocal therapeutic effect. A second OTC gene therapy trial for severely affected infants and children is in advanced preparation as an Anglo-Australian initiative, and will employ one of the newer more efficient capsid variants. It is noteworthy that this academically funded trial (MRC) is being delayed by a global shortage of clinical grade vector production capacity, reflecting a recent explosion of demand. Meanwhile, back in the laboratory even more efficient capsids are being engineered and attention is turning to the development of genome editing approaches involving both homology-dependent and homology-independent approaches. Using a xenograft model, in which patient derived, OTC deficient primary human hepatocytes can be engrafted and expanded in the mouse liver, we have recently achieved repair of a mutation in the OTC locus at single nucleotide resolution in up to 30% of human heptocytes *in vivo*. This exciting result points to a future in which many severe metabolic/genetic liver diseases, will be cured by a single gene therapy intervention using a genome editing approach.

Carnitine Acylcarnitine Translocase Deficiency: 16 Cases with Survival in 10

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Background: Carnitine-acylcarnitine translocase deficiency (CACTD) is a rare disorder of fatty acid oxidation. Patients typically present <48 h with cardiomyopathy or arrhythmias, hypoketotic hypoglycemia, hyperammonemia, hepatomegaly, raised liver transaminases and elevated creatine phosphokinase (CPK). Sudden unexpected death in infancy is common and outcomes remain poor despite treatment. *Method:* Retrospective review of 16 cases from Australia, Canada, England, France, and New Zealand, with diagnosis confirmed by enzyme activity and/or molecular analysis. *Results:* 11/16 presented at 10–48 h of age; 2/16, with affected siblings, were treated from birth, and one pre-symptomatically following newborn screening (NBS). Two presented at 9 and 14 days. Hypoglycemia was noted in 12/13 presenting clinically; hyperammonemia in 10/13. Transaminases were modestly elevated in 10/13 and CPK ranged from normal to >25,000 U/l. Neonatal cardiomyopathy was demonstrated in two cases with reduced contractility in 3/16, and arrhythmias in 5/16. Six cases had acute renal impairment, three had tubulopathy. Free carnitine was low in 9/13. C16-carnitine was elevated in all (3.95–21.1 umol/l). 3/16 patients died in the neonatal period, and 5/16 by age 4. 10/16 patients survived to aged 1–10 years. Neurocognitive outcome was normal in 6/16, including 3/16 treated presymptomatically. *Discussion:* CACTD causes acute metabolic decompensation associated with hyperammonemia, hypoglycemia, cardiac dysfunction and encephalopathy. Gastrointestinal disturbance is common. Less reported renal manifestations include tubulopathy and renal failure. Hyperammonemia is sensitive to high rates of glucose administration but can be difficult to manage long term. NBS may expedite the diagnosis but urgent intervention is required.

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Diet Management of Lipoprotein Lipase Deficiency

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Background: Lipoprotein lipase deficiency is a rare autosomal recessive disorder resulting in accumulation of chylomicrons in plasma and elevated plasma triglyceride (TG) levels, with a high risk of recurrent episodes of pancreatitis. Management guidelines have been published but a review of the first patient managed by our team raized questions about the degree of fat restriction required and optimal quantities of medium chain triglycerides (MCT). *Report:* Following initial plasma triglyceride levels of 87 mmol/l (0.5–1.4) at 4 weeks of age, intravenous dextrose and a modular fat-free feed resulted in a rapid decline. He was discharged home on minimal long chain triglyceride (LCT) formula with MCT, and maintained levels <5 mmol/l during the first year of life. Ongoing restriction of LCT has relied on selection of low fat foods, rather than counting grams of fat. He continues to enjoy the formula, and MCT oil is used in cooking. Median plasma TG was 8.4 mmol/l (range 4.1–16.5) between 1–5 years of age. Some elevations were considered to be due to limited relaxation of the diet (but only including packaged foods with 1–3% fat) but most recently, despite diligence, levels remained above 10 mmol/l. Anthropometry and nutritional parameters are within normal range. *Discussion/Conclusion:* Intake of protein, MCT and simple carbohydrates, timing of samples and difficulties with maintaining compliance with increasing age, all potentially impact plasma TG levels. A similar approach is being used for a second child currently 6 months of age with reduction of TG to 3.6 mmol/l from 248 mmol/l at baseline.

Liver Transplantation in Children with Inborn Errors of Metabolism: 30 Years Experience in NSW, Australia

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Background: Inborn errors of metabolism (IEM) are a diverse group of disorders that can result in significant morbidity and even death. Metabolic management can be challenging and burdensome for families. Liver transplantation (LT) is increasingly being considered a treatment option for some IEMs. IEMs are now considered the second most common reason for LT. *Aim:* To review the data of all children with an IEM who had undergone LT at The Children's Hospital at Westmead (CHW), NSW between January 1986 and January 2019. *Methods:* Retrospective data collected from the medical records and genetic files included patient demographics, parental consanguinity, family history, method of diagnosis of IEM, hospital and intensive care unit admissions, age at LT, graft type, clinical outcomes and metabolic management post-transplant. *Results:* Twenty-four liver transplants were performed for 21 patients. IEM diagnoses were MSUD ($n = 4$), urea cycle disorders ($n = 8$), organic acidopathy ($n = 6$), tyrosinemia I ($n = 2$) and GSD Ia ($n = 1$). Three patients had repeat transplants due to complications. Median age at transplant was 6.21 years (MSUD), 0.87 years (UCD), 1.64 years (OA) and 2.2 years (Tyrosinemia I). Two patients died perioperatively early in the series, one died 3 months after successful transplant from line sepsis. Eighteen LTs were performed since 2008 in comparison to six LT before 2008. Dietary management was liberalized post LT for all patients. *Conclusion:* Referral for LT for IEMs has increased over the last 33 years, with the most referrals in the last 10 years. Early LT has resulted in improved outcomes and survival.

Management of Cobalamin Non-Responsive Methylmalonic Acidemia with Heterozygous Kidney Transplant Followed by Orthotopic Liver Transplantation

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Background: Methylmalonic acidemia (MMA) is a rare organic acidemia that classically presents in infancy with encephalopathy, metabolic acidosis and hyperammonemia. Treatment is imperfect, with long-term complications including tubulointerstitial nephritis, end-stage renal disease, intellectual disability and early mortality. Liver (LT), kidney (KT) or combined liver/kidney transplant are considered experimental treatment options. *Case:* A female infant presented day two with metabolic encephalopathy. NBS was consistent with MMA. Compound heterozygous pathogenic mutations in MMAB were detected. Despite standard management and meticulous attention to detail, she developed autism spectrum disorder (ASD) and intellectual impairment. Measured GFR was 37.4 ml/min/1.73 m^2 (90–120 ml/min) at 20 months. She had progressive tubulopathy requiring 4 l fluid/day. Mean serum MMA was 1922 µmol/l. At 4 years 11 months she underwent a heterozygous live donor KT following bilateral nephrectomies. Initial post-KT MMA was <520 µmol/l. She then developed renal allograft tubular dysfunction with nephrogenic diabetes insipidus requiring 3 l fluid/day. Serum MMA was elevated 86–2852 µmol/l. Six months post-KT, orthotopic LT was undertaken, complicated by acute rejection and tacrolimus-related tremor. Five months post-LT, serum MMA levels stabilized (91–398 µmol/l), CSF MMA was not corrected, renal function normalized, and no metabolic crises occurred. She continues on protein restriction (1.2 g/kg/day) and 2 l fluid/day. Neurocognitive improvement was observed post both transplants. She spent 134 days in hospital. *Discussion:* This patient demonstrates the difficult nature of multi-organ transplantation in MMA. Although biochemical improvement has occurred, there remains uncertainty over her quality of life and stability of her neurocognitive status.

Australasian Society of Diagnostic Genomics

Invited Speaker Presentation
Finding a Needle in a Haystack – How We are Refining the Data that is Generated through the UK 100,000 Genomes Project

Richard Scott

Clinical Lead for Rare Disease, Genomic England, London, UK

To deliver the 100,000 Genomes Project and to serve the new NHS Genomic Medicine Service, Genomics England has developed a

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novel data infrastructure to enable test request and clinical data collection embedded in routine healthcare, a semi-automated interpretation platform and storage and analysis of data for both clinical and research use. Automated bioinformatics processing is carried out by the central Genomics England systems before data is presented back to local diagnostic laboratories for reporting with variants of likely diagnostic relevance highlighted and tools provided to allow wider exploration of the genome data where this is required. The range of variants delivered to laboratories includes small variants, copy number variants and short tandem repeat expansions. Central to the development of the platform has been development of standardized data formats, data stores and applications that interact via application programming interfaces (APIs). This approach allows the individual system components and clinical and research users to interact with the data in a largely automated fashion and results in a modular architecture that facilitates interchange of individual services and components. Central to establishing the infrastructure as a 'learning health system' is the Genomics England Clinical Variant Ark. This stores clinical data together variant annotations of potential clinical relevance for every analysis request and can return results to queries in real time to support clinical and research users.

The Role of Prenatal Diagnosis in Prevention of Mitochondrial DNA Disease

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Background: Mitochondrial donation has received considerable attention as a reproductive option to potentially allow any couple at risk for transmitting mitochondrial DNA (mtDNA) disease to have a healthy child who is genetically related to both parents. However, it remains illegal in most jurisdictions. MtDNA prenatal diagnosis (PND) and PGD have been used by a handful of centers internationally, but relatively few cases have been reported. A quarter of patients with childhood-onset mtDNA disease appear to have de novo mtDNA mutations, suggesting that PND and PGD can be appropriate options to consider. *Hypothesis:* PND for mtDNA mutations is a feasible option for some at-risk couples. *Methods:* Review of laboratory data for 32 pregnancies undergoing mtDNA PND at VCGS between 1996 and 2019. *Results:* Twenty-four pregnancies from 16 women were expected to have low recurrence risk based on knowledge of the mutation and maternal mutant load (<10% heteroplasmy in urine or other appropriate samples). In each case, only wild-type mtDNA was detected in CVS. Eight pregnancies from six women at higher risk (maternal heteroplasmy 32–70%) led to four terminations (67–95% CVS heteroplasmy) and four pregnancies that were continued (0–40% CVS heteroplasmy). Details of clinical outcomes of the pregnancies that were continued to term are being collected. *Conclusion:* mtDNA PND is best suited to couples at relatively low recurrence risk. Important considerations in counseling about mtDNA PND include the maternal mutant load in appropriate tissues, knowledge of genotype/phenotype relationship for specific mutations and fetal mutant loads plus attitudes to potential uncertainty and termination.

Post-Zygotic Origin of Trisomy as a Cause of False-Negative NIPT Results

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Background: A retrospective study of 46,725 consecutive NIPT samples used cytogenetic and pregnancy outcome data to identify true-positive and false-negative cases of trisomy 13, 18 and 21. *Aim:* To determine the cause of known false-negative NIPT results in samples received from April 2015 to June 2018 at Victorian Clinical Genetics Services, Melbourne. *Methods:* Cell-free DNA (cfDNA) samples were tested using whole genome massively parallel sequencing. Cytogenetic testing was performed on chorionic villi, amniotic fluid and/or products of conception. SNP microarray B-allele frequency profiles were used to determine the origin of the trisomy in false-negative cases. *Results:* Six hundred and one cfDNA samples were increased risk for T13, T18 or T21. Ninety-two percent of cases had outcome data. 85.2% (472 cases) represented true-positive results. 0.02% represented false-negative results (seven cases). The false-negative rate (FNR) for T21, T18 and T13 was 0.58%, 5.88% and 0.0% respectively, for a total FNR of 1.5% (95% CI [0.6, 3.0]). Two false-negative cases (1x T18, 1x T21) had low fetal fraction (95% CI [2.8, 3.3]). Five false-negative cases (4x T18, 1x T21) had fetal fractions ranging from 4.5–13.9% (mean 7.9%). These cases involved placental mosaicism for a disomic cell line in cytotrophoblast and a trisomic cell line in chorionic mesenchyme and the fetus. All 5 placental mosaic trisomies had a putative post-zygotic origin. *Conclusions:* Placental mosaicism was involved in 5/7 false-negative results. Depending on the timing of the error, a large population of normal cells can be confined to the cytotrophoblast, while the inner cell mass/fetus are affected by trisomy. This etiology provides a biological cause for these false-negative cfDNA screening results.

Improved Positive Predictive Value for Monosomy X Using a Cell-Free DNA Paired-End Sequencing Assay

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Background: The positive predictive value (PPV) of cell-free DNA (cfDNA) screening for monosomy X is consistently lower than that reported for autosomal aneuploidies (~26% cf >90% for Trisomy 21). Maternal sex chromosome mosaicism contributes to this lower PPV. As fetal cfDNA fragments in maternal plasma are shorter than maternal fragments, an assay using paired-end sequencing can incorporate cfDNA fragment size into the counting algorithm to improve X chromosome aneuploidy assessment. *Aim:* We sought to compare the PPV on a cohort of high risk monosomy X samples, with known cytogenetic outcome, using two methods of cfDNA analysis; one employing single-end sequencing and a counting algorithm and the other paired-end sequencing with cfDNA fragment size incorporated into the counting algorithm. *Methods:* cfDNA from 98 singleton pregnancies (29 true-positive monosomy X, 67 false-positive and 2 false-negative) first tested by VeriSeq v1.0.14 (PCR-based, single-end sequencing) were re-tested using VeriSeq NIPT solution v2 (PCR-free, paired-end

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sequencing). Cytogenetic outcomes were determined for all pregnancies. *Results:* The monosomy X PPV increased from 30.2% (95% CI [25.0, 36.0]) to 62.8% (95% CI [50.4, 73.7]) without compromizing the sensitivity 90.6% (29/32) by VeriSeq v1.0.14 and 87.1% (27/31) by VeriSeq v2. One sample with monosomy X failed QC after retesting with VeriSeq v2. *Discussion/Conclusion:* The VeriSeq v2 assay showed a significant improvement in PPV for monosomy X when compared with the single-end sequencing assay (test-statistic 53.6, $p < .001$). Assays incorporating cfDNA fragment size into the counting algorithms can reduce false-positive monosomy X results caused by maternal monosomy X mosaicism thus avoiding unnecessary invasive diagnostic procedures.

Preconception Genetic Carrier Screening in an Australian Fertility Clinic, the First 1000 Patients

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Preconception screening for 1095 patients was reported using a NATA accredited Illumina Inherited Disease screening panel. Five hundred and fifty-two genes for 592 rare diseases are included. Only pathogenic/likely pathogenic variants were reported, ACMG-AMP variant interpretation guidelines were used. Thirteen carrier couples were identified with variants in the same gene (*CBS_CFTR_DHCR7_ERCC6_GALT_GJB2_PAH_TREX1*). Six hundred and thirty-seven different pathogenic/likely pathogenic variants, in 252 genes, were reported. 57% of variants were in female patients and 43% were in male patients. One hundred and one genes had a single variant reported. No variants were reported for 419 patients. The *CFTR* gene had 72 carriers, with 35 independent variants reported. *GJB2* had 57 carriers with 13 variants, *PAH* had 34 carriers with 15 variants, CBS had 31 carriers with 6 variants, *ATP7B* had 23 carriers with 17 variants and *POLG* had 22 carriers with 11 different variants. Twelve other genes had a carrier rate higher than 1 in 100. Data analysis software utilized MiSeq aligner/variant caller, Illumina Variant Studio, Alamut, ClinVar, HGMD, Google Scholar, PubMed. Nextera Flex Library preparation is currently being validated, which reduced hands-on laboratory time, improved % bases above Q30 and read depth average. Golden Helix/Sentieon, VSPipeline, VarSeq, VSCNV, VSReports and VSWarehouse enabled time savings, recording of work, interpretation/reporting any variant. A local database was created for over 1000 Australasian individuals, for SNVs, deletions, duplications, indels, splice variants and other variants for the 552 genes. Data quality continually assessed with omnomicsQ. Five NIST DNAs/no DNA controls used regularly and the laboratory participated in RCPA/EMQN NGS eQAPs.

Preliminary Results of an Expanded Preconception Carrier Screening Pilot Study in Western Australian

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Expanded preconception carrier screening (EPCS) assesses the chance a couple will have a child affected with a recessive disorder. EPCS has become more affordable with next generation sequencing (NGS) technologies that enables sequencing hundreds of genes simultaneously. This pilot study aims to determine the requirements for successful implementation of a public health system EPCS program using NGS technology in Western Australia. 250 couples planning to fall pregnant are being offered EPCS for 425 severe genetic disorders that are life limiting and/or chronic with onset in infancy or early childhood. Five previously identified at-risk couples were sequenced as positive controls and the data underwent blind analysis to validate the filtering and curation workflow. Couples are considered at-risk if a Class 4/5 variant is identified in the same gene in both individuals. The panel has yielded an average of 170-times coverage with 95% being covered to at least 20-times. Of the 126 individuals sequenced, 199 pathogenic variants were identified indicating that everyone in the study is a carrier for at least one mutation for a severe pediatric disorder. Only two known at-risk couples were correctly assessed to be at-risk of having an affected child in this study. Of the remaining three known at-risk couples, one or both variants in each couple were classified as Class 3 or missed due to technical limitations. The Class 3 variants could have been correctly classified if more information about these rare variants were provided in reference databases highlighting a major limitation in couple-based analysis.

Improving the Efficiency of Variant Prioritization

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Background: The prioritization of variants is an essential step in genomic analysis to determine which variants are clinically relevant and should be investigated fully by variant curation. With the continuous reduction in data generation cost driving a shift from targeted gene panels to exome and genome analysis, the number of variants remaining after variant filtering is often too great to be curated. *Aim:* To assess the value of having interactive variant prioritization clinics (VPCs) with medical scientists and clinical geneticists to prioritize relevant variants for curation and reduce the overall curation time. *Methods:* Analyze genes known to be associated with a Mendelian disorder in 22 singleton exome cases, and compare the number of variants for curation following standard filtering approaches with the number for variants for curation after VPC. The overall time saved on curation due to VPCs will also be investigated. *Results:* The average time taken to curate a variant was 44 min. After filtering, the average number of dominant variants per patient was 77, while the average number of variants per patient with recessive inheritance was 29. After VPC, a total of between 1 and 4 variants remained for curation per patient. *Conclusion:* VPCs substantially reduce time for variant curation by excluding variants in genes which are unlikely to be associated with the patient's phenotype. By utilizing clinical geneticist's expertise during variant prioritization, a higher proportion of variants are able to be excluded based on patient phenotypic information and genotype-phenotype relationships of each variant and the corresponding gene.

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Variant Interpretation Training for the Genomics Era: A 5-Year Comprehensive Strategy Aiming Towards Professional Competencies

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Variant interpretation (VI) is crucial to genomic testing, yet there is a dearth of literature on the educational needs and career pathways for this. Melbourne Genomics has a multimodal educational approach to developing a genomic-competent diagnostic workforce. Applying adult learning theory, we developed a suite of training programs (germline and cancer), culminating in the delivery of >15,000 learning hours in VI over 5 years to Victorian, national and international health professionals. The programs include: workplace immersion experiences (48d cross-laboratory trainees [CLT]); 1–2d professional development workshops (PDW); and two Masters-level subjects. Program evaluation used mixed methods. The majority of CLTs (7/10) were unfamiliar with VI at commencement. Mid-point interviews identified barriers and facilitators of using immersion experiences to acquire and maintain competency, such as the need for an initial PDW. PDW participants ($n = 374$) were Medical Scientists (36.1%), Researchers/Bioinformaticians/Students (26.2%), Clinical Geneticists (16.8%), Other Medical (17.3%), Genetic counselors (3.1%) and other Allied Health Professionals (0.5%). Pre-post surveys (188/374) and case assessments were analyzed to determine actual versus self-assessed capability within and across workshops over time. Average self-assessed understanding of VI increased by 38.4% and 88.7% of participants anticipated incorporating their learning into their professional role. Drawing on the immersion and workshop programs, Masters-level subjects (24 modules across 6 curricula; 44 students to date) were developed using Bloom's taxonomy to align learning outcomes with desired VI competencies; subject evaluation is ongoing. This work provides a basis for an educational framework and competencies in VI that could be applied across the genomic workforce.

Virtual Gene Panel Analysis has Diagnostic Yield Approaching that of Whole Genome Analysis

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Background: Whole genome sequencing (WGS) and subsequent whole genome analysis (WGA) offers high diagnostic yield for rare Mendelian disorders, at the risk of incidental findings, variants of uncertain significance, and high testing costs. We aimed to assess whether phenotype-matched virtual gene panel analysis (VPA) using WGS data approaches the clinical diagnostic yield of WGA, while mitigating these risks and costs. *Methods:* Virtual gene panels were used to retrospectively analyze 65 clinical cases referred for WGS and WGA; in all cases, a variant relevant to the proband's phenotype had previously been clinically reported. Human phenotype ontology terms were assigned to each case based on test request forms, which in turn were used to select crowd-sourced gene panels from PanelApp. *Results:* Virtual gene panel analysis using crowd-sourced gene lists identified 93% of all clinically reported ACMG class 4 and 5 variants. All incidental findings were avoided, and there was a 58–97% reduction in the number of variants requiring manual laboratory curation. For trio analyses, the majority of de novo diagnoses (78%) would have been readily recognized on proband-only testing, due to these being a null variant or previously reported in ClinVar. *Conclusion:* Analysis of WGS data using a phenotype-matched, crowd-sourced virtual gene panel is a viable clinical diagnostic strategy that approaches the diagnostic yield of whole genome analysis while mitigating its disadvantages. For trios, a diagnostic strategy of testing the proband only, and performing reflex segregation testing as required, should also be considered.

Whole Mitochondrial Genome Sequencing at VCGS

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Mitochondria are essential subcellular organelles of virtually all cells, carrying out aerobic metabolism in order to generate energy. They have their own genome, a 16.6 kb circular molecule encoding 37 genes which produce 13 protein subunits of the respiratory chain 2 mRNAs and a full complement of 22 mitochondria-specific tRNAs. Mitochondrial disease can be can be caused by pathogenic mitochondrial DNA (mtDNA) variants, including single nucleotide substitutions, large deletions or duplications, as well as nuclear variants (some of which may cause multiple mtDNA deletions or depletion). In 2017, Victorian Clinical Genetics Services (VCGS) became NATA/RCPA accredited for whole mitochondrial genome NGS-sequencing analysis. The whole mtDNA is amplified with a single long-range PCR, followed by Illumina Nextera® XT library preparation and sequencing on a MiSeq. Using high quality DNA extracted from blood and muscle, this assay is validated for variant detection at heteroplasmy levels as low as 3%. In addition, this assay can also detect large deletions greater than 1 kb, making it a sensitive, robust and efficient assay for the detection of mitochondrial disease. We will present results from over 40 diagnostic and segregation cases that have been tested via mtDNA NGS at Victorian Clinical Genetics Services VCGS, including accurate estimation of variant heteroplasmy, which is important in determining disease status and potentially predicting disease severity. We will discuss the curation process developed and utilized at VCGS and the resources currently available for mitochondrial variant curation, which differ from those available for nuclear gene variants.

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Single Nucleotide Polymorphism (SNP) Microarray for Genome Ploidy and Gene Copy Number Alterations in Pediatric Acute Lymphoblastic Leukemia (PALL)

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Background: Identifying high-risk genetic aberrations in pediatric B-cell acute lymphoblastic leukemia (pB-ALL) could allow personalized treatment intensification and improved outcomes in these patients. Recently, an IKZF1-Plus deletion profile has been associated with poor outcomes; *IKZF1, CDKN2A, CDKN2B, PAX5*, and/or *CRLF2*. Along with genome ploidy (haploidy vs. hyperdiploidy) recurrent gene-fusions also remain important. In T-ALL, deletions of STIL result in *TAL1-STIL* gene fusion. SNP chromosome microarray (SNP-array) is well suited to detect ploidy changes, copy number abnormalities (CNA), and copy neutral loss-of-heterozygosity (cnLOH). *Aim:* Investigate and validate an 850K CytoSNP Beadchip (SNP-array) for identifying ploidy, cnLOH, and CNA in pediatric ALL. *Methods:* We performed 850K CytoSNP-array on a small cohort of pediatric ALL patients at diagnosis in conjunction with karyotype and FISH; which included B-ALL ($n = 20$) and T-ALL ($n = 4$). FISH was performed using probes for common gene-fusions: *BCR-ABL1, ETV6-RUNX1, KMT2A-AFF1, TCF3-HLF*. 850K CytoSNP data was analyzed using BlueFuse Multi v4.5. CNA results were verified using our cancer customized CGH+SNP array and/or FISH. We categorized B-ALL patients into IKZF1wt-other, IKZF1-Plus, and absent IKZF1-Plus. *Results:* SNP-array was concordant for diploidy ($n = 14$), haploidy ($n = 1$), masked haploidy ($n = 2$), masked hypodiploidy ($n = 1$), and hyperdiploiyd ($n = 5$). Overall, total ($n = 23$) recurrent deletions [heterozygous/homozygous] included IKZF1 ($n = 3$), *CDKN2A/2B* ($n = 14$), *PAX5* ($n = 5$), and *EBF1* ($n = 1$) and *STIL* ($n = 2$). B-ALL patient groups were IKZF1-Plus ($n = 4$), IKZF1wt-other ($n = 7$), and IKZF1-Plus absent ($n = 9$). *Conclusion:* Our 850K CytoSNP-array was concordant with karyotype, FISH, or CGH+SNP array results and has been successfully validated for use in the diagnostic laboratory.

Mosaicism for Sequence and Copy Number Variants in Diverse Disorders in a Large Clinical Cohort

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Background: Genetic variation present in only a proportion of cells within an individual can be detected as mosaic abnormalities through next-generation sequencing (NGS) methods. Analysis of a broad diversity of disease genes can provide useful insight into the analytic requirements to detect mosaic variants, how frequently they are encountered, the various forms they occur in, and their clinical implications. *Aim:* We sought to validate a diagnostic NGS approach to detect mosaic variants and to estimate the prevalence and implications of such variants across a broad range of Mendelian disease genes in a clinical setting. *Methods:* Using NGS gene panels with deep coverage, Genome-in-a-Bottle (GiaB) DNA samples were mixed in different ratios and tested to establish the analytic sensitivity for detecting mosaicism. We then evaluated the occurrence of mosaic variants in a large clinical cohort referred for diagnostic genetic testing for one or several of 1600 genes. *Results:* Genome mixing experiments showed that mosaicism of ≥20% can be reliably recognized using deep coverage NGS. In a cohort of 472,991 individuals we identified 2459 mosaic variants across 286 genes, which contributed to ~1% of clinically significant results. Cancer-related genes had the most mosaic variants. Individuals with mosaic variants had either later onset disease or milder clinical phenotypes. *Conclusion:* Carefully tailored NGS can support confident identification of mosaicism and is most influenced by the depth of sequence coverage and a gene's propensity to contain mosaic variants. Mosaic variants are very rare but occur in many types of hereditary disease and influence the phenotype.

Challenges and Benefits of Migrating to the New Genome Build

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Introduction: The current genome build, (GRCh38/Hg38) is now nearly 6 years old; however, most clinical laboratories still operate on the previous build (GRCh37/Hg19) which was originally released 10 years ago. This is despite most, if not all, relevant databases now being available for the new build. Continued analysis to the old builds risks missing out on the significant improvements that have been attributed to GRCh38, and migration should be considered as part of ongoing quality improvement efforts. *Aims:* To evaluate the challenges and benefits of migrating clinical genomic analysis to the new genome build. *Method:* Over the last 6 months, the Victorian Clinical Genetics Services has migrated its exome analysis tools to GRCh38 and has evaluated the quality and robustness of the new build for use in clinical applications compared to previous results derived from our accredited pipelines. Evaluated metrics included coverage, alignment accuracy and accuracy of variant and copy number calling. *Results:* Overall, we observe significantly improved coverage in key genomic regions, especially those now represented by alternative contigs. A key enabler of this improvement is the use of alt-aware alignment in our bioinformatic analyses that improves mappability of primary alignments. Implementation challenges, included the difficulty of comparing results across coordinate systems, and resolving equivalent data resources for the new genome build. *Conclusion:* Overall we found the transition to the new genome build to be both feasible and beneficial, and have now validated a clinical analysis pipeline for exome and genome sequencing for GRCh38.

Survey of Public Opinions About Sharing Genomic Data from Medical Records with Researchers

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Queensland Health (QH) is making a significant investment to introduce genomic testing to the public health system. As QH becomes a repository for patient genomic data, requests to share this data with researchers will increase. However, sharing of genomic data comes with a unique set of ethical, legal and social considerations. This project aimed to understand public opinions about the genomic data contained in medical records being used for research purposes to inform public policy and discussions around genomic data sharing.

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From February to April 2019, members of the public completed a written questionnaire that ask their opinion and concerns about genomic data stored in medical records being shared by QH for use in research. A total of 1661 people participated in the survey. Most participants wanted to be given the choice to have their genomics data from medical records used in research. Their expectations of how often they needed to be approached for permission for genomic data use depended on whether the genomic data was identifiable or anonymous. Participants were most concerned with genomics data sharing resulting in; discrimination (insurance and employment), data being used for marketing, and genomic data being made publically available. Given the sensitive nature of genomics data ensuring that genomic data sharing and management practices in the public health system reflect public expectations is an important consideration to maintain trust. The findings from this survey are an important starting point to inform discussions about the management of genomics data sharing held within Queensland's health system.

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